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Provisional Peer Reviewed Toxicity Values for

n-Heptane

(CASRN 142-82-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	**provisional inhalation unit risk**
p-OSF	**provisional oral slope factor**
p-RfC	**provisional inhalation reference concentration**
p-RfD	**provisional oral reference dose**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may 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), or OSRTI.

INTRODUCTION

No RfD or RfC for n-heptane is available in the HEAST (U.S. EPA, 1997), IRIS (U.S. EPA, 2003a) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2003b). The source document for the HEAST, the Health and Environmental Effects Document (HEED) for n-Heptane (U.S. EPA, 1989), concluded that the data were inadequate for a quantitative risk assessment and assigned n-heptane to a cancer weight-of evidence classification D based on lack of human and animal data. The group D assessment is available on IRIS (U.S. EPA, 2003a). The HEED is the only relevant document included in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2002) has not produced a Toxicological Profile for n-heptane and no Environmental Health Criteria Document is available (WHO, 2002). Neither NTP (2002) nor IARC (2002) has assessed the carcinogenicity of n-heptane. Occupational exposure limits for n-heptane include: a (10-hour) TWA-REL of 85 ppm and a 15-minute ceiling limit of 440 ppm (NIOSH, 2002), an (8-

hour) TWA-TLV of 400 ppm and a STEL of 500 ppm (ACGIH, 2002); and a PEL of 500 ppm (2000 mg/m^3) (OSHA, 2002) established to minimize the potential risk for narcosis and respiratory irritation in exposed workers. Literature searches were conducted from 1988 through 2002 for studies relevant to the derivation of provisional toxicity values for n-heptane. Databases searched included: TOXLINE, MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX.

REVIEW OF PERTINENT DATA

Human Studies

Human volunteers (number and sex not reported) were observed during exposure to 1000, 2000, or 5000 ppm of n-heptane vapor for up to 10 minutes (Patty and Yant, 1929). Subjects reported slight vertigo after 6 minutes at 1000 ppm and 4 minutes at 2000 ppm. With exposure to 5000 ppm, subjects displayed hilarity and inability to walk straight after 4 minutes, incoordination after 7 minutes, and marked vertigo after 10 minutes.

Crespi et al. (1979) performed neurophysiological examinations 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), were examined. The workers complained of numbness and paresthesia of the limbs with a glove and stocking distribution, but neurological examination revealed no clinical evidence of peripheral neuropathy. Neurophysiological measurements (motor conduction velocity [MCV], 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 non-occupational 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 that was not, however, described in the report. The mean MCV of the exposed workers was not significantly different from the controls, and none of the exposed workers had an MCV below the normal range. There was, however, a statistically significant correlation between duration of exposure (years of employment at the factory) and MCV, such that MCV 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 statistically 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. On the basis of significantly increased AD of the MAP in exposed workers, and the significant inverse correlation between MCV and exposure

duration in the exposed workers, the researchers concluded that n-heptane had produced minimal peripheral nerve damage in the exposed workers. The study is not useful for quantitative risk assessment because exposure was not quantified.

Animal Studies

A 3-week oral range finding study was conducted for n-heptane in rats (Krasavage and O'Donoghue, 1979). Groups of 3 male Charles River CD COBS rats were orally administered undiluted n-heptane (95.7% pure) by gavage at dose levels of 1000, 2000, or 4000 mg/kg-day, 5 days/week for 3 weeks. A control group of 9 rats was given tap water by gavage. Animals were observed daily for clinical signs of toxicity, and food consumption and body weight were recorded periodically throughout the study. Surviving animals were sacrificed at the end of the exposure period. Blood for hematology and serum chemistry assays was collected at study termination just prior to necropsy. All animals sacrificed at termination or dying during the study were necropsied. Liver and kidney weights were recorded, and an extensive collection of tissues, including 5 areas of the brain, were examined for histopathology. No chemical-related mortality was found, although one animal in the 1000 mg/kg-day group died due to gavage error. No adverse clinical signs were observed. Mean body weights and food consumption were comparable to controls. Hematology and serum chemistry determinations in treated rats were comparable to controls, with the exception of serum LDH (lactic acid dehydrogenase), which appeared to be increased in the 2000 and 4000 mg/kg-day groups (although no statistical analysis was presented and group mean values were not accompanied by standard deviations, precluding independent statistical analysis). Absolute and relative liver and kidney weights were increased, but the changes in the liver did not appear to be dose-related, the changes in the kidney were small, and the changes in either organ could not be evaluated due to failure to report statistical analysis or standard deviations. Histopathological examination revealed hyperplasia of the gastric non-glandular epithelium that was reported to be moderate in the 4000 mg/kg group and minor in the 2000 mg/kg group. No compound-related lesions were found in the 1000 mg/kg-day group. This study is of limited utility for risk assessment due to the short exposure duration, small group sizes and inadequate reporting of results.

