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Provisional Peer-Reviewed Toxicity Values for

n-Pentane
(CASRN 109-66-0)

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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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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
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
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR *n*-PENTANE (CASRN 109-66-0)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) 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) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. 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 U.S. EPA's 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. 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 documents 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 Resource Conservation and Recovery Act (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 document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

n-Pentane is a high production volume (HPV) chemical mainly extracted from crude oil or natural gas. *n*-Pentane is used as a solvent with in consumer and industrial products and, also, as a component of gasoline and natural gas. Despite this potential for human exposures, no RfD, RfC, or carcinogenicity assessment for *n*-pentane is available on IRIS (U.S. EPA, 2008). The Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) states that subchronic and chronic toxicity data for *n*-pentane were inadequate for quantitative risk assessment based on a Health Effects Assessment (HEA) for *n*-pentane (U.S. EPA, 1987). *n*-Pentane was categorized as a U.S. EPA Group D carcinogen in the HEA (U.S. EPA, 1987). *n*-Pentane is not included on the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006). The Chemical Assessments and Related Activities (CARA) list includes only the above-mentioned HEA (U.S. EPA, 1991, 1994a). The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile for *n*-pentane, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008). The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) recommends a threshold limit value (TLV) of 600 ppm (1,770 mg/m^3) for *n*-pentane as an 8-hour time-weighted average to protect against narcotic and irritation effects and possible peripheral neuropathy. The National Institute of Occupational Safety and Health (NIOSH, 2008) has set a recommended exposure limit (REL) of 120 ppm (350 mg/m^3) for *n*-pentane as an 8-hour time-weighted average to protect against irritation of the eyes, skin, and nose, drowsiness, and narcosis. The Occupational Safety and Health Administration (OSHA, 2008) permissible exposure level (PEL) for *n*-pentane is 1,000 ppm (2,950 mg/m^3). The carcinogenicity of *n*-pentane has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008).

Literature searches were conducted from the 1960s through December 2007, and updated in January 2009, for studies relevant to the derivation of provisional toxicity values for *n*-pentane. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. A review by Galvin and Marashi (1999) was also examined for relevant studies.

REVIEW OF PERTINENT DATA

Human Studies

No information was located regarding the subchronic or chronic oral or inhalation toxicity of *n*-pentane in humans.

Animal Studies

Oral Exposure

Available studies for repeated oral exposure consist of a reproductive study in rats (McKee et al., 1998), and a rat subchronic nephrotoxicity study (API, 1985). Due to the high volatility of *n*-pentane (the boiling point is roughly 36.1°C [95°F]), inhalation is expected as the major pathway of human exposure. Despite the fact the the boiling point of *n*-pentane is below the body temperature of a rat (roughly 37.5°C [99°F]), available repeated-dose oral studies include both short-term (API, 1985) and developmental toxicity (McKee et al., 1998) gavage studies.

As part of an oral nephrotoxicity screening study, API (1985) administered undiluted *n*-pentane daily to groups of 10 male Fischer 344 rats at gavage doses of 0, 500, or 2,000 mg/kg-day 5 days/week for 4 weeks. Control animals received isotonic saline at a dose of 2,000 mg/kg-day. Dosing was carried out with two subgroups per exposure group (designated as subgroups ‘A’ and ‘B’). Each subgroup contained five rats dosed one day apart. Mortality and clinical signs were noted during the treatment period. Body weights were determined prior to dosing and at the time of scheduled euthanasia. Gross examination of tissues and organs was conducted on all treated rats. Kidneys were the only organs examined microscopically. Twenty percent of low-dose rats (2/10) and 40% of high-dose rats (4/10) died before the end of the study period. Prior to death, these rats exhibited observable weight loss (Table 1). Other clinical effects such as labored breathing, prostration, and coldness to touch were not specifically related to *n*-pentane-treatment. API (1985) does not specifically report necropsy results for these animals and does not discuss any further details regarding the potential cause of death. Thus, the cause of death of these rats is unknown. Lesions consisting of raised, pale, white or dark foci were found upon gross examination in the forestomach of treated rats, most notably among rats from the high dose group.

