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OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD 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 focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. An RfD may also be derived for the noncarcinogenic health effects of compounds that are also carcinogenic.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986c, respectively.

EXECUTIVE SUMMARY

2-Hexanone is known by the synonyms butyl methyl ketone, methyl butyl ketone and propyl acetone (Hawley, 1981; Windholz, 1983). It is a colorless liquid that is soluble in alcohol and ether and slightly soluble in water (Windholz, 1983). Production data for 2-hexanone are limited. In 1977, the Tennessee Eastman Company manufactured between 1 and 10 million pounds of 2-hexanone (U.S. EPA, 1977). However, the 1988 Directory of Chemical Producers (SRI, 1988) and the U.S. International Trade Commission (USITC, 1988) do not have listings for 2-hexanone, suggesting that it is not currently manufactured on an industrial scale in the United States for use as an end-product. Current import figures are not available. 2-Hexanone is used as a medium-evaporating solvent for nitrocellulose, acrylates, vinyl and alkyd coatings (Papa and Sherman, 1981).

2-Hexanone appears to be readily degradable in air, water and soil; it is not likely to be a persistent environmental contaminant. If released to the atmosphere 2-hexanone is expected to exist in the vapor phase where it will degrade by reaction with sunlight-formed HO radical. Based upon an experimentally determined rate constant (Wallington and Kurylo, 1987), the half-life for this reaction has been estimated to be ~2.4 days for typical atmospheric conditions. If released to the aquatic environment, 2-hexanone may degrade by biodegradation or be physically removed by volatilization. 2-Hexanone appears to be readily biodegradable based upon results from limited biodegradation screening studies (Babeu and Vaishnav, 1987; Vaishnav et al., 1987; Shelton and Tiedje, 1984). Volatilization half-lives of ~12 hours and 5.7 days can be estimated for a shallow model river and environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986a). If

released to soil, 2-hexanone may be susceptible to significant biodegradation based on analogy to the biodegradation screening studies noted above. Although significant leaching is possible, concurrent biodegradation may decrease the potential importance of leaching. 2-Hexanone is used as a medium-evaporating solvent (Papa and Sherman, 1981) and is expected to undergo significant evaporation from dry surfaces.

2-Hexanone can be released to the aquatic environment by wastewater streams generated at various fossil-fuel processing and chemical manufacturing sites and by leaching from hazardous waste sites and municipal landfills (HSDB, 1989; Brown and Donnelly, 1988; Myers, 1983). This compound is released to the atmosphere by evaporation from its use as a solvent (Graedel et al., 1986). 2-Hexanone occurs naturally. It has been detected as a volatile component of blue cheese, nectarines, raw chicken breast and poultry manure (Day and Anderson, 1965; Takeoka et al., 1988; Grey and Shrimpton, 1967; Yasuhara, 1987). The general population may be exposed to 2-hexanone through ingestion of natural and processed foods (in which it occurs naturally) and through inhalation of vapors from commercial coatings containing 2-hexanone as a solvent (HDSB, 1989). Insufficient monitoring data are available to estimate average human daily intakes of 2-hexanone using food, inhalation or drinking water.

The 96-hour LC_{50} and EC_{50} for the fathead minnow, Pimephales promelas, exposed to 2-hexanone under flowthrough conditions was 428 mg/ℓ (Geiger et al., 1986). The ED_{50} for scud, Gammarus, measured as the loss of an escape response when organisms experienced a mechanical stimulus delivered by hand to either lateral surface when exposed to 2-hexanone was 420 mg/ℓ.

The EC_{50} for mixed microbial cultures, measured as the concentration of 2-hexanone that would reduce the maximum observed biodegradation rate by 50%, was 5510 mg/ℓ (0.055 M) (Vaishnav, 1986). Tests assessing the efficacy of 2-hexanone as a repellent for the bee, Apis florea, revealed that bees exposed to concentrations of 2-hexanone from 62.5 and 4000 mg/ℓ resulted in 64.0 and 82.6% repelled, respectively (Gupta and Mohla, 1986; Gupta, 1987).

2-Hexanone is absorbed readily from the GI tract, the respiratory tract, and through the skin. Respiratory uptake data in humans (DiVincenzo et al., 1978) indicate that ~75-92% of inhaled 2-hexanone was absorbed by the lungs and respiratory mucosa following exposure to 10-100 ppm for 4-7.5 hours. Approximately 65-68% of 2-hexanone vapor was absorbed by the lungs of dogs exposed to 50-100 ppm 2-hexanone for 6 hours. 2-Hexanone can also be absorbed readily through the skin. A dermal absorption rate of 4.8-8.0 $\mu g/min^{-1}cm^{-2}$ was determined in humans from the analysis of excretion data (DiVincenzo et al., 1978).

