United States
Environmental Protection
Agency

EPA/690/R-16/003F
Final
9-08-2016

Provisional Peer-Reviewed Toxicity Values for

n-Heptane
(CASRN 142-82-5)

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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
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
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	glutamic oxaloacetic transaminase, also known as AST
SGPT	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_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-HEPTANE (CASRN 142-82-5)

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 a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by 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.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

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. Environmental Protection Agency (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 National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

n-Heptane, CASRN 142-82-5, is a hydrocarbon solvent that is typically isolated via fractional distillation from light naphtha petroleum streams (OECD, 2010). In addition to being a solvent, *n*-heptane is used as a standard in testing knock intensity of gasoline engines (O'Neil et al., 2013) and is regulated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as an inert ingredient in nonfood-use pesticides (HSDB, 2014).

n-Heptane is a liquid at room temperature. In the environment, *n*-heptane will readily volatilize from dry soil due to its high vapor pressure. Once in the air, it will stay in the vapor phase (HSDB, 2014). Based on its estimated Henry's law constant, *n*-heptane will also exhibit high volatility from moist soil and water surfaces. In addition, *n*-heptane deposited on soil may leach to groundwater or undergo runoff after a rain event based on its moderate water solubility and moderate soil absorption coefficient. As a result, removal of *n*-heptane from soil by leaching with water may compete with volatilization, depending on the local conditions (wet, dry, etc.). The empirical formula for *n*-heptane is C_7H_{16} (see Figure 1). A table of physicochemical properties for *n*-heptane is provided below (see Table 1).

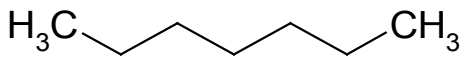


Figure 1. *n*-Heptane Structure

Table 1. Physicochemical Properties of *n*-Heptane (CASRN 142-82-5)[a]

Property (unit)	Value
Physical state	Liquid[b]
Boiling point (°C)	98.5
Melting point (°C)	−90.6
Density (g/cm^3)	0.6795[b]
Vapor pressure (mm Hg at 25°C)	46
pH (unitless)	NA
Solubility in water (g/L at 25°C)	0.0034
Octanol-water partition constant (log K_{ow})	4.66
Henry's law constant (atm-m^3/mol at 25°C) (estimated)	2.27[c]
Soil adsorption coefficient K_{oc} (mL/g) (estimated)	240
Relative vapor density (air = 1)	3.45[b]
Molecular weight (g/mol)	100.21

[a]SRC (2013).
[b]HSDB (2014).
[c]U.S. EPA (2012b).

NA = not applicable.

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

Table 2. Summary of Available Toxicity Values for *n*-Heptane (CASRN 142-82-5)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2016a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2016)
IPCS	NV	NA	IPCS (2016); WHO (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
OSHA (PEL)	500 ppm (2,000 mg/m^3) (TWA)	The PELs are 8-hr TWAs for general industry, construction, and shipyard employment.	OSHA (2006a); OSHA (2006b); OSHA (2011)
NIOSH (REL)	85 ppm (350 mg/m^3) (TWA), 440 ppm (1,800 mg/m^3) (15-min ceiling)	For RELs, TWA indicates a time-weighted average concentration for up a 10-hr work day during a 40-hr work week; the ceiling REL should not be exceeded at any time.	NIOSH (2015)
NIOSH (IDLH)	750 ppm	Based on acute inhalation toxicity data in humans	NIOSH (1994); NIOSH (2015)
ACGIH (TLV-TWA)	400 ppm (1,640 mg/m^3)	Based on narcosis and respiratory irritation	ACGIH (2015)
ACGIH (STEL)	500 ppm (2,050 mg/m^3)	Based on narcosis and respiratory irritation	ACGIH (2015)
Cancer			
IRIS (WOE)	Classification D; not classifiable as to human carcinogenicity	Basis: no human or animal data available	U.S. EPA (2012a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)

Table 2. Summary of Available Toxicity Values for *n*-Heptane (CASRN 142-82-5)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Cal/EPA	NV	NA	Cal/EPA (2016a); Cal/EPA (2016b); Cal/EPA (2011)
ACGIH	NV	NA	ACGIH (2015)

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

NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in May 2015 and April 2016 for studies relevant to the derivation of provisional toxicity values for *n*-heptane, CASRN 142-82-5. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant noncancer and cancer databases, respectively, for *n*-heptane and include all potentially relevant short-term-, subchronic-, and chronic-duration studies. The phrase "statistical significance" or the term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for *n*-Heptane (CASRN 142-82-5)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)[b]								
Acute	M and F volunteers (number not reported), up to 15 min	1,000, 2,000, 3,500, 5,000 ppm 4,000, 8,000, 14,000, 20,000	Vertigo	NDr	NDr	4,000	Patty and Yant (1929)	NPR
Long-term	18 M and F (combined), tire factory workers, neurophysiological screen, 1−9 yr	Solvent containing >95% *n*-heptane; concentrations not reported	Subjective complaints of numbness and paresthesia of limbs; altered neurophysiological parameters indicative of minimal peripheral neuropathy	NDr	NDr	NDr	Crespi et al. (1979)	PR
Animal								
1. Oral (mg/kg-d)[b]								
Short-term	3 M/0 F per exposure (9 M/0 F controls), CD COBS rat, gavage, 5 d/wk, 3 wk	0, 1,000, 2,000, 4,000 ADD: 0, 714, 1,430, 2,860	Potential treatment-related effects include elevated serum LDH, increased kidney and liver weights, and hyperplasia of the gastric nonglandular epithelium	NDr	NDr	NDr	Eastman Kodak, (1979) (Small group sizes and inadequate reporting preclude identification of LOAEL)	NPR
Subchronic	8 M/0 F, CD COBS rat, gavage, 5 d/wk, 13 wk	0, 4,000 ADD: 0, 2,860	Potential treatment-related effects include persistent body-weight depression, gross liver enlargement, organ-weight changes, and histopathology of the forestomach, liver, kidney, and adrenal glands	NDr	NDr	NDr	Eastman Kodak (1980) (High gavage-related mortality [5/8] precludes determination of LOAEL)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for *n*-Heptane (CASRN 142-82-5)								
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
2. Inhalation (mg/m^3)[b]								
Short-term (neurotoxicity)	**9−10 M/0 F, Long-Evans rat, *n*-heptane (99.5% pure), 6 hr/d, 28 d**	**0, 801, 4,006 ppm HEC: 0, 821, 4,105**	**Abnormal auditory brainstem responses and increased auditory threshold, which indicate a loss of hearing sensitivity in anaesthetized rats 2 mo after cessation of exposure**	**821**	**1,170 for loss of hearing sensitivity**	**4,105**	**Simonsen and Lund (1995) (Study examined central auditory effects)**	**PR, PS**
Subchronic (neurotoxicity)	7 M/0 F, Wistar rat, *n*-heptane (>99% pure), 12 hr/d, 7 d/wk, 16 wk	0, 2,960 ppm HEC: 0, 6,066	No neurological or body-weight effects	6,066	NDr	NDr	Takeuchi et al. (1981, 1980) (Study tested for peripheral neuropathy, including neurobehavioral, neurophysiological and neuropathological measurements; central-auditory effects were not examined)	PR
Chronic	15 M/15 F, S-D rat, *n*-heptane (98.5% pure), 6 hr/d, 5 d/wk, 26 wk	0, 398, 2,970 ppm HEC: 0, 291, 2,174	No adverse effects on physical assessment, body weight, hematology, serum chemistry, or urinalysis	NDr	NDr	NDr	Bio Dynamics (1980); Yeshiva University (1980) (Inadequate reporting of neurohistological findings and lack of pathology of non-nervous system tissues preclude determination of NOAEL/LOAEL)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for *n*-Heptane (CASRN 142-82-5)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic (neurotoxicity)	6−9 M/0 F, S-D rat, *n*-heptane (99% pure), 9 hr/d, 5 d/wk, up to 30 wk	0, 1,500 ppm HEC: 0, 1,647	No neurological or body-weight effects	1,647	NDr	NDr	Frontali et al. (1981) (Study tested for peripheral neuropathy, including hind limb spread on landing and tibial nerve histology; central auditory measurements were not conducted)	PR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short-term = repeated exposure for 24 hours to ≤30 days; subchronic = repeated exposure for >30 days ≤10% lifespan for humans or laboratory animal species; and chronic = repeated exposure for >10% lifespan for humans or laboratory animal species (U.S. EPA, 2002).

[b]Dosimetry: Values are converted to an ADD (mg/kg-day) for oral noncancer effects and a HEC (mg/m^3) for inhalation noncancer effects. All repeated exposure values are converted from a discontinuous to a continuous exposure, with the exception of values from animal developmental studies, which are not adjusted to a continuous exposure; HEC_{EXRESP} = (ppm × molecular weight ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient. For *n*-heptane, the blood-air partition coefficient for rats is greater than that for humans (DECOS, 1993), so a default ratio of 1 is applied (U.S. EPA, 1994a).

[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; COBS = cesarean-obtained barrier-sustained; F = female(s); HEC = human equivalent concentration; LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for *n*-Heptane (CASRN 142-82-5)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL/ BMCL**	**LOAEL**	**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								

BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

The database for repeated human exposure to *n*-heptane is limited to a single occupational study lacking quantitative exposure data (Crespi et al., 1979). The only other available human study of inhalation exposure to *n*-heptane is an acute controlled-exposure inhalation study in volunteers (Patty and Yant, 1929).

Acute Exposure

Patty and Yant (1929)

Male and female volunteers (number not reported) between the ages of 20 and 30 years were observed during exposure to 1,000, 2,000, 3,500, or 5,000 ppm (4,000, 8,000, 14,000, or 20,000 mg/m^3) of *n*-heptane vapor in air for up to 15 minutes. The subjects reported slight vertigo after 6 minutes at 1,000 ppm or 4 minutes at 2,000 ppm, moderate vertigo after 4 minutes at 3,500 ppm, and marked vertigo after 4 minutes at 5,000 ppm. Additional effects observed after 4−15 minutes of exposure to 5,000 ppm included hilarity (amusement), incoordination, and inability to walk straight. The effects lasted for up to 30 minutes following a 15-minute exposure.

Long-Term Exposure

Crespi et al. (1979)

In an occupational exposure study, neurophysiological examinations were performed in workers exposed to *n*-heptane at a small tire factory. A total of 18 workers, who had been exposed for 1−9 years to unreported concentrations of vapor from a solvent containing >95% *n*-heptane (and trace amounts of benzene, toluene, and other hydrocarbons), complained of numbness and paresthesia of the limbs with a "glove and stocking" distribution. All workers underwent a neurological examination. However, details of the parameters evaluated were not provided in the report. Neurophysiological measurements (motor nerve conduction velocity [MNCV], distal latency [DL], and amplitude desynchronization [AD] of the evoked muscle action potential [MAP] along the peroneal nerve) were performed on 12 of the workers whose personal and family history excluded any simultaneous causes of peripheral nerve damage. Most, but not all, were female, with a mean age of 35.5 years. Measurements were also made on an age-matched control group; however, control findings were not described in the report.

No signs of peripheral neuropathy were observed during the neurological examinations (data were not reported). The mean MNCV of the exposed workers was not significantly different from the controls, and none of the exposed workers had an MNCV below the normal range. There was, however, a statistically significant correlation between duration of exposure (years of employment at the factory) and MNCV, such that MNCV decreased as exposure duration increased (based on 10 of the 12 subjects; 2 were excluded for unreported reasons). Mean DL in the exposed workers (evaluated in only 10 subjects) did not differ from the age-matched controls, and DL in individual workers was not correlated with duration of exposure. Mean AD was significantly increased in the exposed workers compared with age-matched controls, and 3 of the 12 workers had values at or above the normal limit. AD in individual workers was not correlated with duration of exposure. The researchers noted that increased AD of the MAP is a frequent finding in subclinical polyneuropathies. A cumulative

correlation between pooled electrophysiological data in all subjects and exposure duration was found at a *p*-value of 0.05.

On the basis of significantly increased AD of the MAP, and the significant inverse correlation between MNCV and exposure duration, the researchers concluded that *n*-heptane had produced minimal peripheral nerve damage in the exposed workers. The absence of exposure-level estimates precludes the determination of a no-observed-adverse-effect level/lowest-observed-adverse-effect level (NOAEL/LOAEL).

ANIMAL STUDIES

Oral Exposures

The oral database for *n*-heptane is limited to an unpublished subchronic-duration study in rats and the short-term-duration, range-finding study that preceded it (Eastman Kodak, 1980, 1979).

Short-Term-Duration Studies

Eastman Kodak (1980, 1979)

In a range-finding study, groups of male Charles River CD cesarean-obtained barrier-sustained (COBS) rats (three/group) were administered undiluted *n*-heptane (95.7% pure) via gavage at dose levels of 1,000, 2,000, or 4,000 mg/kg-day, 5 days/week for 3 weeks. The administered gavage doses were converted to adjusted daily doses (ADDs) of 714, 1,430, and 2,860 mg/kg-day, respectively, by multiplying the administered gavage dose by (5/7) days per week. A control group of nine male rats was given tap water via gavage using the same dosing schedule. The animals were observed daily for clinical signs of toxicity, and food consumption and body weights were recorded on Days 0, 3, 7, 14, and 20 of treatment. Surviving animals were sacrificed at the end of the exposure period. Blood was collected at study termination just prior to necropsy for hematology (white blood cell [WBC] count and differential, hemoglobin [Hb] concentration, and hematocrit [Hct]) and serum chemistry (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], blood urea nitrogen [BUN], and glucose). All animals sacrificed at termination or that died during the study were necropsied. Liver and kidney weights were recorded, and an extensive set of tissues from all rats was examined for histopathology, including five areas of the brain. Statistical analyses were not conducted, and reporting of continuous data is inadequate for independent statistical analysis (lacks reporting of standard deviation [SD] values).

No chemical-related mortalities were reported; one animal in the 714-mg/kg-day group died due to gavage error. No adverse clinical signs were observed. Mean body weights and food consumption in exposed rats were comparable to controls. Serum LDH was increased 1.5-fold in the 714-mg/kg-day group and 2.4-fold in the 1,430- and 2,860-mg/kg-day groups (see Table B-1). All other serum chemistry and hematological parameters were comparable between exposed and control rats. Absolute and relative liver weights in exposed rats were increased by 14−39% and 19−38%, respectively, compared with controls (see Table B-1); the larger changes were observed in the low-dose group. Absolute and relative kidney weights in exposed rats were increased by 6−14% and 8−21%, respectively, compared with controls (see Table B-1); the larger changes were observed in the high-dose group. Histopathological examination revealed hyperplasia of the gastric nonglandular (forestomach) epithelium in 1/3, 2/3, and 1/3 rats in the 714-, 1,430-, and 2,860-mg/kg-day groups, respectively (see Table B-1).