In the follow-up study, 8 male Charles River CD COBS rats were orally administered undiluted n-heptane (95.7% pure) by gavage at a dose level of 4000 mg/kg-day, 5 days/week for 13 weeks (O'Donoghue and Krasavage, 1980). A control group of 8 rats was treated by gavage with tap water. 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 collected for hematology and chemistry studies. All animals sacrificed at termination or dying 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 5 areas of the brain, the spinal cord, the sciatic-tibial nerves, and dorsal root ganglia. Five of the 8 rats in the treated group died from gavage trauma.

No clinical signs of toxicity were seen in the other 3 rats in the treated group. Food consumption was reduced 23% in the first week, but was similar to controls subsequently. Mean body weight was statistically significantly reduced by about 10-15% throughout the study. No differences were seen in hematology or serum chemistry determinations, except for a slight statistically significant decrease in glucose. The only statistically significant organ weight changes in rats examined at study termination were slight increases in relative liver, kidney, and adrenal weight that were not accompanied by changes in absolute organ weights and may have been secondary to the previously noted decrease in body weight. Grossly enlarged liver was reported among rats that died early from gavage trauma, but it is not clear if this was found in only 2 of these animals (as reported in the results section) or all 5 of them (as reported in the discussion section). Histopathological examination revealed a strong irritant effect on the gastric mucosa in treated rats. Local contact with the solvent resulted in moderate to severe suppuration and necrosis of the non-glandular gastric mucosa in 4 rats, and mostly moderate hyperkeratosis with pseudoepitheliomatous hyperplasia in 7 rats. Minimal or minor hepatic (hepatocyte vacuolation, focal hepatitis, serosal adhesions, congestion) and renal (hyalin droplets, tubular dilation with casts, regenerating renal tubular epithelium, hemorrhage, congestion, focal nephritis) lesions were seen in treated rats, but it is not clear that the incidence of any specific lesion was increased in comparison to controls. No evidence of neurotoxicity was found. This study is of limited utility for risk assessment due to the small group sizes, high gavage-related mortality, and inclusion of only a single high dose level.

Inhalation studies of n-heptane toxicity have focused primarily on the potential neurological effects of the chemical. Truhaut et al. (1973) exposed Wistar rats (sex and number not reported) to 1500 ppm of technical grade n-heptane (52.4% pure) 5 hours per day, 5 days per week for 1-6 months. Impurities in the solvent included benzene, toluene, 3-methylhexane, cyclohexanes, and other compounds. The investigators removed the sciatic and saphenous nerves after varying durations of exposure and stimulated them with square pulses at various voltages. They found decreased threshold conduction rates and excitability, and increased refractory periods. Microscopic examination after 5-6 months of exposure revealed retraction of myelin sheaths and rupture of Schwann cell membranes. However, it is not clear to what extent the observed effects were due to n-heptane, as high levels of potentially neurotoxic impurities were found in the test solvent and may have contributed to the results.

Subsequent studies did not find evidence of neurological effects due to n-heptane. Takeuchi et al. (1980, 1981) found no neurobehavioral (tests for foot drop, altered gait), neurophysiological (peripheral nerve conduction velocity measured in the tail), or histopathological or ultrastructural (selected peripheral nerves, muscle, and neuromuscular junction) effects in a group of 7 adult male Wistar rats exposed to 3000 ppm of pure n-heptane (>99%) 12 hours/day for 16 weeks, compared with 7 unexposed controls. Body weight gain in the test group was decreased at 8 weeks, but not at 4, 12, or 16 weeks. Frontali et al. (1981) found no effects on body weight gain or hind limb spread, and no degeneration in tibial neural

axons in groups of 6-9 rats (strain and sex not reported) exposed to 1500 ppm of pure n-heptane (99%) 9 hours/day, 5 days/week for 30 weeks. It is unclear whether control data mentioned in the report refer to a concurrent control group, pretreatment results, or historical data.