Although distribution of radioactivity from administered (1-^{14}C)-2-hexanone appears to be rapid and widespread, the highest concentrations of radioactivity following oral administration of 2-hexanone in rats were detected in the liver and blood (DiVincenzo et al., 1977).

Following absorption, 2-hexanone undergoes extensive metabolism and elimination. 2-Hexanone is metabolized by hepatic cytochrome P-450 oxidases with the formation of 5-hydroxy-2-hexanone and 2,5-hexanedione (DiVincenzo et al., 1977; Couri et al., 1978). The metabolism of 2-hexanone to 2,5-hexanedione is regarded as metabolic activation, since there is evidence that 2,5-hexanedione mediates the neurotoxicity and testicular toxicity of 2-hexanone. 2,5-Hexanediol is formed by the oxidation of 2-hexanol or by the reduction of 5-hydroxy-2-hexanone. Urinary metabolites of 2-hexanone

include 2,5-hexanedione, 2-hexanol, 5-hydroxy-2-hexanone and 2,5-dimethylfuran. 2-Hexanol, 5-hydroxy-2-hexanone, and 2,5-dimethylfuran are excreted as glucuronides.

Rats administered ^{14}C-2-hexanone by gavage excreted 44% of the dose in the breath as $^{14}CO_2$ (38%) and 2-hexanone (6%) (DiVincenzo et al., 1977). Forty and 1.4% of the dose was excreted in the urine and feces, respectively. About 14% remained in the carcass 48 hours after dosing.

Humans ingesting 0.1 mg/kg of (1-^{14}C)-2-hexanone excreted 40% of the dose in the breath as $^{14}CO_2$ and 26% in urine (DiVincenzo et al., 1978). Excretion of 2-hexanone is less complete in humans than in rats.

Acute inhalation exposure of animals or humans to high concentrations of 2-hexanone vapor causes an almost immediate irritation to the eyes and nose (Schrenk et al., 1936). In guinea pigs, exposure to 6500-20,000 ppm resulted in ataxia, narcosis and death (Schrenk et al., 1936). The cause of death in guinea pigs was attributed to narcosis. Congestion of the lungs, kidneys and liver was found during autopsy examination. In humans, exposure to 1000 ppm for a few minutes resulted in moderate ocular and nasal irritation (Schrenk et al., 1936).

Results of subchronic inhalation animal studies indicate that 2-hexanone neurotoxicity is characterized by the development of peripheral neuropathy (Mendell et al., 1974; Spencer et al., 1975; Saida et al., 1976; Johnson et al., 1977). Neuropathological features of peripheral nerve damage include giant axonal swellings and axonal degeneration. Peripheral nerve damage is associated with hindlimb drag and weakness of the forelimbs and hindlimbs in rats, monkeys and cats. Electrodiagnostic studies reveal accompanying abnormalities in EMG and MNCV (Johnson et al., 1977; Duckett et al., 1979).

Behavioral studies revealed alterations in rats exposed to levels associated with histopathological evidence of peripheral neuropathy (Johnson

et al., 1977). Intermittent exposure to 50 ppm, the lowest concentration tested in animal inhalation studies, was associated with decreased MNCV and extensive nerve demyelination in rats (Duckett et al., 1979). Clinical signs of neuropathy have been documented in humans exposed to 2-hexanone in the work environment at concentrations as low as 9.2-36.0 ppm (Allen et al., 1975).

Several oral gavage and drinking water studies indicate that the effects of oral exposure to 2-Hexanone are similar to those associated with inhalation exposure (Krasavage et al., 1979, 1980; Homan and Maronpot, 1978; Abdel-Rahman et al., 1978). Generally, large doses were administered to produce the typical neurological syndrome. In one study, testicular atrophy was observed in rats treated by gavage at 600 mg/kg/day for 10 weeks (Krasavage et al., 1980). The oral studies were not performed at dosages sufficiently low to identify thresholds for neuropathy.

Data were not located regarding the carcinogenicity of 2-hexanone to animals or humans exposed by any route. No data were located regarding the mutagenicity of 2-hexanone in prokaryotic or eukaryotic test systems. In a teratogenicity study using pregnant rats, a decrease in maternal weight gain was observed at 1000 or 2000 ppm 2-hexanone for 6 hours/day throughout gestation (Peters et al., 1981). A reduction in the number and weight of live offspring was detected in rats exposed to 2000 ppm 2-hexanone. Postnatal behavioral changes were observed in both the 1000 and 2000 ppm groups.