The forestomach lesions were reported as moderate in the 714- and 2,860-mg/kg-day groups and minor in the 1,430-mg/kg-day group. These lesions were not identified in any control rats. No other treatment-related histopathological findings were noted.

Small group sizes and inadequate reporting of any measure of variability within treatment groups or statistical analyses preclude the determination of a critical effect or a LOAEL for this study. Effects possibly related to short-term gavage treatment with *n*-heptane include elevated serum LDH, increased liver and kidney weights, and hyperplasia of the gastric nonglandular epithelium in rats.

Subchronic-Duration Studies

Eastman Kodak (1980)

Eight male Charles River CD COBS rats were administered undiluted *n*-heptane (95.7% pure) via gavage at a dose level of 4,000 mg/kg-day, 5 days/week for 13 weeks. The administered gavage dose of 4,000 mg/kg-day was converted to an ADD of 2,860 mg/kg-day by multiplying the administered gavage dose by (5/7) days per week. A control group of eight rats was treated via gavage with tap water using the same dosing schedule. The animals were observed daily for clinical signs; body weights and food consumption were recorded twice weekly. Rats surviving treatment were sacrificed at 90 days, and blood was collected for hematology (WBC count and differential, Hb concentration, Hct) and clinical chemistry (ALP, ALT, AST, LDH, BUN, glucose). All animals sacrificed at termination or that died during the study were necropsied. Organ weights were recorded for liver, kidney, brain, adrenal glands, testes, heart, and spleen. An extensive collection of tissues from all rats was examined for histopathology, including five areas of the brain, spinal cord, sciatic-tibial nerves, and dorsal root ganglia. Appropriate statistical tests were conducted.

Five of the eight rats in the treated group died from acute chemically induced pneumonitis after accidental tracheal intubation or aspiration into the lungs possibly related to severe gastric irritation observed at autopsy. Timing of the deaths was not reported, but based on weekly body-weight reporting, it appears that one died during the first week, two died during Week 7, one died during Week 12, and one died during Week 13. An additional animal that survived until sacrifice also showed signs of chemical pneumonitis. No clinical signs of toxicity were seen in treated rats that did not have chemical pneumonitis. Food consumption was significantly reduced by 23% in exposed rats during the first week but similar to controls thereafter. Mean body weights were also significantly reduced during the first week of treatment in exposed rats and remained depressed compared to controls throughout most of the study (8−15%) (see Table B-2). A slight, but statistically significant 20% reduction in serum glucose levels was observed in the three surviving exposed rats, compared with controls (see Table B-2). The relevance of decreased serum glucose levels is uncertain, given that all other serum chemistry and hematological parameters were comparable between exposed and control rats. Statistically significant organ-weight changes in the three exposed rats examined at study termination, compared with controls, included 28% decrease in absolute heart weight, 17% increase in relative liver weight, 16% increase in relative kidney weight, and 36% increase in relative adrenal weight (see Table B-2). Numerous gross lesions were observed in the rats that died by gavage error (e.g., blood in mouth and nares [nostrils], pulmonary edema and hemorrhage, liver enlargement, hematuria). Excluding changes related to chemically induced pneumonitis, grossly enlarged livers were found in all treated animals that died, and hematuria was observed in one rat that died, according to the study authors' descriptions.

Histopathological examination of exposed rats revealed local irritative effects on the forestomach mucosa, including moderate to severe suppuration or necrosis of the nonglandular gastric epithelium in 4/8 rats (3/5 rats that died, 1/3 rats that survived until sacrifice) and mostly moderate hyperkeratosis with pseudoepitheliomatous hyperplasia in 7/8 rats (4/5 rats that died, 3/3 rats that survived until sacrifice) (see Table B-3). Low incidences of several hepatic (hepatocyte vacuolation, serosal adhesions, congestion) and renal (hyaline droplets, increased incidence of tubular dilation with casts, increased incidence of regenerating renal tubular epithelium, hemorrhage, congestion, focal nephritis) lesions were seen in treated rats; these lesions were generally characterized as minimal or minor (see Table B-3). The study authors noted that regenerating renal tubular epithelium and tubular dilation with casts were consistent with renal effects previously reported for ketones, although these lesions were only slightly elevated compared to controls. In rats that died by gavage error, the adrenal glands showed focal cortical hemorrhages in 5/5 rats and congestion in 2/5 rats (minor or moderate for both lesions). No evidence of neurotoxicity or other prominent treatment-related lesions were found based on histopathology.

High mortality due to gavage error (5/8 treated rats) precludes the determination of a critical effect or LOAEL for this study. Potential treatment-related effects include persistent body-weight depression, gross liver enlargement, organ-weight changes, and histopathology of the forestomach, liver, kidney, and adrenal glands.

Chronic-Duration/Carcinogenicity Studies

No studies have been identified.

Reproductive/Developmental Studies

No studies have been identified.

Inhalation Exposures

Repeat-exposure inhalation studies of *n*-heptane toxicity have focused primarily on potential neurotoxicity (Simonsen and Lund, 1995; Frontali et al., 1981; Takeuchi et al., 1981; Bio Dynamics, 1980; Takeuchi et al., 1980; Yeshiva University, 1980). Only one chronic-duration study evaluated a limited set of systemic endpoints; however, non-nervous-system histopathology was not reported (Bio Dynamics, 1980; Yeshiva University, 1980). Acute inhalation studies of *n*-heptane toxicity have also been aimed at examining potential neurotoxicity (see "Supporting Neurotoxicity Studies in Animals" in the "Other Data" section below).

Short-Term-Duration Studies

Simonsen and Lund (1995)

The study by Simonsen and Lund (1995) is selected as the principal study for the derivation of the subchronic and chronic provisional inhalation reference concentrations (p-RfCs). In this neurotoxicity study, groups of male Long-Evans rats (9−10/group) were placed in whole-body chambers and exposed to *n*-heptane (99.5% pure) vapors at reported mean concentrations of 0, 801 ± 79, or 4,006 ± 242 ppm, 6 hours/day for 28 days. The study was aimed at evaluating potential effects of *n*-heptane on the central auditory system, given that exposure to organic solvents has been associated with hearing loss in rats and humans (Simonsen and Lund, 1995). Feed and water were available ad libitum except during exposure periods. Six weeks prior to exposure, screw electrodes were mounted in the skull of the rats for

measurement of auditory brainstem responses. The amplitudes and latencies of Components Ia and IV of the auditory brainstem responses elicited at frequencies 4, 8, 16, or 32 kHz and intensities 25−95 dB were measured in anaesthetized rats 2 months after cessation of exposure using both implanted electrodes and needle electrodes. Body weight was monitored throughout the study. No other systemic endpoints were assessed.

Body-weight gain during the first 2 weeks postexposure was significantly decreased by 53% in the 4,006-ppm group. However, body weights were similar in all three exposure groups during the course of treatment. The peak amplitudes of the Ia and IV components of the auditory brainstem responses were reduced in rats exposed to 4,006 ppm at all frequencies and intensities, compared with control (0-ppm treatment group), but not at 801 ppm. Statistically significant reductions were reported for Component IV, most prominently at higher frequencies and intensities (see Table B-4). Decreases in amplitude of Component Ia displayed a similar pattern to IV; however statistical analyses for this component were not provided. No exposure-related changes were observed in the latencies or interpeak latencies of the Ia and IV components. The reduction in the peak amplitudes corresponded to an approximate 10-dB increase in the auditory threshold. The difference in auditory threshold between the control and the 4,006-ppm group was observed at all frequencies, although statistical significance was only reached at 8 and 16 kHz (see Table B-5; data have been digitally extracted using GrabIt! Software).

A NOAEL of 801 ppm and a LOAEL of 4,006 ppm is identified for abnormal auditory brainstem responses and increased auditory threshold that suggest a loss of hearing sensitivity in rats. Concentrations of 801 and 4,006 ppm are converted to human equivalent concentrations (HECs) of 821 and 4,105 mg/m^3 for extrarespiratory effects by treating *n*-heptane as a Category 3 gas (generally water insoluble and unreactive in the extrathoracic or tracheobronchial regions) and using the following equation (U.S. EPA, 1994a):
HEC_{EXRESP} = (ppm × molecular weight [MW] ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of blood-gas partition coefficient (animal:human). For *n*-heptane, the blood-air partition coefficient for rats is greater than that for humans (Gargas et al., 1989); thus, a default ratio of 1 is applied (U.S. EPA, 1994a).

Subchronic-Duration Studies

Takeuchi et al. (1981, 1980)

In a neurotoxicity study, groups of male Wistar rats (seven/group) were exposed to pure *n*-heptane (>99%) at measured mean concentrations of 0 or 2,960 ± 200 ppm, 12 hours/day for 16 weeks. Neurological endpoints were assessed prior to exposure and after 4, 8, 12, and 16 weeks of exposure, including neurobehavioral tests (foot drop, altered gait) and neurophysiological tests (peripheral nerve conduction velocity measured in the tail). After 16 weeks of exposure, rats were euthanized (one rat/group) and selected peripheral nerves, muscle, and neuromuscular junctions were fixed for histopathological and/or ultrastructural evaluation. Body weight was recorded prior to exposure and after 4, 8, 12, and 16 weeks of exposure. No other systemic endpoints were assessed.

No changes were observed in neurological endpoints between the exposed group and control (0-ppm treatment group). Transient decreases in body weight were observed, with a

significant 13% decrease in the exposed group at 8 weeks, compared with control, but not at 4, 12, or 16 weeks.

The administered concentration of 2,960 ppm is identified as a NOAEL based on a lack of neurotoxicity or persistent body-weight changes. The exposure concentration of 2,960 ppm is converted to an HEC of 6,066 mg/m^3 for extrarespiratory effects by treating *n*-heptane as a Category 3 gas and using the following equation (U.S. EPA, 1994a):
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of blood-gas partition coefficient (animal:human). For *n*-heptane, the blood-air partition coefficient for rats is greater than that for humans (Gargas et al., 1989); thus, a default ratio of 1 is applied (U.S. EPA, 1994a).

Chronic-Duration Studies

Bio Dynamics (1980); Yeshiva University (1980)

Groups of Sprague-Dawley (S-D) rats (15/sex/group) were exposed to *n*-heptane (98.5% reagent grade) vapor at cumulative mean concentrations of 0, 398, or 2,970 ppm for 6 hours/day, 5 days/week for 26 weeks. The animals were observed for mortality twice daily, and full physical assessments and body weight were recorded weekly. Hematology (Hb, Hct, red blood cell [RBC] count, WBC count and differential, and clotting time), serum chemistry (BUN, ALP, ALT, and glucose), and urinalysis determinations (appearance, specific gravity, occult blood, pH, protein, bilirubin, and ketones and glucose) were performed in 10 rats/sex/group after 13 weeks of exposure and in 5 rats/sex/group after 26 weeks of exposure. Rats from the exposure groups were sacrificed for neurohistological examination at 9 weeks (three/sex/group), 18 weeks (five/sex/group), 27 weeks (four/sex/group), and 29 weeks (all survivors). No control rats (0-ppm treatment group) were sacrificed at 9 weeks; however, the remaining sacrifice schedule was the same for control and exposed groups (histology of non-nervous system tissues was not performed). Gross necropsy was conducted on all animals that died spontaneously or were euthanized in extremis, and selected tissues were prepared for potential future histological examination, including bone, bone marrow, kidneys, liver, lungs, pulmonary and mesenteric lymph nodes, sciatic nerves, spinal cord, and gross lesions. In-life-phase systemic measurements were reported in Bio Dynamics (1980), while neurohistological evaluations were summarized in Yeshiva University (1980).

Two deaths occurred in this study: one female in the low-dose group died accidently at Week 18 during retro-orbital bleeding, and one female in the high-dose group exhibiting prolapsed urethra and hyperemic vaginal walls was euthanized. These deaths were not considered exposure related. During the first week of treatment, rats in both the low- and high-dose groups exhibited prostration and difficulty breathing (more common and more severe in the high-dose group). Clinical signs observed in Week 1 were apparently transient, as they were not observed thereafter. No differences in body weights were observed between treated and control rats. ALP levels showed a slight, dose-related increase in exposed females at Week 26, reaching statistical significance only in the high-dose group (1.6-fold change from controls) (see Table B-6). Hematology, urinalysis, and other serum chemistry results were similar between treated rats and their control counterparts. The neurohistological evaluation of the central and peripheral nervous systems revealed the presence of pathological changes in both control and treated animals that were consistent with normal aging, including axonal swelling in the gracile nucleus and tract, isolated myelin bubbles in dorsal roots, and rare

segmental remyelination and Wallerian degeneration in the peripheral nerves. Higher incidence of myelin bubbles was reported at Weeks 27 and 29 in the dorsal roots of exposed rats compared to controls (incidence data were not provided); however, the study authors questioned the significance of such findings, indicating the lack of dose-response relationship and progression of these lesions from Weeks 27−29. Isolated incidences of unilateral and bilateral optic nerve degeneration with or without changes in lateral geniculate nucleus were found in both control and exposed animals (incidence data was not provided) and did not appear to be related to treatment. Due to the lack of reporting on incidence data, the relevance of these neurohistological lesions could not be independently reviewed and is therefore unclear.

The study inadequately reported neurohistological findings and failed to examine pathology of non-nervous system tissues, precluding the determination of critical target organs or a NOAEL/LOAEL. The exposure concentrations of 398 and 2,970 ppm are converted to HECs of 291 and 2,174 mg/m^3 for extrarespiratory effects by treating *n*-heptane as a Category 3 gas and using the following equation (U.S. EPA, 1994a): HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of blood-gas partition coefficient (animal:human). For *n*-heptane, the blood-air partition coefficient for rats is greater than that for humans (Gargas et al., 1989); thus, a default ratio of 1 is applied (U.S. EPA, 1994a).

Frontali et al. (1981)

In a neurotoxicity study, groups of 6−9 male S-D rats were exposed to pure *n*-heptane (99%) at concentrations of 0 or 1,500 ppm, 9 hours/day, 5 days/week for 7, 14, or 30 weeks. Rats were supplied with food ad libitum except during exposure periods. Body weight was monitored throughout the study. Neurological endpoints included hind limb spread on landing after dropping from a 32-cm height and tibial nerve histology after 7, 14, and 30 weeks of exposure.

