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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR n-PENTANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with n-pentane. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

Data regarding n-pentane were insufficient for quantitative risk assessment. The more relevant route of exposure appears to be by inhalation. It is recommended that a complete pharmacokinetic profile and subchronic toxicity testing be performed.

There are no data on the carcinogenicity, chronic toxicity, or pharmacokinetics of n-pentane, and subchronic toxicity experiments are not designed adquately for quantitative assessment of risk. Short-term inhalation exposure to either n-pentane or n-hexane has produced respiratory tract irritation in humans and nervous system aberrations in both man and experimental animals. N-pentane did not increase the number of revertants in a Salmonella typhimurium assay, and had no dominant-lethal effects in mice. A complete pharmacokinetics profile and comprehensive subchronic toxicity testing of inhaled n-pentane are recommended.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CBI	Confidential Business Information
ppm	Parts per million
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of n-pentane are presented in Table 1-1.

In the atmosphere, n-pentane is expected to occur entirely in the vapor phase. The atmospheric half-life listed in Table 1-1 has been calculated based on HO radical reaction rate constants ranging from $(3.51 \pm 0.13) \times 10^{-12}$ to 6.55×10^{-12} cm^3/molecule-sec at 30°C and an ambient HO radical concentration of 8.0×10^5 molecules/cm^3 (Atkinson, 1985).

In water, volatilization is expected to be a dominant fate process. Based on an experimentally determined value for Henry's Law constant of 1.23 atm-m^3/mol at 25°C (Hine and Mookerjee, 1975), the volatilization half-life of n-pentane from a river 1 m deep flowing 1 m/sec with a wind speed of 3 m/sec has been calculated to be 2.5 hours (Lyman et al., 1982). Based on estimated bioconcentration factors of 79-220, bioaccumulation in aquatic organisms should not be significant.

The half-life of n-pentane in soil could not be located in the literature searched. Based on the relatively high Henry's Law constant and vapor pressure of n-pentane and assuming moderate adsorption to soil, this compound should rapidly volatilize from both wet and dry soil surfaces. Its residence time in soil is expected to be higher than in water.

The most probable route of human exposure to n-pentane is by inhalation. n-Pentane is an extremely volatile compound and monitoring data indicates that it is a widely occurring atmospheric pollutant (Arnts and Meeks, 1980; Cavanagh et al., 1969; Uno et al., 1985; Altshuller et al., 1971).

TABLE 1-1

Selected Chemical and Physical Properties
and Environmental Fate of n-Pentane

CAS number:	109-66-0	
Chemical class:	aliphatic hydrocarbon	
Molecular weight:	72.15	
Vapor pressure:	513 mm Hg at 25°C	Mackay and Shui, 1981
Water solubility:	38.5 mg/ℓ at 25°C	Mackay and Shui, 1981
Log octanol/water partition coefficient:	3.39	Hansch and Leo, 1985
Bioconcentration factor:	79-220 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	590 (estimated)	Lyman et al., 1982
Half-life in		
Air:	2-3 days (estimated)	
Water:	hours (estimated)	
Soil:	not available	

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

Pertinent data regarding the absorption of n-pentane after oral or inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

Data regarding the oral toxicity of n-pentane are limited to a single 28-day experiment in rats. American Petroleum Institute (1985) administered n-pentane by gavage at 0, 0.5 or 2.0 g/kg 5 days/week for 4 weeks to groups of 10 male F344 rats. Control rats received saline only. Parameters of toxicity evaluated included twice daily observation for mortality and clinical signs of toxicity, terminal body weights and gross and microscopic appearance of the kidneys. Mortality occurred in 40% of high-dose rats and 20% of low-dose rats. Terminal body weights of both treated groups were significantly less than controls ($p<0.05$). Absolute kidney weights were lower in both treated groups ($p<0.05$) than in controls. The histopathological appearances of the kidneys was not remarkable. This study is inadequate for use in risk assessment.

Data regarding the toxicity of n-pentane after inhalation exposure are limited. Gaultier et al. (1973) found polyneuropathy in five employees exposed by inhalation to a solvent mixture consisting of 5% n-hexane, 14% n-heptane and 80% pentane. Duration of exposure and exposure concentration were not specified. Affected workers had anorexia, paresthesia, symmetrical muscle failure, asthemia, peripheral nerve damage and signs of denervation in the legs. Patty and Yant (1929) found no symptoms of neuromuscular disorder in human volunteers exposed to 5000 ppm (~14,750 mg/m^3) n-pentane for 10 minutes. Ten minutes exposure to 5000 ppm (~17,200 mg/m^3) n-hexane, however, was associated with marked vertigo.

Male rats were exposed to ~3000 ppm (8850 mg/m^3) >99% pure n-pentane, 12 hours/day for 16 weeks, for study of nerve conduction velocities and distal (tail) latency to electrical stimulation (Takeuchi et al., 1980,

1981). One rat was sacrificed at the end of 16 weeks, and light and electron microscopy was performed on the gastrocnemius and soleus muscles, the dorsal trunk of the tail nerve and the tibial nerve. N-pentane had no effect on measures of nerve conduction, body weights or distal latencies. There was slight swelling of the mitochondria and the sarcoplasmic reticulum, and minor dilation of the myofilaments of these muscles. Since the tissues of only one rat were studied microscopically, and the nerve conduction data do not suggest adverse effects, the data of Takeuchi et al. (1980, 1981) are inadequate for quantitative risk assessment.