These results were corroborated by Tyl et al. (1987) who found a decrease in maternal weights in mice and rats only after exposure to 3000 ppm of 2-hexanone during days 6-15 of gestation. Evidence of developmental toxicity was only observed in the group exposed to 3000 ppm and was limited

to increased incidence of dead fetuses (only seen in mice), reduced fetal body weight per litter, and reductions in skeletal ossification (mice and rats). There was no evidence of a dose-dependent increase in developmental toxicity, nor any evidence of any type of treatment-related effect, at 300 or 1000 ppm in either species.

2-Hexanone was assigned to U.S. EPA Group D: not classifiable as to carcinogenicity to humans because of a lack of cancer data in animals or humans for any route of exposure. Therefore, neither estimates of carcinogenic potency nor RQ derivation based on cancer were possible.

Subchronic inhalation and oral data confirm that peripheral neuropathy is the critical effect of exposure to 2-hexanone, and several studies identify FELs associated with gross impairment of neurological function such as paralysis or hindlimb footdrag. NOAELs for this effect were not identified and studies that may have defined LOAELs were insufficiently reported to serve as the basis for RfD derivation. Therefore, RfD values were not derived for subchronic or chronic inhalation or oral exposure.

An RQ of 100 was derived for 2-hexanone based on neuropathy in rats exposed intermittently to 100 ppm in the air (Johnson et al., 1977, 1979).

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biological oxygen demand
BTU	British thermal unit
CNS	Central nervous system
CS	Composite Score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
ED_{50}	Effective dose to 50% of recipients
EEG	Electroencephalograms
EMG	Electromyography
F344	Fischer 344
FEL	Frank effect level
GI	Gastrointestinal
GMAV	Genus mean acute value
GMCV	Genus mean chronic value
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MNCV	Motor nerve conduction velocities
ppb	Parts per billion
ppm	Parts per million

RfD	Reference dose
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Hexanone is also known by the synonyms butyl methyl ketone, methyl butyl ketone and propyl acetone (Hawley, 1981; Windholz, 1983). The structure, molecular weight, empirical formula and CAS number for 2-hexanone are as follows:

$$CH_3\text{-}C(=O)\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3$$

Molecular weight: 100.16

Empirical formula: $C_6H_{12}O$

CAS Registry number: 591-78-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Hexanone is a colorless liquid that is soluble in alcohol and ether (Windholz, 1983). Selected physical properties are as follows:

Melting point:	-55.8°C	Papa and Sherman, 1981
Boiling point:	127.5°C	Papa and Sherman, 1981
Specific gravity:	0.8125 (20/20°C)	Papa and Sherman, 1981
Vapor pressure: at 25°C	11.6 mm Hg	Engineering Sciences Data Unit, 1975
Water solubility: at 25°C	16,000 ppm	Erichsen, 1952
Log K_{ow}:	1.38	Hansch and Leo, 1985
Flash point:	28°C (open cup)	Papa and Sherman, 1981
Odor threshold (air):	0.28-0.35 mg/m³	Verschueren, 1983
Conversion factors: (air at 20°C)	1 mg/m³=0.24 ppm 1 ppm=4.16 mg/m³	

2-Hexanone is flammable and considered a moderate fire risk (Hawley, 1981).

Ketones such as 2-hexanone undergo addition, redox and condensation reactions forming alcohols, ketals, acids and amines (Papa and Sherman, 1981).

1.3. PRODUCTION DATA

The available production data for 2-hexanone are very limited. The public portion of the U.S. EPA TSCA Production File for 1977 lists the following producers of 2-hexanone (U.S. EPA, 1977):

Polak's Frutal Works (Middleton, NY)
Manufacturer: production range confidential

Tennessee Eastman Company (Kingsport, TN)
Manufacturer: production range of 1-10 million lbs.

Roure Bertrand DuPont, Inc. (Teaneck, NJ)
Importer: production range of <1000 lbs.

The 1988 Directory of Chemical Producers (SRI, 1988) and the U.S. International Trade Commission (USITC, 1988) do not have listings for 2-hexanone, suggesting that it is not currently manufactured on an industrial scale for use as an end-product. This compound may be imported into the United States but current import figures are not available. The 1987 OPD Chemical Buyers Directory lists Chemcentral Corp., Chemical Dynamics Corp., Davos Chemical Corp. and Penta Manufacturing Company as suppliers of 2-hexanone (CMR, 1986).

2-Hexanone can be prepared by reacting 1-hexene with 1,4-benzoquinone (Finley, 1982) or by reacting acetyl chloride with butylmagnesium chloride (Moretti, 1978).

1.4. USE DATA

2-Hexanone is used as a medium-evaporating solvent for nitrocellulose, acrylates, vinyl and alkyd coatings (Papa and Sherman, 1981).