Body weights were similar between the exposure group and control (0-ppm treatment group). No differences in hind limb spread (data were not provided) or tibial neural axon histology were observed between exposure and control groups.

The exposure concentration of 1,500 ppm is identified as a NOAEL for lack of neurological or body-weight effects. This concentration was converted to an HEC of 1,647 mg/m^3 for extrarespiratory effects by treating *n*-heptane as a Category 3 gas and using the following equation (U.S. EPA, 1994a): HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × ratio of blood-gas partition coefficient (animal:human). For *n*-heptane, the blood-air partition coefficient for rats is greater than that for humans (Gargas et al., 1989); thus, a default ratio of 1 is applied (U.S. EPA, 1994a).

Reproductive/Developmental Studies

No studies have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Genotoxicity

In the only available genotoxicity study, *n*-heptane did not induce gene mutation in *Salmonella typhimurium* or *Escherichia coli*, mitotic gene conversion in *Saccharomyces cerevisiae,* or chromosome damage in cultured rat liver cells (Brooks et al., 1988).

Supporting Human Toxicity Studies

Valentini et al. (1994) reported a case of peripheral neuropathy in a 32-year-old female after about 6 months of working as a shoemaker at home in her garage (Valentini et al., 1994). After reproducing her working conditions (8−10 hours/day), the measured air concentration of *n*-heptane was 153 mg/m^3. Several other solvent exposures occurred, most notably ethyl acetate (252 mg/m^3) and cyclohexane (375 mg/m^3). The patient's symptoms included vertigo, leg and arm paresthesia, leg pain, abnormal electroencephalogram (EEG), and altered peripheral nerve conduction velocity. A complete recovery was achieved within 7 months after cessation of exposure. Due to exposure to several solvents, it is unknown if exposure to *n*-heptane caused or contributed to the peripheral nervous system deficits.

Supporting Neurotoxicity Studies in Animals

Neurobehavioral changes, including increased motor activity and impaired operant training, were observed in rats and mice exposed to *n*-heptane at concentrations ≥5,600 ppm (23,000 mg/m^3) for 30−240 minutes; no neurobehavioral effects were observed at 3,000 ppm (12,000 mg/m^3) (Gönczi et al., 2000; Glowa, 1991). Mice were prostrate at 10,000 ppm (41,000 mg/m^3) (Glowa, 1991). In another acute inhalation study, isoeffective concentrations for 30% inhibition of propagation and maintenance of an electrically evoked seizure were determined to be 2,740 ppm (11,200 mg/m^3) in rats and 4,740 ppm (19,400 mg/m^3) in mice (Frantík et al., 1994). These values were used as a criterion of the acute neurotropic effect of *n*-heptane.

Altered electrophysiology and histopathological lesions in peripheral nerves were observed in rats exposed to 1,500 ppm of technical-grade *n*-heptane (52.4% pure) 5 hours/day, 5 days/week for 1−6 months (Truhaut et al., 1973). Impurities in the test material included benzene, toluene, 3-methylhexane, cyclohexanes, and other compounds. The extent to which the observed effects were due to *n*-heptane is unclear because high levels of potentially neurotoxic impurities were found in the test material and may have contributed to the effects.

Acute Systemic Toxicity in Animals

Acute lethality tests have reported rat 4-hour inhalation median lethal concentration (LC_{50}) values of >17,937 ppm (73,518 mg/m^3) (Hazleton Laboratories, 1982) and 1 mmol/L (100,210 mg/m^3) (Hau et al., 1999). Saturated air levels of *n*-heptane caused convulsions and death in rats within 20−26 minutes due to asphyxiation (displacement of oxygen due to high vapor pressure); if animals were removed within 12 minutes, they survived but showed slight liver and kidney damage at autopsy (Dow Chemical Co, 1962). Respiratory arrest was observed in Swiss mice exposed to *n*-heptane at concentrations ≥48,000 ppm (200,000 mg/m^3) for up to 5 minutes (Swann et al., 1974). Central nervous system (CNS) depression and cyanosis was observed in mice following brief exposures (2−3 minutes of spraying time) to aerosols containing *n*-heptane at concentrations of 800−2,500 ppm (3,300−10,200 mg/m^3); the animals recovered once removed from the exposure chamber, and no lung damage was observed at autopsy (Yamashita and Tanaka, 1995).

A concentration inducing 50% respiratory depression (RD_{50}) of 17,400 ppm (71,300 mg/m^3) was identified in CF-1 male mice exposed to *n*-heptane for 10 minutes via inhalation; the RD_{50} represents the concentration required to reduce the respiration rate by 50% (Kristiansen and Nielsen, 1988). Respiratory irritation was not observed in outbred specific

pathogen-free male mice (CD-1, COBS) exposed to *n*-heptane for 1-minute intervals at a concentration of 20,000 ppm (80,000 mg/m^3) via inhalation (U.S. EPA, 1994b).

Rats treated with 1 mL/kg (0.684 mg/kg) of *n*-heptane via daily intraperitoneal (i.p.) injection for 1−45 days did not exhibit any overt toxic symptoms, but did show hepatic effects that included significant decreases in serum cholinesterase activity, albumin content, cholesterol content, hepatic protein, total sulfhydryl content, and glucose-6-phosphatase, and a significant increase in fructose-1,6-diphosphate (FDP) and lipid peroxidation (Goel et al., 1988, 1982).

Absorption, Distribution, Metabolism, and Elimination (ADME) Studies

The absorption, distribution, metabolism, and elimination of *n*-heptane are summarized below based on reviews by DECOS (1993), MAK Commission (2012), and EC (1996).

The primary route of exposure to *n*-heptane in humans is via inhalation. Pulmonary retention following inhalation exposure is 25−29% in humans and rats. The blood-air partition coefficients for *n*-heptane are 1.9−2.85 in humans and 4.75−5.4 in rats. A minor amount of dermal absorption is possible. In vitro studies using abdominal rat skin indicate a dermal penetration rate of 0.14−0.15 µg/cm^2-hour.

Organ/air distribution coefficients determined in vitro for humans and rats indicate that *n*-heptane is distributed in the whole body, with the highest accumulation in the adipose tissue (Gargas et al., 1989; Perbellini et al., 1985). At steady-state exposure levels <35 ppm (146 mg/m^3), the body clearance half-lives for *n*-heptane are 0.17 ± 0.02 hours in rats and 1.88 ± 0.20 hours in humans. With repeated exposure at higher concentrations (≥100 ppm), accumulation of *n*-heptane was observed in the brain and perirenal fat of rats exposed for 1−2 weeks via inhalation. *n*-Heptane was no longer detectable following a 2-week recovery period (Savolainen and Pfäffli, 1980).

n-Heptane is metabolized via a number of oxidative steps, which are typical of *n*-alkane metabolism. At least three cytochrome P450 (CYP450) enzymes are responsible for the liver metabolism of heptane, as determined by in vitro studies. *n*-Heptane is initially metabolized to its parent alcohols, mainly 2- and 3-heptanol, and to a minor extent, 1- and 4-heptanol. *n*-Heptane can be further metabolized at relatively high rates via hydroxylation and dehydrogenation, leading to monohydroxy, dihydroxy, hydroxyketo, and diketo derivatives. Metabolic disposition studies in rats revealed that the most abundant metabolites recovered in urine following acute and prolonged inhalation exposures to *n*-heptane include 2- and 3-heptanol, γ-valerolactone, and 6-hydroxy-2-heptanone [see Tables 4−6;(Perbellini et al., 1986; Bahima et al., 1984)]. Biotransformation of 2-heptanol to 2,5-heptanedione, a metabolic product with apparent neurotoxic properties (Misumi and Nagano, 1984; Katz et al., 1980), has also been demonstrated; however, this metabolite is measured in small quantities in rats (<1% of the total concentration or mass of metabolites excreted; see Tables 4−6). 2,5-Heptanedione has been similarly detected in urine samples of factory workers exposed to technical heptane (*n*-heptane concentrations ranging from 5−196 mg/m^3) at lower concentrations (0.1−0.4 mg/L) relative to the primary metabolite, 2-heptanol (0.1−1.9 mg/L) (Perbellini et al., 1986). Correspondingly, Filser et al. (1996) reported that 2,5-heptanedione accounted for 0.01% of the total *n*-heptane metabolized in healthy volunteers exposed to *n*-heptane concentrations of up to 500 ppm. Heptanol metabolites are conjugated by glucuronates or sulfates prior to excretion in

the urine; thus, their detection in urine depends upon pretreatment of the urine by acid hydrolysis and/or glucuronidase.

Table 4. Metabolites Excreted over 24 Hours in Urine of Male S-D Rats Exposed by Inhalation to *n*-Heptane (CASRN 142-82-5) at 1,800 ppm for 6 Hours[a]

Metabolite	Mass Excreted, µg/24 hr[b]	Percent of Total
2-Heptanol	264	46.3%
3-Heptanol	201	35.2%
γ-Valerolactone	65.4	11.5%
2-Heptanone	20	3.5%
3-Heptanone	8.4	1.5%
4-Heptanone	7.3	1.2%
2,5-Heptanedione	4.4	0.8%

[a]Perbellini et al. (1986).
[b]Acid-hydrolyzed urine.

S-D = Sprague-Dawley.

Table 5. Metabolite Concentration in Urine of Female Wistar Rats Exposed by Inhalation to *n*-Heptane (CASRN 142-82-5) at 2,000 ppm for 6 Hours[a]

Metabolite	Concentration, µg/mL[b]	Percent of Total
6-Hydroxy-2-heptanone	63.2	30%
2-Heptanol	60.7	29%
3-Heptanol	46.1	22%
γ-Valerolactone	21.2	10%
2,6-Heptanediol	10.5	5%
5-Hydroxy-2-heptanone	9.4	4%
2,5-Heptanediol	1.3	0.1%

[a]Bahima et al. (1984).
[b]Urine pretreated with acid hydrolysis and β-glucuronidase.

Table 6. Metabolites Excreted in Urine of Female Wistar Rats Exposed by Inhalation to *n*-Heptane (CASRN 142-82-5) at 2,000 ppm for 6 Hours/Day, 5 Days/Week, for 12 Weeks[a]

Metabolite	Mean Daily Excretion, µg/rat[b]	Percent of Total Daily Mass Excreted
2-Heptanol	561.0	29.9%
6-Hydroxy-2-heptanone	433.6	23.1%
3-Heptanol	381.9	20.3%
γ-Valerolactone	190.9	10.2%
2,6-Heptanediol	141.9	7.6%
5-Hydroxy-2-heptanone	74.3	4.0%
1-Heptanol	29.0	1.5%
4-Heptanol	17.2	0.9%
2,5-Heptanediol	14.1	0.8%
6-Hydroxy-3-heptanone	13.6	0.7%
2-Heptanone	10.6	0.6%
2,6-Heptanedione	7.4	0.4%
2,5-Heptanedione	2.4	0.1%

[a]Bahima et al. (1984).
[b]Urine pretreated with acid hydrolysis and β-glucuronidase.

Mode-of-Action/Mechanistic Studies

CNS effects and irritation at the sites of contact could directly result from *n*-heptane due to its lipophilic properties [reviewed by MAK Commission (2012)]. Neurotoxicity could also result from the formation of the γ-diketone metabolite, 2,5-heptanedione. In particular, reactions with primary amino groups in neurofilamentary proteins to form pyrroles have been implicated in the mechanism of peripheral neuropathy of γ-diketone compounds [reviewed by MAK Commission (2012)]. However, in vivo studies suggest that 2,5-heptanedione is a minor metabolite of *n*-heptane (Filser et al., 1996; Perbellini et al., 1986; Bahima et al., 1984).

Limited information is available regarding biochemical changes that may underlie neurological changes observed following exposure to *n*-heptane. In a short-term-duration inhalation study, groups of male Wistar rats exposed to *n*-heptane vapor at concentrations of 100, 500, or 1,500 ppm 6 hours/day, 5 days/week for 2 weeks showed statistically significant increases in acid proteinase activity in the brain, compared with controls; however, increases were small and not concentration related (increased 15, 7, and 9% at 100, 500, and 1,500 ppm, respectively, compared with controls) (Savolainen and Pfäffli, 1980). Rats exposed to 1,500 ppm also showed a significant 6% decrease in brain glutathione content after 1−2 weeks of exposure, compared with control (Savolainen and Pfäffli, 1980). These biochemical changes were not accompanied by clinical signs of neurotoxicity (no other neurological endpoints were assessed). In vitro, *n*-heptane has been shown to increase the production of reactive oxygen species and reactive nitrogen species in cultured rat brain synaptosome fractions (Myhre and Fonnum, 2001).

DERIVATION OF PROVISIONAL VALUES

Tables 7 and 8 present summaries of noncancer and cancer references values, respectively.

Table 7. Summary of Noncancer Reference Values for *n*-Heptane (CASRN 142-82-5)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Mouse/M	Forestomach lesions	3×10^{-3}	$BMDL_{10}$	3.13 (based on surrogate POD)	1,000	Dodd et al. (2003) as cited in U.S. EPA (2009b)
Screening chronic p-RfD (mg/kg-d)	Mouse/M	Forestomach lesions	3×10^{-4}	$BMDL_{10}$	3.13 (based on surrogate POD)	10,000	Dodd et al. (2003) as cited in U.S. EPA (2009b)
Subchronic p-RfC (mg/m^3)	Rat/M	Loss of hearing sensitivity	4	$BMCL_{1SD}$ (HEC)	1,170	300	Simonsen and Lund (1995)
Chronic p-RfC (mg/m^3)	Rat/M	Loss of hearing sensitivity	4×10^{-1}	$BMCL_{1SD}$ (HEC)	1,170	3,000	Simonsen and Lund (1995)

$BMCL_{1SD}$ (HEC) = benchmark concentration lower confidence limit estimated at a default benchmark response of one standard deviation and reported in human equivalent concentration; $BMDL_{10}$ = benchmark dose lower confidence limit estimated at a default benchmark response of 10%; M = male(s); p-RfC = provisional reference concentration; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

Table 8. Summary of Cancer Reference Values for *n*-Heptane (CASRN 142-82-5)

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

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

DERIVATION OF ORAL REFERENCE DOSES

No information was located regarding effects of orally ingested *n*-heptane in humans. Animal studies were limited to a 3-week range-finding study and a 13-week subchronic-duration study (both from the same laboratory) that dosed male CD COBS rats via gavage. The range-finding study reported hyperplasia of the gastric nonglandular epithelium in rats at doses ≥714 mg/kg-day (Eastman Kodak, 1979). Elevations in serum LDH, a general marker of tissue or cellular damage, were also observed in exposed rats, but were not accompanied by changes in organ-specific serum markers (i.e., ALP, AST, and ALT). Additionally, increases in absolute and relative liver and kidney weights (>10%) occurred in

exposed rats but histopathological findings in these organs were unremarkable. Overall, the short-term duration, small group sizes (n = 3), and failure to report either statistical analyses or any measure of variability within groups, limits the use of this study for quantitative assessment.