Table 1. Mean Body Weight Changes and Total Kidney Weight in Rats with Orally Administered *n*-Pentane[a]

Dose (mg/kg-day)	Initial Body Weight (g)	Terminal Body Weight (g)	Total Kidney Weight (g)
0	179	234	1.75
500	180	197[b]	1.61[b]
2000	179	200[b]	1.59[b]

[a]API (1985).
[b]Statistically significantly lower than control at $p \leq 0.05$.

Significant decreases in body-weight gain compared to control rats were observed in both low-dose and high-dose rats (API, 1985), as shown in Table 1. Over the 4-week study, control rats gained 55 g, whereas treated rats gained only 17−21 g (a 62−69% depression in weight gain compared to control rats). The effect on body weight does not demonstrate a clear dose-response relationship because the effect is slightly lessened in high-dose rats compared to low-dose rats. A slight dose-response relationship is observed, however, based on mean absolute kidney weights, as shown in Table 1. Total kidney weight is significantly decreased in low-dose rats (-8%) and high-dose rats (-9%) compared to control rats. The relative kidney weights are not reported, but they can be calculated from the mean data. Relative (to body weight) kidney weights are 0.75, 0.82, and 0.80% for the control, low-dose, and high-dose groups respectively. Histopathological examination of the kidneys for hyaline droplet changes, regenerative epithelium formation, and tubular dilatation is not remarkable.

Aside from the lesions observed in the forestomach of treated rats, as described above, no other significant changes were noted in treated rats based on gross examination (API, 1985). This study by API (1985) was designed as a screening study specifically for evaluating nephrotoxicity in rats. The researchers observed overt effects (death, clinical signs, decreased body weight relative to controls) in rats at both of the *n*-pentane doses tested but did not include investigation of more sensitive systemic endpoints (other than kidney histopathology) and, additionally, only evaluated male rats (no females) for 4 weeks. For these reasons, API (1985) is deemed inadequate for risk assessment purposes.

In McKee et al., 1998, a range-finding developmental toxicity study, groups of Sprague-Dawley rats (7 dams/group) were administered *n*-pentane (>95% purity) in corn oil at gavage doses of 0, 250, 500, 750, or 1,000 mg/kg-day on days 6−15 of gestation. Gross necropsies and uterine examinations (uterine weights, contents, and implantations) were performed on dams at sacrifice on Gestation Day (GD) 21. All live fetuses were weighed, sexed externally, and examined externally for gross malformations. The researchers reported that there were no biologically significant external observations and no differences in fetal body weight or sex ratio between treated and control rats.

In the full study from which a useful NOAEL could be found, groups of 25 mated Sprague-Dawley dams were administered *n*-pentane (>95% purity) in corn oil at gavage doses of 0, 100, 500, or 1,000 mg/kg-day on GDs 6−15 (McKee et al., 1998). There was one control dam and one low-dose dam that delivered prior to scheduled sacrifice. The littering data from these

two animals was not used for further analysis by McKee et al. (1998). Body weights were determined during the treatment period and clinical signs were noted. Gross necropsies and uterine examinations were performed at sacrifice on GD 21. Live fetuses were weighed and examined externally for gross malformations (stunted growth, cleft palate, micrognathia, short tail). After sacrifice, the viscera of about 50% of the fetuses from each litter were examined by fresh dissection. The heads of these fetuses were further examined microscopically for the presence of abnormalities. The remaining fetuses were processed for skeletal staining and examined for the presence of malformations and ossification variations.

McKee et al. (1998) did not observe any clinical signs among treated dams. Based on the figure presented by McKee et al. (1998), it is apparent that all control and treated dams exhibited increases in body weight over their initial values during gestation, and the difference in mean body weights between the control and treated dams was minimal. No significant differences in food consumption or uterine weights were observed between treated and control animals (data not shown). McKee et al. (1998) did not observe any significant changes upon necropsy of treated dams. Data on uterine implantation and fetal parameters showed no evidence of an effect of *n*-pentane on numbers of viable fetuses, resorptions, implantations, pre- or postimplantation loss, or corpora lutea; fetal body weight; Nor was there evidence of total or individual variations or malformations (external, visceral or skeletal) on either a per-fetus or per-litter basis. Although the data are not shown, the authors also reported no statistically significant difference between treated and control groups in number of skeletal ossification sites. Based on the absence of maternal or developmental toxicity, the highest dose of 1,000 mg/kg-day is identified as a freestanding NOAEL for maternal and developmental toxicity.