1.5. SUMMARY

2-Hexanone is known by the synonyms butyl methyl ketone, methyl butyl ketone and propyl acetone (Hawley, 1981; Windholz, 1983). It is a colorless

liquid that is soluble in alcohol and ether -and slightly soluble in water (Windholz, 1983). Production data for 2-hexanone are limited. In 1977, the Tennessee Eastman Company manufactured between 1 and 10 million pounds of 2-hexanone (U.S. EPA, 1977). However, the 1988 Directory of Chemical Producers (SRI, 1988) and the USITC (1988) do not have listings for 2-hexanone, suggesting that it is not currently manufactured on an industrial scale in the United States for use as an end-product. Current import figures are not available. 2-Hexanone is used as a medium-evaporating solvent for nitrocellulose, acrylates, vinyl and alkyd coatings (Papa and Sherman, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Based upon its relatively high vapor pressure of 11.6 mm Hg at 25°C (see Section 1.2.), 2-hexanone is expected to exist almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al., 1981). The dominant degradation process in ambient air is probably reaction with sunlight-formed HO radical. Based upon an experimentally determined rate constant of 6.64×10^{-12} cm^3/mol-sec at 23°C (Wallington and Kurylo, 1987) and an average atmospheric HO radical concentration of $5 \times 10^{+5}$ molecules/cm^3, the half-life for this reaction can be estimated to be ~2.4 days.

In terms of environmental contaminants, 2-hexanone has a relatively high water solubility of 16,000 ppm at 25°C (see Section 1.2.), suggesting that physical removal from air by wet deposition (washout by rainfall, dissolution in clouds, etc.) is possible.

2.2. WATER

2.2.1. **Hydrolysis.** Experimental hydrolysis data regarding 2-hexanone were not located. However, ketones are generally resistant to environmental hydrolysis (Harris, 1982); therefore, hydrolysis of 2-hexanone in the aquatic environment is not expected to be important.

2.2.2. **Microbial Degradation.** 2-Hexanone appears to be readily biodegradable based upon results from limited biodegradation screening studies (Babeu and Vaishnav, 1987; Vaishnav et al., 1987; Shelton and Tiedje, 1984). Using an acclimated mixed culture inocula and the standard BOD technique, 2-hexanone was found to have a BOD of 5.22 over a 5-day inoculation period (Babeu and Vaishnav, 1987; Vaishnav et al., 1987). 2-Hexanone was also found to be susceptible to biodegradation under anaerobic conditions. In a study using an anaerobic digester sludge inocula, conversion to >75% of

theoretical methane production was observed during an 8-week incubation period (Shelton and Tiedje, 1984).

2.2.3. Volatilization. Based upon a water solubility of 16,000 ppm and a vapor pressure of 11.6 mm Hg at 25°C (see Section 1.2.), the Henry's Law constant for 2-hexanone can be estimated to be 9.56×10^{-5} atm-m³/mol. A Henry's Law constant of this magnitude indicates that volatilization from environmental waters may have some significance, but is probably not rapid (Thomas, 1982). Using a model river estimation method (Thomas, 1982), the volatilization half-life of 2-hexanone from a river 1 m deep flowing 1 m/sec with a wind velocity of 3 m/sec can be estimated to be ~12 hours. The volatilization half-life from a model environmental pond can be estimated to be ~5.7 days (U.S. EPA, 1986a).

2.2.4. Adsorption. The relatively high water solubility (in comparison with other environmental contaminants) of 2-hexanone suggests that partitioning from the water column to sediment and suspended material should not be significant.

2.2.5. Bioconcentration. Experimental BCFs for 2-hexanone in fish were not located. A BCF of 6.6 can be calculated using a log K_{ow} value of 1.38 (Hansch and Leo, 1985) and the following equation (Bysshe, 1982): log BCF = 0.76 log K_{ow} - 0.23. This calculated BCF value indicates that bioconcentration in aquatic organisms is probably not important.

2.3. SOIL

2.3.1. Microbial Degradation. Data specific to the microbial degradation of 2-hexanone in soil were not located in the literature cited in Appendix A. However, based upon the limited biodegradation screening tests discussed in Section 2.2.2., 2-hexanone may be readily biodegradable in soil.

2.3.2. Adsorption/Leaching. Data specific to the leaching of 2-hexanone in soil were not located in the literature cited in Appendix A. A K_{oc} of

21 can be estimated using a WS of 16,000 ppm and the following equation (Lyman, 1982): log K_{oc} = 3.64-0.55 log WS. This estimated K_{oc} value indicates very high soil mobility (Swann et al., 1983). Although significant leaching is possible, concurrent biodegradation may decrease the potential importance of leaching.

2.3.3. Evaporation. 2-Hexanone can be expected to evaporate relatively rapidly from dry surfaces. It is used as a medium-evaporating solvent for nitrocellulose, acrylates, vinyl and alkyd coatings (Papa and Sherman, 1981). In an evaporation rate test pertinent to solvents used for coatings, 2-hexanone was found to have an evaporation half-life of ~0.9 hours (Park and Hofmann, 1932).