Evidence for chemical-related effects on the nonglandular gastric mucosa were also found in the 13-week study, most prominently hyperkeratosis with pseudoepitheliomatous hyperplasia occurred in 7/8 rats exposed to a dose of 2,860 mg/kg-day (Eastman Kodak, 1980). Furthermore, effects were noted in the liver, kidney and adrenal glands of rats with subchronic *n*-heptane treatment. Statistically significant increases in relative liver (+17%), kidney (+16%), and adrenal gland (+36%) weights were reported in the three exposed rats surviving until sacrifice. No statistically or biologically relevant changes were observed in the absolute weights of these organs, although animals that died by gavage error exhibited grossly enlarged livers. Histopathological lesions in the liver, kidney, and adrenal glands of exposed rats were for the most part minimal or minor and only slightly elevated from controls. Although statistically significant decreases in absolute heart weight were found in treated animals, these changes are not supported by significant pathological findings and could be secondary to reductions in mean body weight (>10%). Mean body weights were significantly reduced in exposed rats compared to controls during the first week of treatment, which could be in part related to concomitant decreases in food consumption. However, body weights in treated animals did not appear to recover, remaining depressed (8−15%) throughout the study. Ultimately, the 13-week study is also considered unsuitable for deriving provisional toxicity values due to the inclusion of a single dose level along with high gavage-related mortality (5/8 rats) in the treated group (Eastman Kodak, 1980).

In summary, the short-term- and subchronic-duration rat studies provide support for the relevance of forestomach toxicity following gavage administration of *n*-heptane. Other potential treatment-related effects were found in the liver, kidney and adrenal glands, although the significance of such effects are not entirely understood due to the limitations in the available data. As a result of the uncertainties in the oral toxicity database for *n*-heptane, subchronic and chronic provisional reference doses (p-RfDs) were not derived. Instead, screening p-RfDs are derived in Appendix A using an established tiered surrogate approach (Wang et al., 2012). Please refer to Appendix A for further details on the derivation of screening oral values.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Information on the effects of *n*-heptane exposure via the inhalation route in humans is limited but provides support for potential nervous system effects. Male and female volunteers exposed to *n*-heptane vapor at concentrations ≥4,000 mg/m^3 (1,000 ppm) for up to 15 minutes reported vertigo and were observed to experience hilarity, incoordination, and inability to walk straight at a dose of 20,000 mg/m^3 (5,000 ppm) (Patty and Yant, 1929). However, the duration of this study is insufficient for consideration in the derivation of inhalation reference values. Occupational exposure to unknown concentrations of a solvent containing *n*-heptane (>95% purity) for 1−9 years produced minimal peripheral nerve damage in tire factory workers, evidenced by increased AD of the evoked MAP along the peroneal nerve and a correlation between length of exposure and decreased MNCV (Crespi et al., 1979). Residual amounts of other hydrocarbons were present in the solvent at very small quantities; therefore, it is unlikely that these impurities had a major impact in the observed neurophysiological effects. Ultimately, the lack of exposure estimates limits the use of this study for quantitative risk assessment.

Several animal studies have been performed to investigate potential neurotoxicity of inhaled *n*-heptane. Acute-duration studies have reported neurological effects at concentrations of *n*-heptane ≥2,740 ppm in rats and ≥4,740 ppm in mice (Gönczi et al., 2000; Frantík et al., 1994; Glowa, 1991). Similarly, a 28-day inhalation study identified possible neurotoxic effects of *n*-heptane based on a NOAEL (HEC) of 821 mg/m^3 (801 ppm) and a LOAEL (HEC) of 4,105 mg/m^3 (4,006 ppm) for abnormal auditory brainstem responses and increased auditory threshold in male Long-Evans rats 2 months after treatment, which indicate a loss of hearing sensitivity (Simonsen and Lund, 1995). Compounds that cause hearing damage by altering the brainstem or central auditory pathways are considered both ototoxic and neurotoxic, as it appears to be the case for *n*-heptane (Johnson and Morata, 2010). Longer-duration neurotoxicity studies in male rats found no effects at exposures up to HEC of 6,066 mg/m^3 (2,960 ppm) for 16−30 weeks; however, these studies focused primarily on the assessment of peripheral nerve damage (MNCV, mixed nerve conduction velocity, neurobehavioral parameters, and neurohistopathology); thus, measurements of central auditory function were not conducted (Frontali et al., 1981; Takeuchi et al., 1981; Bio Dynamics, 1980; Yeshiva University, 1980).

Chronic systemic toxicity was evaluated in a 26-week study in male and female S-D rats that reported no adverse effects on physical assessment, body weight, hematology, serum chemistry, and urinalysis related to inhalation of *n*-heptane at an HEC of up to 2,174 mg/m^3 (2,970 ppm) (Bio Dynamics, 1980). The study noted significant increases in serum ALP levels in females at the highest exposure group (2,970 ppm) after 26 weeks of treatment. The biological relevance of elevated ALP levels is uncertain given that the effect appeared minor (1.6-fold change from controls) and no corresponding changes occurred in male rats or at the intermediate time-point (Week 13) in females. Additionally, short-term- and subchronic-duration gavage studies reported no significant changes in ALP levels in rats exposed to doses that caused significant forestomach toxicity (2,860 mg/kg-day) (Eastman Kodak, 1980, 1979). A comprehensive neurohistological evaluation of central and peripheral tissues was also conducted under the current study and results were summarized by Yeshiva University (1980). Neurological lesions presumed to be associated with advancing age rather than treatment were observed in control and exposed rats, most notably an increased incidence of myelin bubbles in the dorsal roots of treated animals. However, histological data were not provided for independent review, precluding the determination of the significance of these neurological observations. Overall, the study is considered of limited use for deriving provisional toxicity values as it failed to provide incidence data for the neurohistological findings and to include organ-weight measurements and pathology of non-nervous system tissues.

Altogether, human and animal data indicate that the nervous system is a critical target organ of toxicity for continuous exposure to *n*-heptane via inhalation. Although subchronic- and chronic-duration inhalation studies in rats suggest that *n*-heptane does not induce peripheral nerve damage up to HEC of 6,066 mg/m^3, the central auditory deficits in male rats exposed for 28 days at an HEC of 4,105 mg/m^3 demonstrate potential neurotoxic responses for *n*-heptane. Systemic toxicity has not been rigorously tested in animals following inhalation exposure to *n*-heptane, but a 26-week study in rats showed no adverse effects on limited systemic endpoints, including physical assessment, body weight, hematology, serum chemistry, and urinalysis at an HEC of up to 2,174 mg/m^3. Evidence of neurological effects in experimental animals from acute inhalation studies (Gönczi et al., 2000; Frantik et al., 1994;

Glowa, 1991) and in tire factory workers with long-term exposure (Crespi et al., 1979) provide further support for the neurotoxicity of *n*-heptane.

Derivation of a Subchronic Provisional Reference Concentration (p-RfC)

The Simonsen and Lund (1995) study is selected as a principal study for the derivation of the subchronic p-RfC. Although the study is of short-term duration (28 days), it is adequate in design and in assessing the dose-response relationship of central auditory function in rats exposed to *n*-heptane via inhalation. It identified both a NOAEL (HEC) of 821 mg/m^3 (801 ppm) and a LOAEL (HEC) of 4,105 mg/m^3 (4,006 ppm) based on evidence for loss hearing sensitivity, a relevant endpoint of toxicity for organic solvents. *n*-Hexane, an aliphatic solvent and structural analog of *n*-heptane, caused abnormalities in the auditory brainstem response in rats at similar inhalation concentrations (4,000 ppm, 14 hours/day, 7 days/week for 9 weeks) as those reported with *n*-heptane treatment (Pryor and Rebert, 1992). The effects of *n*-hexane and *n*-heptane on the auditory system are primarily attributed to their neurotoxic potential (Johnson and Morata, 2010), although *n*-hexane appears to be a more potent neurotoxicant (see Appendix A for further details).

Benchmark dose (BMD) analyses were performed to model central auditory effects in rats exposed to *n*-heptane in the Simonsen and Lund (1995) study. The reduction in peak amplitude of auditory brainstem responses reflected a similar increase (8−10 dB) in the auditory threshold across frequencies 4−32 kHz. As a result, continuous data for auditory threshold at all frequencies tested were considered for BMD modeling, although statistical significance was only achieved at 8 and 16 kHz (see Table B-5). Appendix C provides details on the BMD modeling procedures and results for the selected data. The data sets at frequencies 4 and 8 kHz were unsuitable for BMD analyses (see Table C-2). The estimated benchmark concentration lower confidence limits (BMCLs) for the remaining endpoints were very similar (1,170 and 1,440 mg/m^3 at frequencies 16 and 32 kHz, respectively). Thus, the lowest **$BMCL_{1SD}$ (HEC) of 1,170 mg/m^3 identified for loss of hearing sensitivity in rats from the 28-day inhalation study is selected as a point of departure (POD) for the derivation of the subchronic p-RfC.**

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL_{1SD}\ (HEC) \div UF_C \\ &= 1{,}170\ mg/m^3 \div 300 \\ &= \textbf{4 mg/m}^3 \end{aligned}$$

The composite uncertainty (UF_C) for the subchronic p-RfC for *n*-heptane is 300, as summarized in Table 9.

Table 9. Uncertainty Factors for the Subchronic p-RfC for *n*-Heptane (CASRN 142-82-5)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for remaining uncertainty (e.g., the toxicodynamic differences between rats and humans) following inhaled *n*-heptane exposure. The toxicokinetic uncertainty has been accounted for by calculation of an HEC as previously described (U.S. EPA, 1994a).
UF_H	10	A UF_H of 10 is applied to account for intraspecies variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *n*-heptane in humans.
UF_D	10	UF_D of 10 is applied in the absence of acceptable studies that inform of potential systemic, developmental, and multi-generational reproductive effects that may potentially be more sensitive than the central auditory effects identified in the 28-d rat study. Although systemic toxicity has not been rigorously studied in animals exposed by inhalation (lack of organ-weight measurements and histopathology of non-nervous system tissues), information available from a 26-wk study in rats suggest a lack of significant effect on (limited) systemic endpoints (e.g., physical assessment, body weight, hematology, serum chemistry, and urinalysis).
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMCL.
UF_S	1	A UFs for subchronic-to-chronic extrapolation is not relevant for the derivation of the subchronic RfC; thus, a 1 is applied.
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMCL = 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; UF = uncertainty factor.

The confidence in the subchronic p-RfC for *n*-heptane is low as explained in Table 10.

Table 10. Confidence Descriptors for the Subchronic p-RfC for *n*-Heptane (CASRN 142-82-5)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study (Simonsen and Lund, 1995) is medium. The study is peer-reviewed and its methodology was adequate for the examination of central auditory effects in rats. Furthermore, the study identified both a NOAEL and LOAEL on the basis of abnormal auditory brainstem responses, a relevant endpoint of toxicity for solvents. However, confidence is reduced because it is a short-term-duration study (28 d), only male rats were tested, and limited endpoints were analyzed.
Confidence in database	L	There are no acceptable developmental or multi-generational reproductive studies. Systemic toxicity via the inhalation route was examined in only one chronic-duration study that lacked organ-weight measurements and histopathology of a comprehensive set of tissues.
Confidence in subchronic p-RfC[a]	L	The overall confidence in the subchronic p-RfC is low.

[a]The overall confidence cannot be greater than the lowest entry in the table (low).

L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration.

Derivation of a Chronic Provisional Reference Concentration (p-RfC)

As previously discussed, two chronic-duration studies in rats are available in the database for inhalation of *n*-heptane. One is a neurotoxicity study that examined only a few endpoints related to peripheral neuropathy (hind limb spread on landing and tibial nerve histology) and identified a NOAEL (HEC) of 1,647 mg/m^3 (1,500 ppm) for the absence of effects in male S-D rats exposed for up to 30 weeks (Frontali et al., 1981). Similarly, another study in male and female S-D rats reported no adverse effects on a limited number of systemic endpoints at an HEC of 2,174 mg/m^3 (2,970 ppm) (Bio Dynamics, 1980); however, the study is considered inadequate because it lacked complete data reporting for neurohistology results, while also excluding organ-weight measurements and pathology of non-nervous system tissues. Due to the failure to identify any critical effects that are more sensitive than the loss of hearing sensitivity reported in male rats with short-term exposure to *n*-heptane (Simonsen and Lund, 1995), the two aforementioned studies are not considered appropriate for the derivation of the chronic p-RfC. Although the Simonsen and Lund (1995) study is only 28 days, it reported the lowest NOAEL (HEC) of 821 mg/m^3 (801 ppm) in the inhalation database for *n*-heptane. These findings are consistent with studies from acute exposure in rodents (Gönczi et al., 2000; Frantik et al., 1994; Glowa, 1991) and long-term occupational exposure in humans that suggest the nervous system is a target organ of *n*-heptane toxicity (Crespi et al., 1979). Thus, **the $BMCL_{1SD}$ (HEC) of 1,170 mg/m^3 previously identified for loss of hearing sensitivity in rats is selected as a POD for the derivation of the chronic p-RfC.**

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{1SD}\,(HEC) \div UF_C \\ &= 1{,}170\ mg/m^3 \div 3{,}000 \\ &= \mathbf{4 \times 10^{-1}\ mg/m^3} \end{aligned}$$

Table 11 summarizes the UF_C for the chronic p-RfC for *n*-heptane.

Table 11. Uncertainty Factors for the Chronic p-RfC for *n*-Heptane (CASRN 142-82-5)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for remaining uncertainty (e.g., the toxicodynamic differences between rats and humans) following inhaled *n*-heptane exposure. The toxicokinetic uncertainty has been accounted for by calculation of an HEC as previously described (U.S. EPA, 1994a).
UF_H	10	A UF_H of 10 is applied to account for intraspecies variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *n*-heptane in humans.
UF_D	10	UF_D of 10 is applied in the absence of acceptable studies that inform of potential systemic, developmental, and multi-generational reproductive effects that may potentially be more sensitive than the central auditory effects identified in the 28-day rat study. Although systemic toxicity has not been rigorously studied in animals exposed by inhalation (lack of organ-weight measurements and histopathology of non-nervous system tissues), information available from a 26-week study in rats suggest a lack of significant effect on (limited) systemic endpoints (e.g., physical assessment, body weight, hematology, serum chemistry, and urinalysis).
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMCL.
UF_S	10	A UF_S of 10 is applied to account for the chronic extrapolation from a 28-day study used in the derivation of the chronic p-RfC.
UF_C	3,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMCL = 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; UF = uncertainty factor.