Inhalation Exposure

Available studies for repeated inhalation exposure consist of a subchronic study in rats (McKee et al., 1998), two independent subchronic neurotoxicity studies (Takeuchi et al., 1980, 1981; Frontali et al., 1981), and a range-finding developmental toxicity study (Hurtt and Kennedy, 1999; E.I. Dupont De Nemours & Co., 1994).

McKee et al. (1998) (the key study in this document) exposed groups of Sprague-Dawley rats (10/sex/concentration) to *n*-pentane vapors (>95% purity) via whole-body inhalation to target concentrations of 0, 5,000, 10,000, or 20,000 mg/m^3, 6 hours/day, 5 days/week, for 13 weeks. The highest concentration tested (20,000 mg/m^3) is one-half the lower explosive limit of *n*-pentane (McKee et al., 1998). The mean measured concentrations were 0, 5,097 ± 79, 10,203 ± 151 and 20,483 ± 734 mg/m^3. Concentrations were chosen based on no apparent effects seen at the same concentration levels during a 5-day range finding study. Exposure was continued into the 14th week to ensure that each animal was exposed on the day prior to sacrifice. Control rats were exposed to air only. All rats were evaluated for survival, body-weight changes, clinical signs, ophthalmoscopic examination, hematology (specific endpoints not identified), clinical chemistry (specific endpoints not specified), and organ weights (adrenals, brain, epididymis, kidneys, liver, lungs, trachea, prostate, seminal vesicles, spleen, testes or ovaries, thymus, and uterus). All tissues from rats of the high-exposure group, including the brain, liver, kidneys, heart, respiratory tissues, reproductive tissues, gastrointestinal tissues, and any gross lesions were examined microscopically. Respiratory tract tissues and gross lesions from the mid- and low-exposure groups were also subject to microscopic examination.

No rats died during treatment through the 90-day study (McKee et al., 1998). Incidental clinical signs (not described) were not considered by the researchers to be related to treatment with *n*-pentane. Based on a figure presented by the researchers, all rats grew normally throughout the 90-day study. A small (<10%) but statistically significant ($p < 0.05$) increase in mean body weight was observed among male rats exposed to 5000 mg/m^3 *n*-pentane from Day 36 to Day 92 compared to control rats, but this is not considered treatment related, as similar increases were not seen among the higher exposure groups. McKee et al. (1998) reported slight statistically significant increases ($p < 0.05$) in food consumption and body-weight gain among some treated rats compared to control rats, but the researchers noted that the differences were sporadic and not related to treatment level.

McKee et al. (1998) reported that there were no treatment-related changes in hematology or clinical chemistry among treated rats (data not shown). Increased absolute liver weight among male rats exposed to 5,000 mg/m^3 was the only significant difference ($p < 0.05$) observed based on organ weights among treated rats compared to control rats. Similar increases were not observed among the higher exposure groups, indicating this effect is not related to exposure. No notable changes were observed as part of the ophthalmological investigation or at necropsy upon gross examination (McKee et al., 1998). McKee et al. (1998) did not provide specific details on the types of lesions that were observed following microscopic examination, but the researchers did report that the microscopic changes observed were known to occur spontaneously and concluded that neither incidence nor type of lesion were related to exposure. In the absence of biologically significant systemic effects following inhalation of *n*-pentane, the highest concentration tested, 20,483 mg/m^3 for a 90-day exposure, is identified as a freestanding NOAEL for systemic toxicity.

In a supportive study, Takeuchi et al. (1980, 1981) conducted a neurotoxicity study in rats evaluating the effects of *n*-pentane. A group of 7 male Wistar rats was exposed to vapors of *n*-pentane (99% purity) via whole-body inhalation at a target concentration of 3,000 ppm (8,853 mg/m^3) for 12 hours/day, 7 days/week for 16 weeks. This concentration was chosen based on previous experiments with *n*-hexane (Takeuchi et al., 1980, 1981). A group of 7 control rats were exposed to air only. The measured mean vapor concentration at the end of the study was 3,080 ± 200 ppm (9,089 mg/m^3). Takeuchi et al. (1980, 1981) evaluated neurotoxicity by measuring the conduction velocity of the peripheral nerve and distal (tail) latency to electrical stimulation. Body weights, motor nerve conduction velocity, distal latency, and mixed nerve conduction velocity were measured prior to treatment and again after 4, 8, 12, and 16 weeks of exposure. Gross and microscopic examination was performed on one rat following the 16-week exposure to *n*-pentane. The researchers minimized artifacts in the fixation for the microscopic examination by fixing tissues while under anesthesia. The rats were perfused from the left ventricle with a fixative containing paraformaldehyde and glutaraldehyde. Tissue was fixed in the same fixative and then postfixed with osmium tetroxide. Specifically, the gastrocnemius and soleus muscles, the dorsal trunk of the tail nerve, and the tibial nerve were examined microscopically in this rat.