2.4. SUMMARY

2-Hexanone appears to be readily degradable in air, water and soil; therefore, it is not likely to be a persistent environmental contaminant. If released to the atmosphere, 2-hexanone is expected to exist in the vapor phase where it will degrade by reaction with sunlight-formed HO radical. Based upon an experimentally determined rate constant (Wallington and Kurylo, 1987), the half-life for this reaction has been estimated to be ~2.4 days for typical atmospheric conditions. If released to the aquatic environment, 2-hexanone may degrade by biodegradation or be physically removed by volatilization. 2-Hexanone appears to be readily biodegradable based upon results from limited biodegradation screening studies (Babeu and Vaishnav, 1987; Vaishnav et al., 1987; Shelton and Tiedje, 1984). Volatilization half-lives of ~12 hours and 5.7 days can be estimated for a shallow model river and environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986a). If released to soil, 2-hexanone may be susceptible to significant biodegradation based on analogy to the biodegradation screening studies

noted above. Although significant leaching is possible, concurrent biodegradation may decrease the potential importance of leaching. 2-Hexanone is used as a medium-evaporating solvent (Papa and Sherman, 1981) and is expected to undergo significant evaporation from dry surfaces.

3. EXPOSURE

2-Hexanone occurs as a natural product. It has been detected as a volatile component of blue cheese, nectarines, raw chicken breast and poultry manure (Day and Anderson, 1965; Takeoka et al., 1988; Grey and Shrimpton, 1967; Yasuhara, 1987). Hence, the general population may be exposed to 2-hexanone through ingestion of natural and processed foods (in which it occurs naturally) and through inhalation of vapors from commercial coatings containing 2-hexanone as a solvent (HDSB, 1989).

Another possible source of exposure to 2-hexanone is through inhalation during its manufacture, formulation into products and use as an evaporating-medium solvent (HSDB, 1989). The National Occupational Exposure Survey has estimated that 810 U.S. workers are potentially exposed to 2-hexanone based upon surveys conducted between 1981 and 1983 (NIOSH, 1988).

3.1. WATER

2-Hexanone is released to the aquatic environment by various wastewater emissions. It has been found in process water from in situ coal gasification in Gillette, WY (7 ppm), in the aqueous condensate from low-BTU gasification of rosebud coal in Morgantown, WV (202 ppm), and in retort water from in situ oil shale processing at Rock Springs, WY (53 ppm) (HSDB, 1989). It has also been detected in one of 63 wastewater effluents and 22 intake waters from a wide range of chemical manufacturing areas across the United States (HSDB, 1989).

2-Hexanone can also be released to groundwater by leaching from waste sites. Leachates collected from municipal landfills have been found to contain 2-hexanone at levels of 0.148 ppm (Brown and Donnelly, 1988). A

concentration ranging from not detected to 0.38 ppm was identified in a leachate discharge to a ditch near an abandoned landfill in Tybouts Corner, DE (HSDB, 1989). 2-Hexanone was detected at a concentration of 87 ppb in the Biscayne Aquifer (groundwater) in Dade County, FL, in 1982 in the vicinity of an inactive waste drum recycling site (Myers, 1983). An average concentration of 7135 ppb (maximum of 14,000 ppb) was found in two well water samples at an unauthorized hazardous waste disposal site in Lang township, NJ (HSDB, 1989). In 1984, 2-hexanone was detected in 3 of 11 well waters at an abandoned landfill in Tybouts Corner, DE (HSDB, 1989).

3.2. FOOD

2-Hexanone has been qualitatively detected as a volatile component of tree-ripened nectarines (Takeoka et al., 1988), raw chicken breast muscle (Grey and Shrimpton, 1967), mountain cheese (Dumont and Adda, 1978), blue cheese (Day and Anderson, 1965) and roasted filberts (Kinlin et al., 1972).

3.3. INHALATION

2-Hexanone is released to the atmosphere by evaporation from its use as a solvent (Graedel et al., 1986). The primary environmental release of manufactured ketones (such as 2-hexanone) is reported to be evaporation from solvent uses (Lande et al., 1976). 2-Hexanone is also reported to occur in tobacco smoke (Graedel et al., 1986).

2-Hexanone has been qualitatively detected in air samples from the southern Black Forest in southwest Germany and in suburban air samples from Tubingen, West Germany (Juttner, 1986).

3.4. DERMAL

Pertinent monitoring data regarding the dermal exposure of 2-hexanone were not located in the available literature as cited in Appendix A.