The confidence in the chronic p-RfC for n-heptane is low as explained in Table 12.

Table 12. Confidence Descriptors for the Chronic p-RfC for *n*-Heptane (CASRN 142-82-5)

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study (Simonsen and Lund, 1995) is medium. The study is peer-reviewed and its methodology was adequate for the examination of central auditory effects in rats. Furthermore, the study identified both a NOAEL and LOAEL on the basis of abnormal auditory brainstem responses, a relevant endpoint of toxicity for solvents. However, confidence is reduced because it is a short-term-duration study (28 d), only male rats were tested, and limited endpoints were analyzed.
Confidence in database	L	There are no acceptable developmental or multi-generational reproductive studies and systemic toxicity via the inhalation route was examined in a single chronic-duration study that lacked organ-weight measurements and histopathology of a comprehensive set of tissues.
Confidence in subchronic p-RfC[a]	L	The overall confidence in the subchronic p-RfC is low.

[a]The overall confidence cannot be greater than the lowest entry in the table (low).

L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 13 identifies the cancer weight-of-evidence (WOE) descriptor for n-heptane.

Table 13. Cancer WOE Descriptor for *n*-Heptane (CASRN 142-82-5)			
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 adequate information for an assessment of human carcinogenic potential. No data in humans are available to assess carcinogenicity of *n*-heptane. The only chronic-duration study in experimental animals that evaluated systemic toxicity after inhalation exposure to *n*-heptane failed to report pathological findings from non-nervous system tissues (Bio Dynamics, 1980; Yeshiva University, 1980). Limited data indicate that this chemical is not genotoxic (Brooks et al., 1988).**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of quantitative estimates of cancer risk for *n*-heptane is precluded by the absence of carcinogenicity data for *n*-heptane.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main provisional peer-reviewed toxicity value (PPRTV) document, the database for continuous exposure to *n*-heptane is inappropriate for the derivation of provisional oral toxicity values. 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. In this particular case, the search for surrogate chemicals was limited to oral noncancer effects based on the available toxicity data. 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 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 the U.S. EPA's DSSTox database and the National Library of Medicine's (NLM's) ChemIDplus database at a similarity level ≥60%. Two structural analogs to *n*-heptane were identified that have oral toxicity values: *n*-hexane (U.S. EPA, 2009a, 2008) and *n*-nonane (U.S. EPA, 2009b). Table A-1 summarizes their physicochemical properties and similarity scores. *n*-Heptane and the identified analogs are straight-chain alkanes that share comparable physicochemical properties. In addition, the ChemIDplus and DSSTox similarity scores for the analogs were relatively high (≥83% for ChemIDplus and ≥86% for DSSTox). Thus, the two compounds are considered to be appropriate structural surrogate candidates for *n*-heptane.

Table A-1. Physicochemical Properties of *n*-Heptane (CASRN 142-82-5) and Structural Analogs[a]

Chemical	***n*-Heptane**	***n*-Hexane**	***n*-Nonane**
Structure			
CASRN	142-82-5	110-54-3	111-84-2
Molecular weight	100.21	86.18	128.26
DSSTox similarity score (%)[b]	100	85.7	87.5
ChemIDplus similarity score (%)[c]	100	82.7	84.6
Melting point (°C)	−90.6	−95.3	−53.5
Boiling point (°C)	98.5	68.7	150.8
Vapor pressure (mm Hg at 25°C)	46	151.3	4.45
Henry's law constant (atm-m^3/mole at 25°C)	2.27 (estimated)[a]	1.71 (estimated)[a]	4 (estimated)[a]
Water solubility (mg/L)	3.4	9.5	0.22
Log K_{ow}	4.66	3.9	5.65
pKa	NA	NA	NA

[a]Data was gathered from PHYSPROP database for each respective compound unless otherwise specified (U.S. EPA, 2012b).
[b]DSSTox (2015).
[c]ChemIDplus Advanced, similarity scores (ChemIDplus, 2016).

NA = not applicable.

Metabolic Surrogates

The primary route of exposure for *n*-heptane and structurally related alkanes in humans occurs via inhalation; thus, toxicokinetics data following oral administration of these compounds is largely unavailable. Pulmonary retention in humans is similar for *n*-heptane and *n*-hexane, 25 and 22−24%, respectively, indicating that these compounds are well-absorbed by inhalation (EC, 1996; Veulemans et al., 1982). Absorption of *n*-hexane and *n*-nonane via the oral route can be inferred from the recovery of primary metabolic products of the parent chemicals in urine (Baelum et al., 1998; Serve et al., 1995; Krasavage et al., 1980). Information regarding the distribution of orally ingested *n*-heptane and its two structural analogs is currently lacking; however, inhalation exposure to rats revealed that these compounds are widely distributed throughout the body, with a tendency to concentrate in nervous system and adipose tissues. Indeed, linear relationships between exposure levels and solvent concentrations in the brain and perirenal fat were found in rats after inhalation of *n*-heptane (100−1,500 ppm, 12 hours/day) for 1 week, and during the second week of treatment, accumulation was noted in the brain (Savolainen and Pfäffli, 1980). High concentrations of *n*-hexane were detected in the sciatic nerve of rats relative to blood, liver, and kidney following a single or repeated exposure to this alkane (1,000 ppm, 6 hours/day) (Bus et al., 1981). Similarly, *n*-nonane concentrations in the brain exceeded those of blood, and accumulation was observed in adipose tissue following continuous exposure in rats (100 ppm, 12 hours/day for up to 3 days) (Zahlsen et al., 1992).

In general, metabolism pathways are similar for *n*-heptane, *n*-hexane, and *n*-nonane, although routes of exposure from available rat disposition studies differ among chemicals (see Table A-2 in Appendix A and Tables 4, 5, and 6 under the "Absorption, Distribution, Metabolism, and Excretion [ADME] Studies" section in the main document). Each compound undergoes hydroxylation to one or more alcohols (1-, 2-, 3-, or 4-heptanol for *n*-heptane; 1-, 2-, or 3-hexanol for *n*-hexane; and 2-, 3-, or 4-nonanol for *n*-nonane). The alcohols are then subjected to further hydroxylation and/or dehydrogenation, leading to monohydroxy, dihydroxy, hydroxyketo, and diketo derivatives.

Of particular importance with respect to the metabolism of these compounds is the degree to which each forms a γ-diketone metabolite. Studies with *n*-hexane, the most well-studied compound of the group, have shown that 2,5-hexanedione, a principal metabolite of *n*-hexane (see Table A-2), is the compound primarily responsible for the axonopathy and peripheral neuropathy that is characteristic of *n*-hexane exposure, and represents the critical effect of both the inhalation and oral routes (U.S. EPA, 2009a, 2008). Metabolism of *n*-hexane after inhalation in rats yields relatively high quantities of the γ-diketone metabolite (2,5-hexanedione) (33%; see Table A-2) and a number of studies have confirmed formation of urinary 2,5-hexanedione in humans with oral and inhalation exposure to *n*-hexane (Prieto et al., 2003; dos Santos et al., 2002; Mayan et al., 2002; Baelum et al., 1998). In contrast, studies in rats suggest that, while metabolism of inhaled *n*-heptane may yield a γ-diketone metabolite (2,5-heptanedione), the quantity of this metabolite formed in vivo is low (<1%; see Table A-2 in Appendix A and Tables 4, 5, and 6 under the "Absorption, Distribution, Metabolism, and Excretion [ADME] Studies" section in the main document). Moreover, Filser et al. (1996) showed that excretion of the corresponding γ-diketone metabolites in urine was seven times lower in rats and four times lower in humans after inhalation exposure to *n*-heptane (500 ppm) in comparison to *n*-hexane (50 ppm). No disposition studies that can inform on the metabolism and elimination of *n*-heptane following oral ingestion have been found.

Available data on urinary metabolites of *n*-nonane are limited to an oral exposure study. Serve et al. (1995) reported the relative abundance of metabolites from the urine of rats given *n*-nonane by gavage; 2,5-hexanedione, the only γ-diketone metabolite detected, was present at the smallest relative abundance of 1.0 (see Table A-2).

Table A-2. Summary of Metabolites for *n*-Heptane (CASRN 142-82-5) and Structural Analogs

Chemical	Route	Species	Metabolites in Urine	References
n-Heptane	Inhalation (1,800 ppm for 6 h)	Rat/M	2-heptanol (46.3), 3-heptanol (35.2), γ-valerolactone (11.5), 2-heptanone (3.5), 3-heptanone (1.5), and 4-heptanone (1.2), 2,5-heptanedione (0.8) over 24 h[a]	Perbellini et al. (1986)
n-Hexane	Inhalation (1,000 ppm for 8 h)	Rat/M	2-hexanol (57), 2,5-hexanedione (33), 3-hexanol (6), and 1-hexanol (3), 2-hexanone (1) over 24 h[a]	Fedtke and Bolt (1986)
n-Nonane	Oral (800 mg/kg-d)	Rat/M	γ-valerolactone (38.6), 2-nonanol (17.9), 3-nonanol (10.7), 4-nonanone (6.8), δ-heptanolactone (6.5), 1-heptanol (5.7), 4-nonanol (3.5), 5-methyl-2-(3-oxobutyl) furan (3.2), δ-hexanolactone (2.8), 2,5-hexanedione (1) over 48 h[b]	Serve et al. (1995)

[a]Percentage of total metabolites in urine.
[b]Relative abundance of metabolites in urine.

M = male(s).

In summary, the pattern of metabolic disposition in rats for *n*-nonane is similar to *n*-heptane with high relative amounts of the 2- and 3-alcohols and γ-valerolactone metabolites and low production of the γ-diketone compound (see Table A-2), although routes of exposure from available studies are different. In contrast to *n*-heptane, metabolism of *n*-hexane appears to favor the formation of the neurotoxic γ-diketone metabolite by inhalation exposure [see Table A-2 and Filser et al. (1996)]. *n*-Nonane is, therefore, considered to be the most appropriate metabolic surrogate for *n*-heptane.

Toxicity-Like Surrogates

Table A-3 summarizes available oral toxicity data for *n*-heptane and the structural analogs identified. Consistent findings of chemical-related irritative and hyperplastic effects in the nonglandular gastric mucosa of rats were observed after gavage *n*-heptane treatment for 3 or 13 weeks, providing evidence of forestomach toxicity following oral exposure to this chemical (Eastman Kodak, 1980, 1979). These studies also found potential effects in the liver, kidney, and adrenal glands with *n*-heptane treatment. Therefore, information from structurally related analogs of *n*-heptane was analyzed, anticipating similar toxicities in rodent studies.

Table A-3. Comparison of Available Repeated-Dose Oral Toxicity Data for *n*-Heptane (CASRN 142-82-5) and Structural Analogs

Chemical	***n*-Heptane**	***n*-Hexane**	***n*-Nonane**
Structure			
CASRN	142-82-5	110-54-3	111-84-2
Repeat-dose toxicity—oral, subchronic			
POD (mg/kg-d)	NA	785	3.13
POD type	NA	LOAEL	$BMDL_{10}$
Subchronic UF_C	NA	3,000	1,000
Subchronic p-RfD (mg/kg-d)	NA	3×10^{-1}	3×10^{-3}
Critical effects	Irritative and proliferative forestomach lesions and potential effects in the liver, kidney, and adrenal glands at a dose of 2,860 mg/kg-d. Lack of neurotoxicity at doses up to 2,860 mg/kg-d based on histological evaluation (13-wk rat study).	Decreased MNCV associated with peripheral neuropathy	Proliferative forestomach lesions with varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium
Other effects		Hind-limb paralysis accompanied by evidence of peripheral neuropathy and testicular effects based on histopathology at a dose of 2,843 mg/kg-d (90-d rat study)	Additional effects in principal study: histopathological lesions in the duodenum (rats) and rectum (rats and mice) at doses ≥1,000 mg/kg-d; nasal and pulmonary lesions, possibly due to aspiration (rats and mice). Increases in liver and lung weights at a dose of 5,000 mg/kg-d and dose-related increases in adrenal gland and ovary weights at doses ≥1,000 mg/kg-d. No significant neurohistopathology or neurobehavioral abnormalities reported in rats or mice at doses up to 5,000 mg/kg-d
Species	NA	Rat (M)	Mouse (M) and Rat (F)
Duration	NA	8 wk	90 d
Route (method)	NA	Oral (gavage)	Oral (gavage)

Table A-3. Comparison of Available Repeated-Dose Oral Toxicity Data for *n*-Heptane (CASRN 142-82-5) and Structural Analogs

Chemical	*n*-Heptane	*n*-Hexane	*n*-Nonane
Notes	NA	Available oral studies did not examine histology of the gastrointestinal tract or a comprehensive battery of systemic endpoints.	Quantitation is based on male mice, but the same types of lesions were observed in female rats.
Source	U.S. EPA (2016b)	U.S. EPA (2009a)	U.S. EPA (2009b)
Repeat-dose toxicity—oral, chronic			
POD (mg/kg-d)	NA	NA	3.13
POD type	NA	NA	$BMDL_{10}$
Chronic UF_C	NA	NA	10,000
Chronic p-RfD (mg/kg-d)	NA	NA	3×10^{-4} (screening)
Critical effects	NA	NA	Proliferative forestomach lesions with varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium
Other effects	NA	NA	NA
Species	NA	NA	Mouse (M)
Duration	NA	NA	90 d
Route	NA	NA	Oral (gavage)
Notes	NA	NA	No oral chronic-duration studies are available.
Source	U.S. EPA (2016b)	U.S. EPA (2009a)	U.S. EPA (2009b)

BMDL = benchmark dose lower confidence limit (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MNCV = motor nerve conduction velocity; NA = not applicable; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

The critical effect for *n*-hexane following oral exposure is peripheral neuropathy (measured as decreased motor nerve conduction velocity [MNCV]), identified in rats gavaged with 785 mg/kg-day for 8 weeks and presumably related to the formation of the toxic metabolite, 2,5-hexanedione (U.S. EPA, 2009a, 2008). At higher doses (2,843 mg/kg-day), *n*-hexane induced testicular toxicity concomitantly with peripheral neuropathy in a 90-day rat study. The available database for oral exposure to *n*-hexane is limited to the evaluation of putative neurotoxic and testicular effects; information on the gastrointestinal tract or other major systemic organs is lacking. On the other hand, no evidence of neurotoxicity was found in rats with short-term or subchronic oral exposure to *n*-heptane at doses up to 2,860 mg/kg-day, based on histological evaluation of central and peripheral nervous system tissues (Eastman Kodak, 1980, 1979). Comparative inhalation studies in rats exposed to *n*-heptane or *n*-hexane for 16 weeks (3,000 ppm, 12 hours/day, 7 days/week) revealed a decrease in MNCV and morphological impairments in the peripheral nerves, muscle, and neuromuscular junction for *n*-hexane only (Takeuchi et al., 1981, 1980), suggesting that *n*-hexane is a more potent neurotoxicant than *n*-heptane via the inhalation route. These findings are in agreement with toxicokinetic data that demonstrate an enhanced formation of the neurotoxic γ-diketone metabolite from the metabolism of *n*-hexane in rats and humans compared to that of *n*-heptane (Filser et al., 1996). Altogether, *n*-hexane is not considered to be an appropriate toxicity-like surrogate for *n*-heptane via the oral route based on apparent differences in target organs and the absence of comprehensive data on potential gastrointestinal effects.