Takeuchi et al. (1980, 1981) did not observe any statistically significant treatment-related effects on nerve conduction, body weight, or distal latency. Microscopic examination revealed slight swelling of the mitochondria and sarcoplasmic reticulum and a slight dilatation of myofilament bundles in the gastrocnemius and soleus muscles. Takeuchi et al. (1980, 1981) tested only one concentration of *n*-pentane using a small number of male rats, examined only

endpoints for evaluating peripheral neuropathy, and examined only one rat microscopically. Based on these limitations of the study and the absence of effects, the data of Takeuchi et al. (1980, 1981) are of limited usefulness for risk assessment.

In an additional supportive study, Frontali et al. (1981) also investigated the neurotoxic effects in rats following inhalation of *n*-pentane vapors. Frontali et al. (1981) exposed male Sprague-Dawley rats (6−9 rats) to *n*-pentane vapors (99% purity) via whole-body inhalation at a target concentration of 3,000 ppm (8,853 mg/m^3) for 9 hours/day, 5 days/week, for 30 weeks. Control rats were exposed to air only. Body weights were recorded intermittently throughout the study, although it is unclear if weights were recorded at weekly or monthly intervals. Additionally, all rats were subjected intermittently throughout the study (at the same time intervals for measuring body weight) to a physiological test of neuromuscular function based on the measure of hindlimb spread on landing after falling from 32 cm height. After 30 weeks of exposure to *n*-pentane vapors, rats were euthanized for histological examination of the tibial nerves, optic nerves, and medulla oblongata. Frontali et al. (1981) did not observe any signs of neuropathy in treated rats. Absolute body weight values were analyzed by two statistical means: two-way analysis of variance and Student's *t*-test for the comparison of two slopes. Treated rats demonstrated a significant decrease in body weight ($p < 10 \times 10^{-5}$) based on two-way analysis of variance. However, based on a Student's *t*-test, significance was not attained ($p = 0.092$). Although these results are contradictory, Frontali et al. (1981) suggest that the results from the *t*-test were the result of dispersion of data. The deviation in slope from the control curve in the *t*-test was of the same order of magnitude as in other treatments (*n*-hexane, 2-methylpentane), where significant differences were attained using the Student's *t*-test ($p < 0.05$). No alterations in nervous tissues were observed by microscopic examination. Frontali et al. (1981) examined a small number of male rats per concentration and only examined neurological endpoints. Although this study does provide evidence that *n*-pentane is not neurotoxic, based on the limitations of the study as listed above and the absence of effects, the data of Frontali et al. (1981) are of limited usefulness for the derivation of an RfC.

In a range-finding developmental toxicity study, groups of Crl:CD®BR rats (7−8 dams/concentration) were exposed to *n*-pentane vapors (99.6% purity) via whole-body inhalation at target concentrations of 0, 1,000, 3,000, or 10,000 ppm (0, 2,951, 8,853, or 29,509 mg/m^3), for 6 hours/day, from GDs 6 to 15 (Hurtt and Kennedy, 1999; E.I. Dupont De Nemours & Co., 1994). Control dams were exposed to air only. GD 0 was assigned on the day a copulatory plug was detected. This study was previously described by E.I. Dupont De Nemours & Co. (1994), although the day when copulation was confirmed was previously designated GD 1. Body weights and food consumption were monitored and recorded on GDs 0, 6, 8, 10, 12, 14, 16, and 21. Clinical signs were recorded each morning throughout the study and each afternoon during the exposure period. Dams were euthanized on GD 21. Following sacrifice, gross pathologic examination was made on the thoracic and abdominal cavities. Gravid uteri were weighed and examined for the number of corpora lutea observed per ovary and the number and position of all live, dead, and resorbed fetuses. Fetuses were weighed, sexed, and examined for gross malformations.