3.5. SUMMARY

2-Hexanone can be released to the aquatic environment by wastewater streams generated at various fossil-fuel processing and chemical manufacturing sites and by leaching from hazardous waste sites and municipal landfills (HSDB, 1989; Brown and Donnelly, 1988; Myers, 1983). This compound is released to the atmosphere by evaporation from its use as a solvent (Graedel et al., 1986). 2-Hexanone occurs naturally. It has been detected as a volatile component of blue cheese, nectarines, raw chicken breast and poultry manure (Day and Anderson, 1965; Takeoka et al., 1988; Grey and Shrimpton, 1967; Yasuhara, 1987). The general population may be exposed to 2-hexanone through ingestion of natural and processed foods (in which it occurs naturally) and through inhalation of vapors from commercial coatings containing 2-hexanone as a solvent (HDSB, 1989). Insufficient monitoring data are available to estimate average human daily intakes of 2-hexanone through food, inhalation or drinking water.

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. Geiger et al. (1986) assessed the acute toxicity of 2-hexanone to the fathead minnow, Pimephales promelas, under flowthrough conditions at 25°C. Minnows used in the test were 26-37 days old. Concentrations of 2-hexanone in test solutions were analytically verified. Investigators reported a 96-hour LC_{50} and EC_{50} of 428 mg/ℓ. Confidence limits to this estimate could not be calculated.

Elliott and McElwee (1988) assessed the anaesthetic action of 2-hexanone in the scud, Gammarus. Test organisms were transferred in groups of six to 400-2000 mℓ of test solution. Their responses were observed until a steady state was achieved. The endpoint used to determine the ED_{50} was the loss of an escape response when organisms experienced a mechanical stimulus delivered by hand to either lateral surface. The investigators reported an ED_{50} of 420 mg/ℓ (4.23 mmol/ℓ).

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Pertinent data regarding the effects of chronic exposure of aquatic fauna to 2-hexanone were not located in the available literature cited in Appendix A.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- Experimentally generated BCFs for 2-hexanone in fish were not located in the available literature cited in appendix A. A BCF of 6.6 was calculated using the log K_{ow} value of 1.38 (see Chapter 2) and the following equation (Lyman et al., 1982): log BCF = 0.76 log K_{ow} - 0.23. This BCF indicates that bioconcentration in fish is not significant.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Pertinent data regarding the toxic effects of exposure of aquatic flora to 2-hexanone were not located in the available literature cited in Appendix A.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of 2-hexanone in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. Vaishnav (1986) manometrically assessed the ability of 2-hexanone to inhibit the biodegradation of 2-hexanone by acclimated mixed microbial cultures. Assays were conducted on a Warburg apparatus at 30°C over a 75-minute exposure period. The EC_{50}, the concentration of 2-hexanone that would reduce the maximum observed biodegradation rate by 50%, was 5510 mg/ℓ (0.055 mol/ℓ).

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Gupta and Mohla (1986) assessed the efficacy of 2-hexanone as a bee repellent. The number of bees in the control and test area of an olfactometer were counted at 1-minute intervals for 5 minutes before application of 2-hexanone at 0.0625 and 0.5 g/ℓ. These levels repelled 64.1 and 81.8% of the bees in the test area versus control. Subsequently, Gupta (1987) assessed the efficacy of 2-hexanone as a repellent for the bee, Apis florea. Average repellency ranged from 64.0% at 62.5 mg/ℓ to 82.6% at 4000 mg/ℓ.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to 2-hexanone were not located in the available literature cited in Appendix A.

4.3. FIELD STUDIES

Pertinent data regarding the effects of 2-hexanone on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. AQUATIC RISK ASSESSMENT

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to 2-hexanone precluded the development of a freshwater criterion (Figure 4-1). Development of a freshwater criterion requires the results of acute assays with a salmonid fish species, a nonsalmonid fish or amphibian, planktonic and benthic crustaceans, an insect, a nonarthropod and nonchordate species and an insect or species from a phylum not previously represented. The development of a freshwater criterion also requires data from chronic toxicity tests with two species of fauna and one species of algae or vascular plant and at least one bioconcentration study.

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to 2-hexanone precludes the development of a saltwater criterion. Development of a saltwater criterion will require the generation of data in all of the required categories.

4.5. SUMMARY

The 96-hour LC_{50} and EC_{50} for the fathead minnow, Pimephales promelas, exposed to 2-hexanone under flowthrough conditions was 428 mg/ℓ (Geiger et al., 1986). The ED_{50} for scud, Gammarus, measured as the loss of an escape response when organisms experienced a mechanical stimulus delivered by hand to either lateral surface when exposed to 2-hexanone was 420 mg/ℓ.