Gastric lesions were observed in a 90-day gavage study of *n*-nonane (neat) in rats and mice (U.S. EPA, 2009b) that were similar to the histopathological findings in the forestomach of rats exposed to 2,860 mg/kg-day of *n*-heptane for 13 weeks (Eastman Kodak, 1980, 1979). Specifically, hyperplasia and hyperkeratosis of the forestomach epithelium with occasional erosion or ulceration of the mucosa occurred with *n*-nonane at doses ≥100 mg/kg-day in the two species, although only female rats and male mice were tested based on concerns of possible alpha 2u-globulin (α2u-g) nephropathy in male rats. Higher *n*-nonane doses produced mild inflammation of the proximal duodenum in rats only (5,000-mg/kg-day treatment group) and perianal hyperplasia, hyperkeratosis, and inflammation of the rectum in both rats and mice (1,000- and 5,000-mg/kg-day treatment groups). Irritative nasal lesions in exposed animals were consistent with evidence of aspiration of *n*-nonane into the rat lung and do not appear to be chemical-specific effects targeting the nasal mucosa. Statistically significant increases in liver weights were reported in rats and mice at a dose of 5,000 mg/kg-day. Other significant organ-weight effects occurring only in rats included increased lung weights at a dose of 5,000 mg/kg-day and dose-related changes in adrenal gland weights (increased) and ovary (decreased) weights at doses ≥1,000 mg/kg-day. No treatment-related histopathological changes were noted in these organs. Examinations of neurobehavioral activity and histology of central and peripheral nervous system tissues were unremarkable, except for a pattern of reduced locomotor activity in mice and rats with no clear dose-response relationship. In summary, the gastrointestinal tract, in particular the nonglandular epithelium, appears to be a critical target organ in rodents for both *n*-heptane and *n*-nonane via the oral route.

Despite the lack of evidence for significant neurotoxicity from gavage treatment with *n*-nonane or *n*-heptane, these chemicals appear to target the central nervous system (CNS) by inhalation exposure. Acute inhalation studies reported neurological effects at *n*-heptane concentrations ≥2,740 ppm in rats and ≥4,740 ppm in mice (Gönczi et al., 2000; Frantík et al., 1994; Glowa, 1991). Similarly, *n*-nonane induced neurobehavioral changes in rats exposed to

concentrations ≥3,580 ppm for 8 hours and severe histopathological damage was observed in cerebellar neurons after a 14-day observation period at an exposure of 4,438 ppm (Nilsen et al., 1988). In a 28-day study, abnormal auditory brainstem responses were identified in rats treated with *n*-heptane at concentrations of 4,006 ppm (Simonsen and Lund, 1995) and used as critical effects in the derivation of inhalation toxicity values for *n*-heptane (see the "Derivation of Inhalation Reference Concentrations" section). Although repeat-exposure studies that adequately address the neurotoxic potential of inhaled *n*-nonane are currently unavailable, Carpenter et al. (1978) noted behavioral symptoms (mild coordination loss and fine tremors) in rats during the first 4 days of *n*-nonane treatment. These symptoms were accompanied by clinical signs of toxicity (salivation and lacrimation) and marginally depressed body weights (−7%) that persisted throughout the 13-week study at an inhalation exposure of 1,600 ppm (U.S. EPA, 2009b).

Due to the aforementioned similarities in the toxicity profile of *n*-heptane and *n*-nonane, primarily the induction of gastrointestinal effects following gavage treatment in experimental animals, *n*-nonane is identified as a toxicity-like surrogate for *n*-heptane by the oral route.

Weight-of-Evidence Approach

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

Overall, *n*-nonane was selected as an appropriate surrogate chemical for *n*-heptane oral toxicity based on the following WOE:

1) The critical effect identified for *n*-nonane is "proliferative forestomach lesions with varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium (U.S. EPA, 2009b)." This effect is similar to the gastrointestinal lesions observed after gavage *n*-heptane treatment.
2) *n*-Nonane is metabolized in vivo similarly to *n*-heptane, resulting in the formation of higher relative amounts of the 2- and 3-alcohol and γ-valerolactone metabolites compared to the neurotoxic γ-diketone compounds.
3) *n*-Nonane displays a high structural similarity of 84.6 and 87.5% to *n*-heptane, using the National Library of Medicine's (NLM's) ChemIDplus database (ChemIDplus, 2016) and the EPA DSSTox database, respectively.

4) *n*-Hexane, the other structural analog, is not considered to be a metabolic or a toxicity-like surrogate for *n*-heptane. The principal metabolite of *n*-hexane is the γ-diketone derivative, 2,5-hexanedione, which is primarily responsible for the axonopathy and peripheral neuropathy (measured as decreased MNCV) observed with oral and inhalation exposure to *n*-hexane. The quantity of 2,5-heptanedione formed from *n*-heptane metabolism is very low (<1%), and decreased MNCV has been reported for inhalation exposure to *n*-hexane, but not *n*-heptane.
5) A lack of significant adverse effects on neurological endpoints were reported from gavage studies in rodents at exposures up to 2,860 mg/kg-day for *n*-heptane and up to 5,000 mg/kg-day for *n*-nonane, although findings from acute and short-term-duration studies indicate that these alkanes are capable of targeting the CNS via the inhalation route.

ORAL TOXICITY VALUES

Derivation of a Screening Subchronic Provisional Reference Dose (p-RfD)

Based on the overall surrogate approach presented in this PPRTV assessment, *n*-nonane is selected as an acceptable surrogate for *n*-heptane for the derivation of oral toxicity values. The study used for the p-RfD for *n*-nonane is a 13-week gavage study in male C57BL/6 mice and female Fischer 344 rats [Dodd et al. (2003) as cited in U.S. EPA (2009b)]. A summary of the study design and main histopathological findings described in the PPRTV report for *n*-nonane are provided below [for further details refer to U.S. EPA (2009b)]:

> *Dodd et al. (2003) treated groups of 10 male C57BL/6 mice and 10 female Fischer 344 rats with doses (neat) of 0, 100, 1000, or 5000 mg/kg-day of n-nonane (99% purity) by gavage 7 days/week for 90 days. The test protocol required two rodent species and both male and female animals. Because of a concern for the development of α-2u-globulin nephropathy in male rats, only female rats were dosed. The study authors dosed only male mice. The dosages were established based on a 7-day range-finding study conducted by the same researchers, which are discussed in further detail below. Dodd et al. (2003) randomly assigned mice and rats to dose groups (10/group). Due to unexpected mortality in the high-dose rats during the first 4 days of dosing, two additional rats were assigned to this group. Animals were allowed free access to food and water and were housed individually in plastic cages. Body weights were determined and recorded immediately prior to the initiation of the study. Body weights and food consumption were determined and recorded weekly thereafter. Animals were fasted at least 12 hours prior to sacrifice following the 90-day exposure period.*
>
> *Effects on general toxicity, neurobehavioral activity (grip strength and locomotor activity), hematology (hematocrit [HCT], hemoglobin [HGB] concentration, erythrocyte count [RBC], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], total and differential leukocyte count [WBC], and platelet count), clinical chemistry (calcium, phosphorus, chloride, sodium, potassium, glucose, alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transpeptidase, alkaline phosphatase [ALP], blood urea nitrogen*

[BUN], albumin, globulin, total protein, creatinine, and total bilirubin), and organ weights (liver, kidneys, adrenals, gonads, spleen, lungs, and brain) were evaluated in all animals (Dodd et al., 2003). In addition, a few additional serum chemistry measurements of cholesterol, triglycerides, and magnesium were made only in rats. Gross necropsy, including examination of the external surface of the body, all the orifices, and the cranial, thoracic, and the abdominal cavities and their contents, were conducted on each animal. Histopathologic examination of 32 tissues and organs, including any gross lesions identified at necropsy, were conducted on all control and high-dose animals and on "target" tissues from low- and mid-dose animals.

(...)

Table 5 summarizes the tissue lesion incidence reported by Dodd et al. (2003) in exposed animals. Lesions occurred primarily along the alimentary tract. Varying degrees of hyperplasia and hyperkeratosis of the squamous epithelium were found in the nonglandular stomach (forestomach) of mice and rats from all dose groups. Occasionally, erosion and ulceration of the mucosa were also present. No lesions were observed in the glandular stomach of any treated animal. Other lesions observed were mild inflammation in the proximal duodenum mucosa (high-dose rats), perianal hyperplasia accompanied by hyperkeratosis often with mild inflammation (mid- and high-dose mice and rats), and multifocal minimal-to-mild necrosis and suppurative inflammation of the nasal turbinates (high-dose mice; low-, mid-, and high-dose rats). In rats, the nasal lesions were often accompanied by pulmonary lesions (incidence not reported) consistent with aspiration of foreign material, ranging from peribronchial histiocytic infiltrates to necrohemorrhagic bronchopneumonia. Based on the pathology of these lesions and the pulmonary foreign body response observed in rats, Dodd et al. (2003) suggest that the lesions in the nasal turbinates resulted from direct contact with the gavaged test agent—rather than from specific xenobiotic targeting of nasal mucosa. Based on the lesions observed in the forestomachs of both rats and mice at all dose levels, the lowest dose tested of 100 mg/kg-day is identified as a LOAEL for the purposes of this review. A NOAEL is not identified in this study.

Table 5. Incidence of Tissue Lesions[a]

Lesion	Dose (mg/kg-day)							
	0		100		1000		5000	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Stomach (nonglandular)—squamous epithelial hyperplasia/hyperkeratosis	0/9	0/10	6/10	8/10	7/8	10/10	8/8	10/11
Proximal Duodenum—inflammation (mild)	0/7	0/10	0/10	0/10	0/10	0/10	0/10	2/10
Rectum—perianal hyperplasia, hyperkeratosis and inflammation	0/9	0/10	0/10	0/10	2/10	5/10	8/10	9/11
Nasal Turbinates—rhinitis	0/9	0/10	0/10	1/9	0/10	7/10	4/10	9/10

[a]*Dodd et al., 2003; C57BL/6 mice; Fischer 344 rats*

The critical effect for the derivation of oral reference values for *n*-nonane identified in the Dodd et al. (2003) study is forestomach lesions, including squamous epithelial hyperplasia and hyperkeratosis. Proliferative lesions in the forestomach mucosa, occasionally accompanied by suppuration and necrosis were also detected following gavage *n*-heptane treatment (Eastman Kodak, 1980). These portal-of-entry effects are reflective of the strong irritating properties of *n*-heptane and *n*-nonane and provide support for the relevance of gastrointestinal toxicity after oral exposure to these alkanes. Similar to *n*-heptane, effects were found in the liver and adrenal glands with exposure to *n*-nonane, but at doses 10−50 times higher than those inducing forestomach toxicity. U.S. EPA (2009b) performed BMD analyses of forestomach incidence data from animals treated with *n*-nonane. A 10% benchmark dose lower confidence limit ($BMDL_{10}$) of 3.13 mg/kg-day derived from male mice was identified as the most sensitive endpoint and the point of departure (POD) for *n*-nonane (U.S. EPA, 2009b); this value is adopted as the POD for the screening subchronic provisional reference dose (p-RfD) for *n*-heptane.

The *n*-nonane $BMDL_{10}$ of 3.13 mg/kg-day was not adjusted for molecular-weight differences in the derivation of the *n*-heptane provisional toxicity value because the molecular-weight difference between *n*-heptane and *n*-nonane is less than twofold (Wang et al., 2012). EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure. For oral portal-of-entry effects occurring in laboratory animal studies in which the agent is administered via food, direct application of the $BW^{3/4}$ approach is recommended (U.S. EPA, 2011b). The forestomach lesions induced by *n*-nonane or *n*-heptane treatment represent portal-of-entry effects likely resulting from direct contact between the chemical agents and the nonglandular gastric mucosa; however, the use of the $BW^{3/4}$ scaling for dose extrapolation is precluded because the test chemicals were administered via gavage treatment.

The subchronic p-RfD value for *n*-nonane was derived using a composite uncertainty factor (UF_C) of 1,000, reflecting 10-fold uncertainty factor values for interspecies extrapolation

(UF_A), intraspecies variability (UF_H), and database uncertainties (UF_D, primarily reflecting the absence of data evaluating neurotoxic, reproductive, and developmental toxicity, including a multi-generation study) (U.S. EPA, 2009b). Wang et al. (2012) indicated that the uncertainty factors typically applied in deriving a toxicity value for the chemical of concern are the same as those applied to the surrogate unless additional information is available. In deriving a screening subchronic p-RfD for *n*-heptane, the same UF_C of 1,000 is applied to the surrogate POD of 3.13 mg/kg-day based on forestomach lesions in male mice. The screening subchronic p-RfD for *n*-heptane is derived as follows:

$$\begin{aligned}\textbf{Screening Subchronic p-RfD} &= \text{Surrogate POD} \div UF_C \\ &= 3.13 \text{ mg/kg-day} \div 1{,}000 \\ &= \mathbf{3 \times 10^{-3} \text{ mg/kg-day}}\end{aligned}$$

Table A-4 summarizes the uncertainty factors for the screening subchronic p-RfD for *n*-heptane.