In a study that also included systemic endpoints, groups of 15 male and 15 female Sprague-Dawley rats were exposed to n-heptane (98.5% reagent grade) vapor at concentrations of 0, 400, or 3000 ppm for 6 hours/day, 5 days/week for 26 weeks (Bio/Dynamics, 1980; Yeshiva University, 1980). Animals were observed for mortality twice daily, and full physical assessments and body weight were recorded weekly. Hematology, serum chemistry, and urinalysis determinations were performed in 10 rats/sex/group after 13 weeks and in 5 rats/sex/group after 26 weeks of exposure. Neurohistological examination was performed on rats withdrawn from the study in the following sequence: 3 rats/sex/group, 5 rats/sex/group, and 4 rats/sex/group on weeks 9, 18, and 27, respectively. Gross necropsy was conducted on all animals that died spontaneously or were killed in-extremis and selected tissues prepared for histological examination, including bone, bone marrow, kidneys, liver, lungs, pulmonary and mesentaric lymph nodes, sciatic nerves, spinal cord, and gross lesions. Two deaths occurred in this study: one female in the high-dose group and one female in the low-dose group, neither of which were considered exposure-related. During the first week of exposure, 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 subsequently. No differences in body weights were observed between treated and control rats. Hematology, urinalysis, and serum chemistry results in the treated group were similar to controls, except that serum alkaline phosphatase activity in the high-dose female group was significantly increased at week 26. The results of gross and histopathological evaluations for systemic effects were not reported. The neurohistological evaluation of the central and peripheral nervous systems did not show any signs of chemical-related pathological changes. The utility of this study for risk assessment is limited, as pathology results for non-nervous system tissues were not reported, and target organ effects of n-heptane were not identified.

Other Studies

Rats treated with 1 ml/kg (≈684 mg/kg) of n-heptane via daily intraperitoneal injection for 1-45 days did not exhibit any overt toxic symptoms, but did show hepatic effects that included significant decreases in hepatic protein, total sulfhydryl content, and glucose-6-phosphatase, and a significant increase in lipid peroxidation (Goel et al., 1988).

n-Heptane did not induce reverse 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).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR n-HEPTANE

No information was located regarding effects of orally ingested n-heptane in humans. Oral animal studies were limited to a 3-week range-finding study in rats and a 13-week rat study from the same laboratory. The range-finding study (Krasavage and O'Donoghue, 1979) included 3 dose levels, but used very small group sizes and failed to report either statistical analyses or any measure of variability within groups, making it impossible to evaluate the data reported. The 13-week study (O'Donoghue and Krasavage, 1980) was also unsuitable for risk assessment due to the small group sizes, high gavage-related mortality in the treated group, and inclusion of only a single high dose level. No oral p-RfD values for n-heptane were derived due to the lack of adequate data.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR n-HEPTANE

A study of a small number of workers at a tire factory found that occupational exposure to n-heptane (with very low levels of impurities) produced minimal peripheral nerve damage in workers exposed for 1-9 years (Crespi et al., 1979). However, exposure levels were unknown. Several animal studies have been done to investigate neurotoxicological effects of inhaled n-heptane. The only study that reported neurotoxic effects (Truhaut et al., 1973), including decreased threshold conduction rates and excitability and increased refractory periods in electrophysiological studies and retraction of myelin sheaths and rupture of Schwann cell membranes in histopathology examinations, was inconclusive, as the tested material was technical grade solvent containing only 52.4% n-heptane and high levels of potentially neurotoxic impurities, such as benzene, toluene, 3-methylhexane, and cyclohexanes. Subsequent evaluations of n-heptane neurotoxicity that used pure material found no neurological effects (Takeuchi et al., 1980, 1981; Frontali et al., 1981; Bio/Dynamics, 1980; Yeshiva University, 1980). Systemic endpoints have not been satisfactorily studied by inhalation exposure. The only study that included any assessment of systemic endpoints (Bio/Dynamics, 1980) was of limited utility because pathology results for non-nervous system tissues were not reported, and target organ effects of n-heptane were not identified. Due to the lack of reliable data establishing an effect or no-effect level, inhalation p-RfC values were not derived for n-heptane.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR n-HEPTANE

No data in humans or animals are available to assess the carcinogenic potential of n-heptane. Limited data indicate that this chemical is not genotoxic (Brooks et al., 1988). Under

the proposed U.S. EPA (1999) cancer guidelines, the data for n-heptane are inadequate for an assessment of human carcinogenic potential.

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

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