The EC_{50} for mixed microbial cultures, measured as the concentration of 2-hexanone that would reduce the maximum observed biodegradation rate by 50%, was 5510 mg/ℓ (0.055 M) (Vaishnav, 1986). Tests assessing the efficacy of 2-hexanone as a repellent for the bee, Apis florea, revealed that bees exposed to concentrations of 62.5 and 4000 mg/ℓ of 2-hexanone resulted in 64.0 and 82.6% repelled, respectively (Gupta and Mohla, 1986; Gupta, 1987).

Family	TEST TYPE		
	GMAV[a]	GMCV[a]	BCF[a]
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	428b	NA	NA
#3 Chordate (fish or amphibian)	NA	NA	NA
#4 Crustacean (planktonic)	NA	NA	NA
#5 Crustacean (benthic)	NA	NA	NA
#6 Insectan	NA	NA	NA
#7 non-Arthropod/-Chordate	NA	NA	NA
#8 New Insectan or phylum representative	NA	NA	NA
#9 algae	XXXXXXXXXXX XXXXXXXXXXX	NA	NA
#10 Vascular plant	XXXXXXXXXXX XXXXXXXXXXX	NA	NA

[a]NA=Not Available, [b]LC_{50} and EC_{50} in mg/L for the fathead minnow, Pimephales promelas

FIGURE 4-1

Organization Chart for Listing GMAVs, GMCVs and BCFs Required to Derive Numerical Water Quality Criteria to Protect Freshwater Aquatic Life from Exposure to 2-Hexanone

Source: U.S. EPA/OWRS, 1986

5. PHARMACOKINETICS

5.1. ABSORPTION

2-Hexanone is absorbed readily by the lungs, by the GI tract and through the skin in humans and animals. A study in which three healthy male humans were exposed for 4 hours to 100 ppm 2-hexanone or for 7.5 hours to 10 or 50 ppm 2-hexanone indicated, by the difference between concentrations in inhaled and exhaled air, that 75-92% of the inhaled 2-hexanone is absorbed by the respiratory mucosa and lungs (DiVincenzo et al., 1978). Exposure to 10 and 50 ppm for 7.5 hours resulted in 2-hexanone concentrations of 1.4 and 9.3 ppm in expired air, respectively. An average 2-hexanone breath concentration of 22 ppm was achieved following exposure to 100 ppm for 4 hours.

Steady state appears to have been achieved within the first hour. A serum concentration of 1.2 µg/mℓ 2-hexanone was obtained following a 4-hour exposure to 100 ppm. 2-Hexanone was not detectable in the serum after exposure to 10 or 50 ppm. In similar experiments, DiVincenzo et al. (1978) determined that ~65-68% of 2-hexanone vapor was absorbed by the lungs of four young male beagle dogs that were exposed to 50 or 100 ppm 2-hexanone for 6 hours. Steady state appears to have been reached within the first 2 hours of exposure.

DiVincenzo et al. (1977) examined the absorption of 2-hexanone following a single gavage dose of 20 or 200 mg/kg ^{14}C-labeled 2-hexanone in corn oil to young adult male CD rats. 2-Hexanone was absorbed rapidly from the GI tract. Serum 2-hexanone concentration peaked at 38 µg/mℓ within 2 hours of treatment at 200 mg/kg. Of the administered dose of radioactivity, 38-42% was excreted as CO_2, while 2.2-6% was excreted unchanged in expired air. Over a 48-hour period, 35-40% was excreted in urine, and 0.8-1.4% was recovered in feces. From 13.6-17.6% was retained in the body, primarily in

the blood and liver. Total recovery ranged from 97-99% of the administered dose of radioactivity.

Humans also absorb 2-hexanone from the GI tract readily. Two male humans that were given a single oral dose of 0.1 mg/kg ^{14}C-2-hexanone eliminated 29.0-50% of the radioactivity in the breath as $^{14}CO_2$. Expiration of $^{14}CO_2$ reached a peak 4 hours after treatment: Urinary excretion accounted for 25.0-27.6% of the radio-activity. Overall recovery of ^{14}C was 65.8% (DiVincenzo et al., 1978).

The skin is also an effective route of absorption for 2-hexanone in humans. On the basis of excretion data, an absorption rate of 4.8-8.0 $\mu g/min^{-1}cm^{-2}$ has been estimated in humans (DiVincenzo et al., 1978). The average amount of ^{14}C-2-hexanone absorbed through the human skin was 21.4 mg. In male beagle dogs exposed dermally to ^{14}C-2-hexanone, excretion data indicated that the rate of dermal absorption plateaued at <20 minutes, then rose markedly over the next 40 minutes. The 8-hour cumulative excretion accounted for 16.8% of a dose of unspecified magnitude (DiVincenzo et al., 1978).