Table A-4. Uncertainty Factors for the Screening Subchronic p-RfD for *n*-Heptane (CASRN 142−82−5)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty, including toxicokinetic and toxicodynamic differences, between rats and humans following *n*-heptane ingestion. A DAF was not applied because the critical effect was a portal-of-entry effect (i.e., forestomach lesions), and the principal study dosed animals via gavage (U.S. EPA, 2011b).
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*-heptane in humans.
UF_D	10	A UF_D of 10 is applied due to the absence of reliable studies evaluating systemic, nervous system, reproductive, and developmental toxicity of *n*-heptane via the oral route.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMDL_{10}$.
UF_S	1	A UFs for subchronic-to-chronic extrapolation is not relevant for the derivation of the screening subchronic RfD; thus, a 1 is applied.
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; UF = uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose (p-RfD)

No chronic-duration oral studies are available for either *n*-heptane or its surrogate chemical, *n*-nonane. A screening chronic p-RfD value for *n*-nonane was derived using the same POD as the subchronic p-RfD (3.13 mg/kg-day) and applying a UF_C of 10,000 (U.S. EPA, 2009b). The UF_C included a UF_S of 10 to account for increased uncertainty associated with extrapolating to a longer *n*-nonane exposure duration, and 10-fold uncertainty factor values for interspecies extrapolation (UF_A), intraspecies variability (UF_H), and database uncertainties (UF_D, primarily reflecting the absence of oral data evaluating chronic duration systemic, neurotoxic,

reproductive, and developmental toxicity, including a multi-generation study). The screening chronic p-RfD for *n*-heptane is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{Surrogate POD} \div UF_C \\ &= 3.13 \text{ mg/kg-day} \div 10{,}000 \\ &= \mathbf{3 \times 10^{-4} \text{ mg/kg-day}} \end{aligned}$$

Table A-5 summarizes the uncertainty factors for the screening chronic p-RfD for *n*-heptane.

Table A-5. Uncertainty Factors for the Screening Chronic p-RfD for *n*-Heptane (CASRN 142−82−5)

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty, including toxicokinetic and toxicodynamic differences, between rats and humans following *n*-heptane ingestion. A DAF was not applied because the critical effect was a portal-of-entry effect (i.e., forestomach lesions), and the principal study dosed animals via gavage (U.S. EPA, 2011b).
UF_H	10	A UF_H of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of *n*-heptane in humans.
UF_D	10	A UF_D of 10 is applied due to the absence of reliable studies, evaluating systemic, nervous system, reproductive, and developmental toxicity of *n*-heptane via the oral route.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a $BMDL_{10}$.
UF_S	10	A UF_S of 10 is applied due to increased uncertainty associated with longer exposure to *n*-heptane.
UF_C	10,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; DAF = dosimetric adjustment factor; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional oral reference dose; UF = uncertainty factor.

APPENDIX B. DATA TABLES

Table B-1. Treatment-Related Effects in Male CD COBS Rats Exposed to *n*-Heptane (CASRN 142-82-5) 5 Days/Week for 3 Weeks via Gavage[a]

Dose (ADD in mg/kg-d)[b]	0	1,000 (714)	2,000 (1,430)	4,000 (2,860)
LDH (IU/L)[c]	326	502 (1.5-fold)	788 (2.4-fold)	771 (2.4-fold)
Absolute liver weight (g) [c]	9.79	13.61 (+39%)	11.99 (+22%)	11.13 (+14%)
Relative liver weight (% BW) [c]	3.06	4.21 (+38%)	3.86 (+26%)	3.64 (+19%)
Absolute kidney weight (g) [c]	2.51	2.72 (+8%)	2.67 (+6%)	2.87 (+14%)
Relative kidney weight (% BW) [c]	0.78	0.84 (+8%)	0.86 (+10%)	0.94 (+21%)
Hyperplasia of the nonglandular (forestomach) gastric epithelium[d]	0/9	1/3 (moderate)	2/3 (minor)	1/3 (moderate)

[a]Eastman Kodak (1979).
[b]Administered doses in mg/kg-day (as reported by study authors) were converted to an ADD (mg/kg-day) by multiplying the administered gavage dose by (5/7) days per week.
[c]Values represent group means (fold change from control or percent change from control); fold change = treatment mean ÷ control mean; percent change control = [(treatment mean – control mean) ÷ control mean] × 100. The study authors did not report any measure of variability within treatment groups or statistical analyses.
[d]Values represent incidence data for the forestomach epithelium.

ADD = adjusted daily dose; COBS = cesarean-obtained barrier-sustained; BW = body weight; LDH = lactate dehydrogenase.

Table B-2. Treatment-Related Effects in Male CD COBS Rats Exposed to *n*-Heptane (CASRN 142-82-5) 5 Days/Week for 13 Weeks via Gavage[a,b]

Dose (ADD in mg/kg-d)[c]	0	4,000 (2,860)
Body weight (g)		
Wk 0	295 ± 17.3	282 ± 45.4 (−4%)
1	320 ± 16.0	282 ± 33.7* (−12%)
2	351 ± 17.1	324 ± 37.2 (−8%)
3	369 ± 23.5	328 ± 27.8 (−11%)
4	397 ± 20.2	359 ± 29.6* (−10%)
5	410 ± 33.1	348 ± 47.9* (−15%)
6	434 ± 26.7	384 ± 20.8* (−12%)
7	452 ± 30.9	403 ± 20.1* (−11%)
8	455 ± 36.1	411 ± 22.0 (−10%)
9	479 ± 30.4	428 ± 20.2* (−11%)
10	494 ± 34.3	427 ± 31.2* (−14%)
11	504 ± 35.5	443 ± 28.7* (−12%)
12	512 ± 39.9	450 ± 28.5* (−12%)
13	516 ± 45.4	468 ± 32.1 (−9%)
Terminal	495 ± 40.3	429 ± 37.5* (−13%)
Glucose[d]	137 ± 12.5	110 ± 10.0* (−20%)
Absolute heart weight[d]	1.74 ± 0.427	1.26 ± 0.237* (−28%)
Relative heart weight[d]	0.35 ± 0.071	0.29 ± 0.033 (−17%)
Absolute liver weight[d]	13.38 ± 1.336	13.31 ± 2.444 (−0.5%)
Relative liver weight[d]	2.70 ± 0.126	3.16 ± 0.319* (+17%)
Absolute kidney weight[d]	3.10 ± 0.276	3.13 ± 0.631 (+1%)
Relative kidney weight[d]	0.63 ± 0.030	0.73 ± 0.853* (+16%)
Absolute adrenal gland weight[d]	0.053 ± 0.0054	0.063 ± 0.0053 (+19%)
Relative adrenal gland weight[d]	0.011 ± 0.0009	0.015 ± 0.0026* (+36%)

[a]Eastman Kodak (1980).
[b]Values are mean ± standard deviation (percent change compared with control); percent change control = [(treatment mean – control mean) ÷ control mean] × 100.
[c]Administered doses in mg/kg-day (as reported by study authors) were converted to an ADD (mg/kg-day) by multiplying the administered gavage dose by (5/7) days per week.
[d]Units of measurement were not specified in the report.
*Significant difference from control at $p < 0.05$, as calculated by the study authors.

ADD = adjusted daily dose; COBS = cesarean-obtained barrier-sustained.

Table B-3. Histopathological Findings for Male CD COBS Rats Exposed to *n*-Heptane (CASRN 142-82-5) 5 Days/Week for 13 Weeks via Gavage[a]

Dose (ADD in mg/kg-d)[b]	**0**	**4,000 (2,860)**
No. of animals examined	8	8[c]
Nonglandular (forestomach) gastric mucosa		
Acute suppurative gastritis[d]	0	2 (2/5 dead rats)
Acute necrotizing gastritis[d]	0	1 (1/5 dead rats)
Superficial necrosis[d]	0	1 (1/3 surviving rats)
Hyperkeratosis with pseudoepithelimatous hyperplasia[e]	0	7 (4/5 dead rats and 3/3 surviving rats)
Liver		
Vacuolated hepatocytes[f]	0	1 (1/3 surviving rats)
Serosal adhesions[g]	0	1 (1/3 surviving rats)
Congestion[f]	0	1 (1/5 dead rats)
Kidney		
Regenerating tubular epithelium[f]	2	5 (4/5 dead rats and 1/3 surviving rats)
Tubular dilation with casts[f]	1	3 (2/5 dead rats and 1/3 surviving rats)
Hyaline droplets[f]	0	2 (2/5 dead rats)
Hemorrhage[h]	0	2 (2/5 dead rats)
Congestion[h]	0	3 (3/5 dead rats)
Adrenal glands		
Cortical hemorrhage[h]	0	5 (5/5 dead rats)
Congestion[h]	0	2 (2/5 dead rats)

[a]Eastman Kodak (1980).
[b]Administered doses in mg/kg-day (as reported by study authors) were converted to an ADD (mg/kg-day) by multiplying the administered gavage dose by (5/7) days per week.
[c]Five of the eight rats in the exposed group died from acute chemically-induced pneumonitis associated with gavage treatment at different time points throughout the study. The remaining three rats that survived were euthanized after 13 weeks of treatment.
[d]Moderate to severe.
[e]Mostly moderate.
[f]Minimal or minor.
[g]Present.
[h]Minor or moderate.

ADD = adjusted daily dose; COBS = cesarean-obtained barrier-sustained.

Table B-4. Amplitude of Component IV of the Auditory Brainstem Responses in Male Long-Evans Rats Exposed to *n*-Heptane (CASRN 142-82-5) for 28 Days via Inhalation[a,b]

Parameter	Exposure Group, ppm *n*-Heptane (HEC in mg/m^3)[c]		
	0	801 (821)	4,006 (4,105)
4 kHz of frequency:			
95 dB	18.1 ± 3.1	19.8 ± 3.5 (+9%)	14.9 ± 4.0 (−18%)
85 dB	14.9 ± 2.5	15.3 ± 2.3 (+3%)	10.9 ± 3.1* (−27%)
75 dB	9.2 ± 1.9	9.3 ± 2.3 (+1%)	7.2 ± 2.1 (−22%)
65 dB	7.5 ± 2.0	7.9 ± 2.1 (+5%)	5.8 ± 2.5 (−23%)
55 dB	5.3 ± 2.5	6.5 ± 1.9 (+23%)	5.0 ± 2.0 (−6%)
45 dB	3.3 ± 1.4	4.6 ± 1.9 (+39%)	3.2 ± 1.3 (−3%)
35 dB	1.8 ± 0.5	2.6 ± 1.2 (+44%)	2.7 ± 0 (+50%)
25 dB	–	–	–
8 kHz of frequency:			
95 dB	22.9 ± 4.4	24.5 ± 4.3 (+7%)	18.0 ± 5.8 (−21%)
85 dB	20.2 ± 3.5	21.0 ± 3.8 (+4%)	14.8 ± 5.6* (−27%)
75 dB	13.8 ± 2.5	13.3 ± 3.2 (+4%)	10.3 ± 4.2 (−25%)
65 dB	8.4 ± 1.5	8.9 ± 1.9 (+6%)	6.8 ± 2.0 (−19%)
55 dB	6.3 ± 1.6	6.7 ± 1.6 (+6%)	5.1 ± 1.9 (−19%)
45 dB	5.1 ± 1.6	5.1 ± 1.5 (0%)	4.4 ± 1.3 (−14%)
35 dB	3.3 ± 1.0	3.8 ± 1.2 (+15%)	3.0 ± 1.2 (−9%)
25 dB	2.1 ± 0.6	3.2 ± 0.9 (+52%)	2.2 ± 0.5 (−5%)
16 kHz of frequency:			
95 dB	18.7 ± 3.1	20.1 ± 3.7 (+7%)	14.5 ± 5.0* (−22%)
85 dB	18.5 ± 3.5	19.6 ± 3.8 (+6%)	14.3 ± 4.8* (−23%)
75 dB	14.5 ± 3.0	15.0 ± 3.5 (+3%)	10.4 ± 3.7* (−28%)
65 dB	10.4 ± 2.4	10.4 ± 2.6 (0%)	7.8 ± 2.9 (−25%)
55 dB	7.5 ± 1.7	7.6 ± 2.0 (+1%)	5.7 ± 2.0 (−24%)
45 dB	5.7 ± 1.2	5.4 ± 1.5 (−5%)	4.1 ± 1.8 (−28%)
35 dB	4.3 ± 1.3	3.9 ± 1.1 (−9%)	3.4 ± 1.2 (−21%)
25 dB	3.1 ± 1.0	3.1 ± 1.2 (0%)	2.6 ± 1.2 (−16%)

Table B-4. Amplitude of Component IV of the Auditory Brainstem Responses in Male Long-Evans Rats Exposed to *n*-Heptane (CASRN 142-82-5) for 28 Days via Inhalation[a,b]

Parameter	Exposure Group, ppm *n*-Heptane (HEC in mg/m^3)[c]		
	0	801 (821)	4,006 (4,105)
32 kHz of frequency:			
95 dB	12.4 ± 2.1	13.7 ± 1.9 (+10%)	11.3 ± 3.1 (−9%)
85 dB	15.2 ± 3.7	15.5 ± 2.8 (+2%)	11.2 ± 3.6* (−26%)
75 dB	14.8 ± 3.0	15.6 ± 3.2 (+5%)	10.8 ± 3.8* (−27%)
65 dB	12.3 ± 2.9	12.6 ± 2.7 (+2%)	8.7 ± 3.4* (−29%)
55 dB	9.8 ± 3.1	10.1 ± 2.3 (+3%)	7.4 ± 2.4 (−24%)
45 dB	7.4 ± 2.1	7.42 ± 1.7 (0%)	5.7 ± 2.1 (−22%)
35 dB	4.7 ± 1.5	5.2 ± 1.4 (+11%)	4.3 ± 1.3 (−9%)
25 dB	–	–	–

[a]Simonsen and Lund (1995).
[b]Amplitude is reported in µV at different kHz and dB. Values are mean ± standard deviation (percent change compared with control); percent change control = [(treatment mean – control mean) ÷ control mean] × 100.
[c]Mean exposure concentrations in ppm (as reported by study authors) were adjusted for continuous exposure and converted to HECs (mg/m^3) for extrarespiratory effects by applying the following formula:
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
*Significant difference from control at $p < 0.05$, as calculated by the study authors.
−Indicates a lack of detection of Peak IV.

kHz = frequencies; HEC = human equivalent concentration; µV = microvolts; MW = molecular weight; dB = sound intensities.