Hurtt and Kennedy (1999) did not observe any mortality, unusual clinical signs, or changes in food consumption among treated dams. Hurtt and Kennedy (1999) report tabular summaries of maternal body-weight changes and effects on reproduction parameters in dams exposed to *n*-pentane by inhalation. The results do not indicate any significant exposure-related

effects of *n*-pentane exposure on maternal body weights, number of pregnant females, mean number of viable fetuses, or mean number of implantations. Though mean resorptions per litter at the two highest concentrations tested are increased compared to controls, as shown in Table 2, these changes are not statistically significant ($p > 0.05$) and do not appear to be exposure related. Though the fetal weights are slightly lower in all treatment groups when compared to controls, the differences are not statistically significant, ($p > 0.05$) nor is there an exposure-related trend. No external malformations among the pup fetuses were observed (data not shown). Based on these negative findings, Hurtt and Kennedy (1999) did not conduct a full-spectrum developmental toxicity study in rats.

Table 2. Reproductive Parameters in Dams Exposed to *n*-Pentane by Inhalation[a]

	Exposure Group (ppm)			
	0	**1,000**	**3,000**	**10,000**
No. pregnant/No. treated	8/8	8/8	7/8	7/8
Implants/litter	17.6 ± 0.5[b]	17.8 ± 0.4	17.7 ± 0.3	17.1 ± 1
Resorptions/litter	0.8 ± 0.3	0.8 ± 0.2	1.3 ± 0.5	1.1 ± 0.5
Live fetuses/litter	16.9 ± 0.4	17 ± 0.5	16.4 ± 0.6	16 ± 1.2
Fetal body weight	5.37 ± 0.1	5.22 ± 0.1	5.17 ± 0.1	5.23 ± 0.1

[a]Hurtt & Kennedy (1999)
[b]Values are presented as means ± SE

The findings by Hurtt and Kennedy (1999) support the findings by McKee et al. (1998) described above for oral exposure, suggesting that the developing fetus is not a sensitive target of *n*-pentane in rats. Based on the absence of maternal or developmental toxicity, the high concentration of 10,000 ppm (29,509 mg/m^3) is identified as a NOAEL for maternal and developmental toxicity. However, the small group sizes and lack of detailed examination for skeletal and visceral variations limit the usefulness of this study for risk assessment purposes.

Other Studies

Acute/Short-term Toxicity

n-Pentane does not appear to be acutely toxic following oral or inhalation exposure, as summarized below.

Eastman Kodak Company (1966) reported an acute oral LD_{50} for rats of 400−3200 mg/kg. Similarly, an acute oral LD_{50} value of >2,000 mg/kg was reported in rats by McKee et al. (1998). Human volunteers exposed to 5000-ppm (14,755 mg/m^3) *n*-pentane for 10 minutes did not exhibit any adverse symptoms and, in particular, did not demonstrate mucous membrane irritation (Carreón, 2001). Phillips Petroleum Company (1982) was unable to induce upper airway irritancy in mice exposed to 74,000 mg/m^3 *n*-pentane vapors for 2 minutes.

Stadler et al. (2001) exposed male Crl:CD BR rats to *n*-pentane vapors via whole-body inhalation at target concentrations of 0, 1,000, 3,000, or 10,000 ppm (0, 2,951, 8,853, or 29,509 mg/m^3), respectively, for 6 hours/day, 5 days/week, for 2 weeks. Five rats from each exposure group were observed postexposure over a 14-day recovery period. Stadler et al. (2001) did not observe any unusual clinical signs among the treated rats, and body weights were not

altered. No unusual behavior response was observed among the treated rats subjected to behavioral assessments. Significant increases in serum calcium and phosphorus concentrations were observed among rats exposed to 8,853 and 29,509 mg/m^3 *n*-pentane, but these changes are slight; the phosphorus values are within the range of historical control values, and they are reversible (levels returned to normal following the 2-week recovery period). Stadler et al. (2001) suggested that the combination of increased calcium and phosphorus may indicate potentially adverse alterations in mineral metabolism or homeostasis but noted that these effects could be part of background variation and not related to *n*-pentane exposure. No other clinical pathology changes were observed, and there is no indication of *n*-pentane toxicity based on tissue pathology. Based on these findings, the highest concentration tested, 29,509 mg/m^3, is identified as the NOAEL for systemic effects in rats following repeated inhalation of *n*-pentane vapors over 2 weeks.