Administration of 3000 ppm (~10,300 mg/m³) n-hexane, on the same treatment schedule, resulted in severe decreases in body weight gain and nerve conduction velocity, and increases in distal latency (Takeuchi et al., 1980, 1981). Treated rats had clinical signs of neuropathy. Microscopic examination of tissues from two n-hexane exposed rats revealed myelin damage, denervated neuromuscular junctions, muscle structure irregularities and axonal degeneration.

IIT (1985) exposed rats to 1000 ppm (~2650 mg/m³) and 4500 ppm (~12,000 mg/m³) of a 50:50 mixture of n-butane and n-pentane, 6 hours/day, 5 days/week for 13 weeks. Exposure was associated with a transient hunched appearance, tremors and a nonconcentration related inhibition in body weight gain, which was reversible in males. There were no treatment-related changes on gross necropsy observations, renal histopathology or organ weights.

Lazarew (1929) found that 2-hour exposure to 200-300 mg/ℓ (200-300 g/m³) n-pentane caused mice to lay on their sides, whereas only 100 mg/ℓ (100 g/m³) n-hexane for 2 hours was needed for the same effect. Swann et

al. (1974) observed no anesthesia in mice exposed for 5 minutes to ≤16,000 ppm (~47,200 mg/m³) n-pentane. At 32,000 ppm (~94,400 mg/m³), light anesthesia was observed during recovery, and at higher concentrations there were signs of respiratory irritation and deep anesthesia. NIOSH (1977) concluded that, within the alkane series C5-C8, physiological potency increases as chain length increases.

Epstein et al. (1982) studied the potential dominant-lethal effects of n-pentane, collected as fractions of particulate atmospheric pollutants in 9-60% ether, in mice. Before mating, between seven and nine male mice were injected once intraperitoneally with between 48 and 666 mg/kg of one of the pentane fractions. Females were sacrificed 13 days after the midweek of their presumed mating, and autopsied. Treatment had no effect on early fetal deaths or preimplantation losses.

There are no data on the interactive effects of n-pentane with other toxicants. CBI data indicate that concentrations of ≥10% n-propane, n-butane, isobutane or isopentane sensitized dog hearts to the effects of exogenous epinephrine.

4. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of n-pentane, by any route of exposure, could not be located in the available literature. The CBI files contained the results of an unpublished mutagenicity study in which n-pentane did not increase the number of revertants in six strains of Salmonella typhimurium, with or without metabolic activation. NIOSH (1977) stated that C5-C8 alkanes probably do not have carcinogenic or mutagenic activity because they are not chemically related to compounds that express such activity.

N-pentane should be considered a U.S. EPA Group D (U.S. EPA, 1986), or IARC Group 3 compound in terms of the available evidence of carcinogenic potential. These classifications are for compounds with inadequate animal evidence of carcinogenicity, and no human data.

5. REGULATORY STANDARDS AND CRITERIA

NIOSH (1977) recommended a TWA occupational standard for n-pentane exposure of 350 mg/m³ and a 15-minute ceiling concentration limit of 1800 mg/m³. These levels were determined by analogy to n-hexane, which produces polyneuropathy at levels <1800 mg/m³. NIOSH (1977) did not clearly indicate how the standard was developed based on these data. Because workers are typically exposed to mixtures of alkanes, and because data on the metabolism of individual alkanes are incomplete, NIOSH (1977) recommended the same standard for all alkanes.

ACGIH (1985) adopted a TWA of 600 ppm (~1800 mg/m³) and a STEL of 750 ppm (~2250 mg/m³) for n-pentane. ACGIH (1986) proposed that the TLV and the STEL should provide a margin of safety for narcotic and irritant effects. They did not rule out the possibility of polyneuropathy after chronic exposure based on the report by Gaultier et al. (1973), but stated that the effect would occur for n-pentane at higher exposure levels than for n-hexane. The workplace standard of 350 mg/m³ (NIOSH, 1977), based primarily on n-hexane exposure data, was therefore considered unneccesarily conservative for n-pentane. The OSHA (1985) occupational standard is 1000 ppm (~2950 mg/m³) for an 8-hour workday.

6. RECOMMENDATIONS

Because n-pentane exists in the atmosphere completely in the vapor phase (Atkinson, 1985), and volatilization from both water (Hine and Mookerjee, 1975) and soil is apparently rapid, it is likely that the more relevant route of exposure for humans is by inhalation. Limited evidence suggests that the major toxic effects of inhaled short-chain alkanes involve the nervous system (Gaultier et al., 1973; Takeuchi et al., 1980, 1981; IIT, 1985; Lazarew, 1929), although there have been few assessments of other endpoints.

Both acutely and subchronically, n-hexane was found to be consistently more toxic than n-pentane (NIOSH, 1977) at equimolar concentrations, so that risk assessment by analogy is not recommended. The ACGIH (1986) TLV appears to be too weak a basis for quantitative risk assessment.

Assays for reverse mutations (CBI files) and dominant-lethal effects (Epstein et al., 1982), as well as the chemical structure of n-pentane (NIOSH, 1977), all suggest that it is not a carcinogenic or mutagenic threat.

It is recommended that a complete pharmacokinetic profile of inhaled n-pentane in experimental animals be conducted. Results of acute toxicity testing in a relevant species should be a guideline for the development of a multi-concentration subchronic test. Although gross disruption in nervous system activity is consistently found at higher concentrations, it is important to establish whether lower concentrations interfere with more subtle measures of behavioral performance. Hematological, blood biochemical and histopathological parameters should also be assessed at all concentrations in a subchronic study.

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