Table B-5. Auditory Threshold in Male Long-Evans Rats Exposed to *n*-Heptane (CASRN 142-82-5) for 28 Days via Inhalation[a,b]

Parameter	Exposure Group, ppm *n*-Heptane (HEC in mg/m^3)[c]		
	0	801 (821)	4,006 (4,105)
Frequency:			
4 kHz	46.1 ± 1.2	42.2 ± 2.0 (−4%)	53.9 ± 3.5 (8%)
8 kHz	36.2 ± 1.0	32.3 ± 2.0 (−4%)	47.0 ± 4.4* (11%)
16 kHz	31.7 ± 1.7	33.4 ± 1.6 (2%)	42.0 ± 3.9* (10%)
32 kHz	29.5 ± 1.5	28.7 ± 1.4 (−1%)	37.9 ± 3.9 (8%)

[a]Simonsen and Lund (1995).
[b]Auditory threshold is defined as the lowest sound pressure level in 10 dB steps at which Component I of the auditory brain stem responses could be detected. Values are mean ± SEM (percent change compared with control); percent change control = [(treatment mean – control mean) ÷ control mean] × 100. Values were calculated for this review based on graphically reported sound pressure levels (data was digitally extracted using GrabIt! Software).
[c]Mean exposure concentrations in ppm (as reported by study authors) were adjusted for continuous exposure and converted to HECs (mg/m^3) for extrarespiratory effects by applying the following formula:
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
*Significant difference from control at $p < 0.05$, as calculated by the study authors.

HEC = human equivalent concentration; MW = molecular weight; SEM = standard error of the mean.

Table B-6. Serum Alkaline Phosphatase Levels in S-D Rats Exposed to *n*-Heptane (CASRN 142-82-5) for 26 Weeks via Inhalation[a,b]

Parameter	Exposure Group, ppm *n*-Heptane (HEC in mg/m^3)[c]		
	0	398 (291)	2,970 (2,174)
Males			
ALP (IU)			
Wk 13	98 ± 4	115 ± 10 (1.2-fold)	108 ± 9 (1.1-fold)
26	92 ± 3	83 ± 3 (0.9-fold)	86 ± 8 (0.9-fold)
Females			
ALP (IU)			
Wk 13	40 ± 5	42 ± 4 (1.1-fold)	40 ± 3 (1.2-fold)
26	25 ± 1	30 ± 4 (1-fold)	39 ± 3* (1.6-fold)

[a]Bio Dynamics (1980).
[b]Values are mean ± SEM (fold change from control); fold change = treatment mean ÷ control mean.
[c]Mean exposure concentrations in ppm (as reported by study authors) were adjusted for continuous exposure and converted to HECs (mg/m^3) for extrarespiratory effects by applying the following formula:
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
*Significant difference from control at $p < 0.05$, as calculated by the study authors.

ALP = alkaline phosphatase level; HEC = human equivalent concentration; IU = international unit; MW = molecular weight; S-D = Sprague-Dawley; SEM = standard error of the mean.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with the EPA's Benchmark Dose Software (BMDS, Version 2.6). For these data, all continuous models available within the software were fit using a default benchmark response (BMR) of 1 standard deviation (SD) relative risk. An adequate fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark concentration lower confidence limit (BMCL) was selected if the BMCLs estimated from different models varied greater than threefold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was selected as a potential point of departure (POD) from which to derive the provisional reference concentration (p-RfC).

BMD Modeling for Loss of Hearing Sensitivity in Male Long-Evans Rats Exposed to *n*-Heptane (CASRN 142-82-5) via Inhalation for 28 Days (Simonsen and Lund, 1995)

Table C-1. Selected Continuous Data for Effects of *n*-Heptane (CASRN 142-82-5) on Auditory Threshold across Different Frequencies[a]

Number of animals	**9**	**11**	**10**
HEC, mg/m^3	**0**	**821**	**4,105**
Increased auditory threshold at 4 kHz	46.1 ± 1.2	42.2 ± 2.0	53.9 ± 3.5
Increased auditory threshold at 8 kHz	36.2 ± 1.0	32.3 ± 2.0	47.0 ± 4.4*
Increased auditory threshold at 16 kHz	31.7 ± 1.7	33.4 ± 1.6	42.0 ± 3.9*
Increased auditory threshold at 32 kHz	29.5 ± 1.5	28.7 ± 1.4	37.9 ± 3.9

[a]Auditory threshold is defined as the lowest sound pressure level in 10 dB steps at which Components I of the auditory brain stem responses could be detected. Values are mean ± SEM, as calculated for this review based on graphically reported sound pressure levels (data was digitally extracted using GrabIt! Software).
*Significant difference from control at $p < 0.05$, as calculated by the study authors.

HEC = human equivalent concentration; SEM = standard error of the mean.

Table C-2. Summary of Benchmark Concentration Modeling of Data from the 28-Day Inhalation Study with Rats Exposed to *n*-Heptane (CASRN 142-82-5)

Endpoint	Model	*p*-Value[a]	AIC for Fitted Model	Scaled Residual	BMC_{1SD} (HEC in mg/m^3)	$BMCL_{1SD}$ (HEC in mg/m^3)
Increased auditory threshold at 4 kHz[b]	No fit					
Increased auditory threshold at 8 kHz[b]	No fit					
Increased auditory threshold at 16 kHz	**Exponential (2-degree)**	**0.757**	**151.2442**	**−0.0476**	**1,940**	**1,170**
Increased auditory threshold at 32 kHz	Polynomial (3-degree)	0.7584	145.8827	0.00669	3,230	1,440

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]For increased auditory thresholds at frequencies 4 and 16 kHz, both the homogenous and nonhomogeneous variance models failed to provide an appropriate fit (Tests 2 and 3; $p < 0.1$); thus, the data were considered unamenable for BMC modeling.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; NA = not applicable; SD = standard deviation.

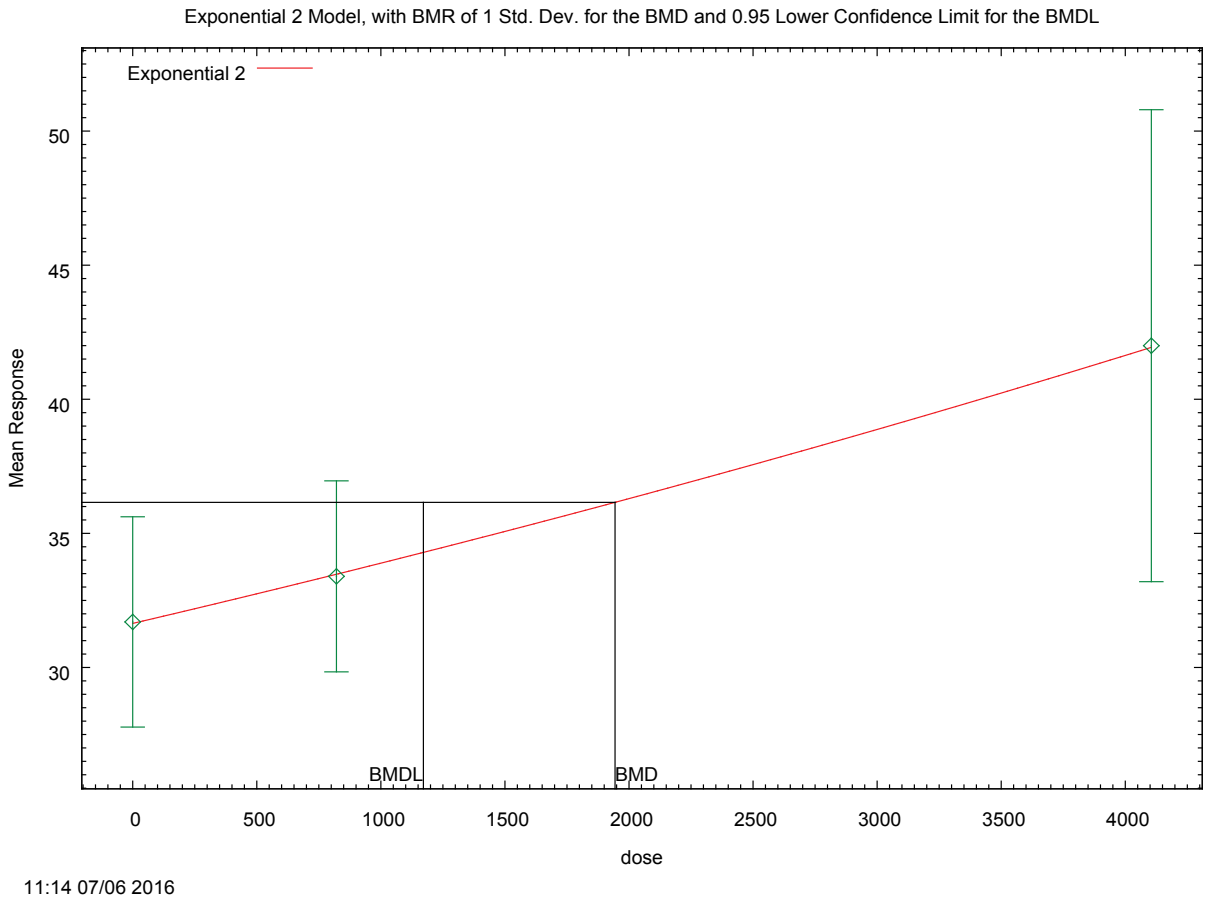
The BMDS results for all modeled endpoints from the 28-day rat study are summarized in Table C-2. Graphical and statistical outputs for the lowest $BMCL_{1SD}$ human equivalent concentration (HEC) of 1,170 mg/m^3 identified as the POD for the derivation of inhalation reference values are provided in Table C-3 and Figure C-1, respectively. For increased auditory threshold at 16 kHz, with a nonhomogeneous variance model applied, only the Exponential (2-degree) and Linear models provided an adequate fit of the data when judged for goodness-of-fit ($p > 0.1$), scaled residuals (<2.0), and visual inspection of the model fit. The $BMCL_{1SD}$s from adequate models were within two to threefold difference; therefore, the model with the lowest AIC was selected (Exponential, 2-degree).

Table C-3. Modeling Results for Increased Auditory Threshold at 16 kHz in Male Long-Evans Rats Treated with *n*-Heptane (CASRN 142-82-5) via Inhalation

Model	Variance *p*-Value[a]	Means *p*-Value[a]	AIC	Scaled Residuals[b]	BMC_{1SD} (HEC in mg/m^3)	$BMCL_{1SD}$ (HEC in mg/m^3)
Constant variance						
Exponential (Model 2)[c]	**0.7487**	**0.757**	**151.2442**	**−0.0476**	**1,943.69**	**1,171.45**
Exponential (Model 3)[c]	0.7487	NA	153.1484	0.1384	2,258.29	1,180.77
Exponential (Model 4)[c]	0.7487	NA	153.341	−0.1266	1,806	1,010.17
Hill[c]	No Fit					
Linear[d]	0.7487	0.6608	151.340905	−0.127	1,806.07	1,010.24
Polynomial (2-degree)[d]	0.7487	NA	153.148404	0.138	2,316.1	1,029.12
Polynomial (3-degree)[d]	0.7487	NA	153.148404	0.138	2,456.23	1,029.13
Power[c]	0.7487	NA	153.148404	0.138	2,209.52	1,029.12

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group near the BMC.
[c]Power restricted to ≥1.
[d]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; HEC = human equivalent concentration; NA = not applicable.




```
================================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File: C:/Users/llizarra/Desktop/BMDS2601/Data/exp_Simonsen
1995_auditthreshold_16khz_Opt.(d)
        Gnuplot Plotting File:
                                                  Wed Jul 06 11:14:09 2016
 ================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
```

```
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

   Total number of dose groups = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	-19.6284	-19.6284	-19.6284	NC
rho	6.58707	6.58707	6.58707	NC
a	31.6317	31.6317	30.115	NC
b	6.89466e-005	6.89466e-005	6.13142e-005	NC
c	0 *	0 *	2.78931	NC
d	1 *	1	1 *	NC

* Indicates that this parameter has been specified

Parameter Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5
lnalpha	-19.9154	-19.7896	-20.1873	NC
rho	6.6376	6.60048	6.71594	NC
a	31.6444	31.8845	31.5749	NC
b	6.86114e-005	8.46574e-005	3.99086e-008	NC
c	--	--	1969.01	NC
d	--	1.20885	--	NC

NC = No Convergence

-- Indicates that this parameter does not appear in model

Std. Err. Estimates by Model

Variable	Model 2	Model 3	Model 4	Model 5

lnalpha	4.60651e-157	10.9882	11.4246	NC
rho	3.14984	3.10239	3.22657	NC
a	1.21472	1.46257	1.24629	NC
b	2.40768e-005	6.09515e-005	4.8527e-006	NC
c	NA	NA	239282	NC
d	NA	0.81223	NA	NC

NA - Indicates that this parameter was specified (by the user or because of the model form)
or has hit a bound implied by some inequality constraint and thus has no standard error.

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	9	31.7	5.1
821	11	33.4	5.3
4105	10	42	12.3

Estimated Values of Interest

Model	Dose	Est Mean	Est Std	Scaled Residual
2	0	31.64	4.514	0.03694
	821	33.48	5.442	-0.0476
	4105	41.94	11.5	0.01683
3	0	31.88	4.623	-0.1197
	821	33.18	5.272	0.1384
	4105	42.13	11.6	-0.03595
4	0	31.57	4.479	0.08377
	821	33.61	5.524	-0.1266
	4105	41.75	11.45	0.06792

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-76.83094	4	161.6619
A2	-71.5229	6	155.0458
A3	-71.5742	5	153.1484
R	-81.03714	2	166.0743
2	-71.62209	4	151.2442
3	-71.5742	5	153.1484
4	-71.67049	5	153.341

Additive constant for all log-likelihoods = -27.57. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Test 5a: Does Model 3 fit the data? (A3 vs 3)
Test 5b: Is Model 3 better than Model 2? (3 vs. 2)

Test 6a: Does Model 4 fit the data? (A3 vs 4)
Test 6b: Is Model 4 better than Model 2? (4 vs. 2)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	19.03	4	0.0007759
Test 2	10.62	2	0.004952
Test 3	0.1026	1	0.7487
Test 4	0.09578	1	0.757
Test 5a	-1.276e-011	0	N/A
Test 5b	0.09578	1	0.757
Test 6a	0.1926	0	N/A
Test 6b	-0.09679	1	N/A

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Degrees of freedom for Test 5a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 5b is greater than .05. Model 3 does not seem to fit the data better than Model 2.

Degrees of freedom for Test 6a are less than or equal to 0. The Chi-Square test for fit is not valid.

The p-value for Test 6b is less than .05. Model 4 appears to fit the data better than Model 2.

Benchmark Dose Computations:

Specified Effect = 1.000000

Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD and BMDL by Model

Model	BMD	BMDL	
2	1943.69	1171.45	
3	2259.29	1180.77	
4	1806	1010.17	
5	-0	-0	Not computed

APPENDIX D. REFERENCES

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