As mentioned previously McKee et al. (1998) conducted a 5-day range-finding study whereby Sprague-Dawley rats (5/sex/concentration) were exposed to *n*-pentane vapors via whole-body inhalation at target concentrations of 0, 5,000, 10,000, or 20,000 mg/m^3 for 6 hours/day on 5 consecutive days. No apparent effects are noted at any concentration. These data suggest the LC_{50} for *n*-pentane is >20,000 mg/m^3 for acute exposures (6 hours/day for 5 days) (approximately 6,778 ppm). Lazarew (1929) found that exposure to 200,000−300,000 mg/m^3 *n*-pentane vapors caused mice to lie on their side. Studies summarized in a review by Galvin and Marashi (1999), demonstrate that in single acute exposures, large quantities of *n*-pentane act as an anesthetic and as an asphyxiant at high concentrations (>300,000 mg/m^3).

Toxicokinetics

The toxicokinetic literature on *n*-pentane is not robust, but there are some conclusions that can be drawn. Frommer et al. (1970) showed that the initial step of metabolism was a P450 mediated hydroxylation to 2-pentanol and 3-pentanol in a 2:1 ratio. Subsequent work in other laboratories demonstrated further metabolism to 2-pentanone. Filser et al. (1983) developed a pharmacokinetic model that demonstrates a half-time for elimination/excretion of 0.13 hours. Considering the rapid metabolism (to pentanol and pentanone) and excretion, there is little potential for tissue accumulation (McKee et al., 1998).

Genotoxicity

Genotoxicity studies indicate that the potential for *n*-pentane to induce any significant mutagenic activity is low, as summarized below. *n*-Pentane was not mutagenic in a *Salmonella* gene mutagenicity assay that was modified for low-volatility materials (Kirwin et al., 1980). An increasing, dose-related trend ($p < 0.01$) has been observed in the percentage of aberrant cells in an in vitro chromosome aberration test with Chinese hamster ovary (CHO) cells during a 20-hour repeat harvest in the presence of metabolic activation (McKee et al., 1998). However, as the highest concentrations tested may have exceeded a level at which artifacts can be produced (10 mM) and since similar increases of aberrant cells were not observed in the initial 20-hour treatment, the increase in chromosomal aberrations during the repeated treatment is not considered biologically important. *n*-Pentane did not induce micronuclei formation and did not produce cytotoxicity in the bone marrow of rats exposed in vivo to 5,000, 10,000, or 20,000 mg/m^3 (McKee et al., 1998). *n*-Pentane was not mutagenic in male mice in a dominant lethal study following injection of 48−666 mg/kg into the peritoneum (Epstein et al., 1972).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR *n*-PENTANE

Oral studies of *n*-pentane are limited to short-term (API, 1985) and developmental toxicity (McKee et al., 1998) gavage studies. API (1985) demonstrated significant decreases in body weights and absolute kidney weights of male rats at both doses of *n*-pentane tested (500 or 2,000 mg/kg-day). No signs of nephrotoxicity were observed based on histopathology. In addition, though API (1985) reported 20% mortality among low-dose rats and 40% mortality among high-dose rats, the researchers did not provide enough information to ascertain the cause of death. As described above, this study is of limited usefulness for risk assessment based on poor reporting of study details, limited assessment of endpoints, and evaluation of only male rats over short exposure duration. Contrary to the results reported by API (1985), McKee et al. (1998) did not observe any statistically significant treatment-related effects on maternal body weights or survival of rats exposed to *n*-pentane concentrations up to 1,000 mg/kg-day via gavage during the gestation period. One factor potentially contributing to the differences between the API (1985) study and the McKee et al. (1998) study is the dosing vehicle: the API study used saline while the McKee study used corn oil. Finally, McKee et al. (1998) did not observe any significant changes in reproductive parameters in dams or any adverse effects on fetal development of pups. The available data are not sufficient for derivation of a provisional subchronic or chronic RfD for *n*-pentane because systemic toxicity has not been adequately studied.

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

Subchronic p-RfC

Data on the subchronic inhalation toxicity of *n*-pentane come from a subchronic study in rats (McKee et al., 1998), three subchronic neurotoxicity studies (Takeuchi et al., 1980, 1981; Frontali et al., 1981) and a range-finding developmental toxicity study (Hurtt and Kennedy, 1999; E.I. Dupont De Nemours & Co., 1994) were used to calculate the $NOAEL_{ADJ}$ and $NOAEL_{HEC}$ values. McKee et al. (1998) did not observe any significant treatment-related effects in rats exposed to concentrations of *n*-pentane up to 20,483 mg/m^3 for 6 hours per day, 5 days per week, for 13 weeks. The neurotoxicity studies (Takeuchi et al., 1980, 1981; Frontali et al., 1981) are of limited usefulness for risk assessment based on small sample sizes and evaluation of a limited number of endpoints. However, the results from these studies (Takeuchi et al., 1980, 1981; Frontali et al., 1981) show that *n*-pentane does not induce neurotoxic (changes in conduction velocity or microscopic changes) effects in rats exposed to concentrations up to 9,089 mg/m^3. The developmental toxicity study by Hurtt and Kennedy (1999) found that *n*-pentane exposure did not induce developmental effects in rat fetuses from dams exposed to *n*-pentane vapor during gestation up to the highest concentration tested (29,509 mg/m^3), although the usefulness of the study is limited because group sizes are small and complete fetal examinations were not performed.

The NOAEL, $NOAEL_{ADJ}$, and $NOAEL_{HEC}$ values from McKee et al. (1998), Takeuchi et al. (1980, 1981), Frontali et al., (1981), and Hurtt and Kennedy (1999) are given in Table 3. The NOAEL for each study (the highest concentration tested in each study) has been adjusted for continuous exposure ($NOAEL_{ADJ}$), and the human equivalent concentrations ($NOAEL_{HEC}$) have been subsequently calculated, as recommended by U.S. EPA (1994b). The $NOAEL_{ADJ}$ values have been calculated as follows:

$NOAEL_{ADJ}$ = (NOAEL) (# hours dosed/24) (# days dosed/7)
3,657.7 = 20,483 × (6/24) × (5/7)

Table 3. $NOAEL_{ADJ}$ and $NOAEL_{HEC}$ Values for *n*-Pentane Inhalation Studies

Study	NOAEL (mg/m^3)	$NOAEL_{ADJ}$ (mg/m^3)	$NOAEL_{HEC}$ (mg/m^3)
McKee et al. (1998)	20,483	3,658	3,658
Takeuchi et al. (1980, 1981)	9,089	4,545	4,545
Frontali et al. (1981)	8,853	2,371	2,371
Hurtt and Kennedy (1999)	29,509	7,377	7,377

The $NOAEL_{HEC}$ values shown in Table 3 are based on the $NOAEL_{ADJ}$ values and were calculated for remote effects (extrarespiratory) of a Category 3 gas by multiplying the $NOAEL_{ADJ}$ values by the ratio of the blood:gas (air) partition coefficient of *n*-pentane for the laboratory animal species to the human value ($[H_{b/g}]_A/[H_{b/g}]_H$). Blood:air partition coefficients of 1.48 and 0.38 have been estimated in rats (Meulenberg and Vijverberg, 2000) and humans (Perbellini et al., 1985), respectively. The reliability of the rat value reported above is uncertain because it is a predicted value based on a model using knowledge of empirical relations between olive oil ($P_{oil:air}$), saline ($P_{saline:air}$), and tissue partition coefficients ($P_{tissue:air}$) for rat tissues (Meulenberg and Vijverberg, 2000). In accordance with U.S. EPA (1994b), the value of 1.0 is used for the ratio of $[H_{b/g}]_A/[H_{b/g}]_H$ when $[H_{b/g}]_A > [H_{b/g}]_H$. The resulting $NOAEL_{HEC}$ values are listed in Table 3.

Although limited in various ways, the neurotoxicity studies (Takeuchi et al., 1980, 1981; Frontali et al., 1981) and the developmental toxicity study (Hurtt and Kennedy, 1999) support the negative findings made by McKee et al. (1998) in rats exposed to *n*-pentane vapors for 90 days. The $NOAEL_{HEC}$ of 3,658 mg/m^3 from McKee et al. (1998) is suitable for use as the point of departure (POD) for derivation of subchronic and chronic p-RfC values because this study evaluates both male and female rats based on a number of endpoints including physical changes, clinical chemistry and hematology, and gross and microscopic examination of target organs. A lack of adverse effect levels precludes the use of benchmark dose analysis in this study. As no significant effects are seen in any of the subchronic studies, the threshold for toxic effects of *n*-pentane is not established. Note however, that higher concentrations would approach the lower explosive level, and it would not be rational to do so. Information from acute studies shows that at extremely high concentrations (>200,000 mg/m^3), *n*-pentane exposure may act as an anesthetic (Lazarew, 1929; McKee et al., 1998; Galvin and Marashi, 1999).

A **subchronic p-RfC of 10 mg/m^3** for *n*-pentane, based on the $NOAEL_{HEC}$ of 3,658 mg/m^3 in rats (McKee et al., 1998), is derived as follows:

Subchronic p-RfC = $NOAEL_{[HEC]} \div UF$
= 3,658 mg/m^3 ÷ 300
= **10 or 1 × 10^1 mg/m^3**

The UF of 300 is composed of the following:

- A partial UF of 3 ($10^{0.5}$) is applied for interspecies extrapolation to account for potential pharmacodynamic differences between rats and humans. Converting the rat data to human equivalent concentrations by the dosimetric equations accounts for pharmacokinetic differences between rats and humans; thus, it is not necessary to use the full UF of 10 for interspecies extrapolation.
- A 10-fold UF for intraspecies differences is used to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF of 10 is included for database insufficiencies. The database includes only freestanding NOAEL values, and it lacks a supporting systemic study and a multigenerational reproduction study. While only one range-finding developmental toxicity study by the inhalation route is available, an oral study in the same species suggests that developmental toxicity is not a sensitive endpoint for *n*-pentane; however, a second species has not been tested by either route of exposure.

Confidence in the principal study (McKee et al., 1998) is medium. The study evaluated 10 animals per gender per dose and assessed a wide variety of potential endpoints. However, no LOAEL was determined in the principal study and some data were not reported beyond the authors stating that no effects were seen (hematology, serum chemistry, microscopic changes). Confidence in the database is low because the database is limited to freestanding NOAEL values and lacks adequate supporting systemic, multigenerational reproduction and developmental toxicity studies. Reflecting medium confidence in the principal study and low confidence in the database, confidence in the provisional subchronic RfC is low.

Chronic p-RfC

To derive the chronic p-RfC, a 10-fold UF for exposure duration is applied to the $NOAEL_{HEC}$, resulting in a total UF of 3,000. Although the exposure duration in the critical study was only 90 days, a UF of 10 for exposure duration is considered appropriate because of the toxicokinetic data showing that the half-life of *n*-pentane is 0.13 hours. Considering the rapid metabolism (to pentanol and pentanone) and excretion, there is little potential for tissue accumulation (McKee et al., 1998). As no significant effects are seen in any of the subchronic studies, the threshold for toxic effects of *n*-pentane is not established, and the value derived below is likely quite conservative, as there is no evidence of chronic toxicity. The **chronic p-RfC of 1 mg/m^3** for *n*-pentane is derived below:

Chronic p-RfC = $NOAEL_{HEC} \div UF$
= $3{,}658\ mg/m^3 \div 3{,}000$
= **1 or $1 \times 10^0\ mg/m^3$**

Confidence in the subchronic toxicity study used to derive the chronic p-RfC is medium, as discussed in the subchronic p-RfC derivation. Confidence in the database is low due to the lack of a chronic study and for the reasons discussed in the subchronic p-RfC derivation. Low confidence in the chronic p-RfC follows.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR *n*-PENTANE

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to *n*-pentane in humans or animals were not identified in the available literature. Genotoxicity data suggest that the potential for *n*-pentane to induce any significant mutagenic or cytogenetic activity is low. Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is '*Inadequate Information to Assess [the] Carcinogenic Potential*' of *n*-pentane.

Quantitative Estimates of Carcinogenic Risk

The lack of suitable data precludes derivation of quantitative estimates of cancer risk for *n*-pentane.

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