5.2. DISTRIBUTION

Forty-eight hours after rats were orally administered (1-^{14}C)-2-hexanone (200 mg/kg) the highest concentrations of radioactivity were found in the liver and blood (DiVincenzo et al., 1977). Without providing data, the investigators also stated that distribution of radioactivity was widespread. DiVincenzo et al. (1976) determined a serum half-life of 2-hexanone in guinea pigs to be 78 minutes following intraperitoneal administration of 450 mg/kg 2-hexanone in corn oil. The clearance time of 2-hexanone in the serum was 6 hours. The amount of 2-hexanone equivalents in the blood compartment at 1 hour after dosing was 1.4% of the administered dose, indicating extensive distribution.

Abdel-Rahman et al. (1976) determined a peak blood level of 650 µg/mℓ, achieved within 30 minutes, in adult male Wistar rats treated intraperitoneally with ~460 mg/kg 2-hexanone. The half-life for the rapid initial phase of elimination from blood was 10 minutes, followed by a slower phase of elimination with a 7-hour half-life. A similar serum elimination time of 6 hours for 2-hexanone was determined in rats after oral administration of 200 mg/kg (DiVincenzo et al., 1977), although the peak serum concentration was only 38 µg/mℓ.

DiVincenzo et al. (1977) studied the subcellular distribution of radioactivity in the liver, kidney and brain of rats ≤24 hours after oral treatment with 200 mg/kg of (1-^{14}C)-2-hexanone. Tissue fractions examined included the acid-soluble fraction, DNA, RNA, crude lipid fraction and original homogenate. Subcellular distributions of radioactivity in liver, kidney and brain were similar among the tissues. Radioactive incorporation into lipids and protein reached a peak at 8 hours and remained unchanged or decreased at 24 hours.

5.3. METABOLISM

The metabolism of (1-^{14}C)-2-hexanone has been studied following gavage administration of a 20 or 200 mg/kg dose to rats (DiVincenzo al. 1977). Thirty-eight percent of the administered dose was identified as $^{14}CO_2$ in the breath. Radioactive metabolites of 2-hexanone in the serum included 2-hexanol, 5-hydroxy-2-hexanone and 2,5-hexanedione. Metabolites detected in the urine included 2-hexanol, 5-hydroxy-2-hexanone, 2,5-hexanedione, 2,5-dimethylfuran, γ-valerolactone, norleucine and urea.

DiVincenzo et al. (1978) exposed three male volunteers to 2-hexanone for 4 hours (100 ppm) or 7.5 hours (10 or 50 ppm). Exposure to 100 ppm for 4 hours produced an average 2-hexanone concentration in the expired air of 22

ppm; exposures to 10 and 50 ppm for 7.5 hours produced mean breath concentrations of 1.4 and 9.3 ppm, respectively. 2,5-Hexanedione, a neurotoxic and testicular toxic metabolite, was still detected in the serum after exposure to 50 and 100 ppm of 2-hexanone up to 3 hours after cessaton of the exposure.

The metabolism of 2-hexanone in guinea pigs following a single intraperitoneal injection of 450 mg/kg 2-hexanone was investigated by DiVincenzo et al. (1976). The principal serum metabolite of 2-hexanone was 2,5-hexanedione. 5-Hydroxy-2-hexanone and 2-hexanol were also identified in the serum. Couri et al. (1978) detected 2-hexanol and 2,5-hexanedione in the blood and urine of guinea pigs treated with 114 mg/kg 2-hexanone by the intraperitoneal route. Abdel-Rahman et al. (1976) detected 2-hexanol and 2,5-hexanedione in the blood of rats and guinea pigs following intraperitoneal injection of 2-hexanone. Rats and guinea pigs were administered ~213 and 356 mg/kg 2-hexanone, respectively. Abdel-Rahman et al. (1976) were unable to detect 2,5-hexanedione in the blood of rats exposed continuously by inhalation to 400 ppm 2-hexanone for $\leq$60 days.

There is some evidence for the involvement of hepatic cytochrome P-450 in the ω-1 oxidation of 2-hexanone to 5-hydroxy-2-hexanone and 2,5-hexanedione (Couri et al., 1978; DiVincenzo et al., 1977). DiVincenzo et al. (1977) reported that pretreatment of rats with 35 mg/kg SKF 525A, a mixed-function oxidase inhibitor, markedly increased the respiratory excretion of $^{14}CO_2$ and decreased urinary radioactivity (DiVincenzo et al., 1977).

Figure 5-1 depicts a proposed metabolic scheme for 2-hexanone based upon the studies of DiVincenzo et al. (1977, 1978). 2-Hexanone can undergo metabolism by several pathways, such as reduction, α-oxidation, ω-1 oxidation, decarboxylation and transamination. One step of the metabolism of 2-hexanone involves the reduction of the carbonyl group to the secondary

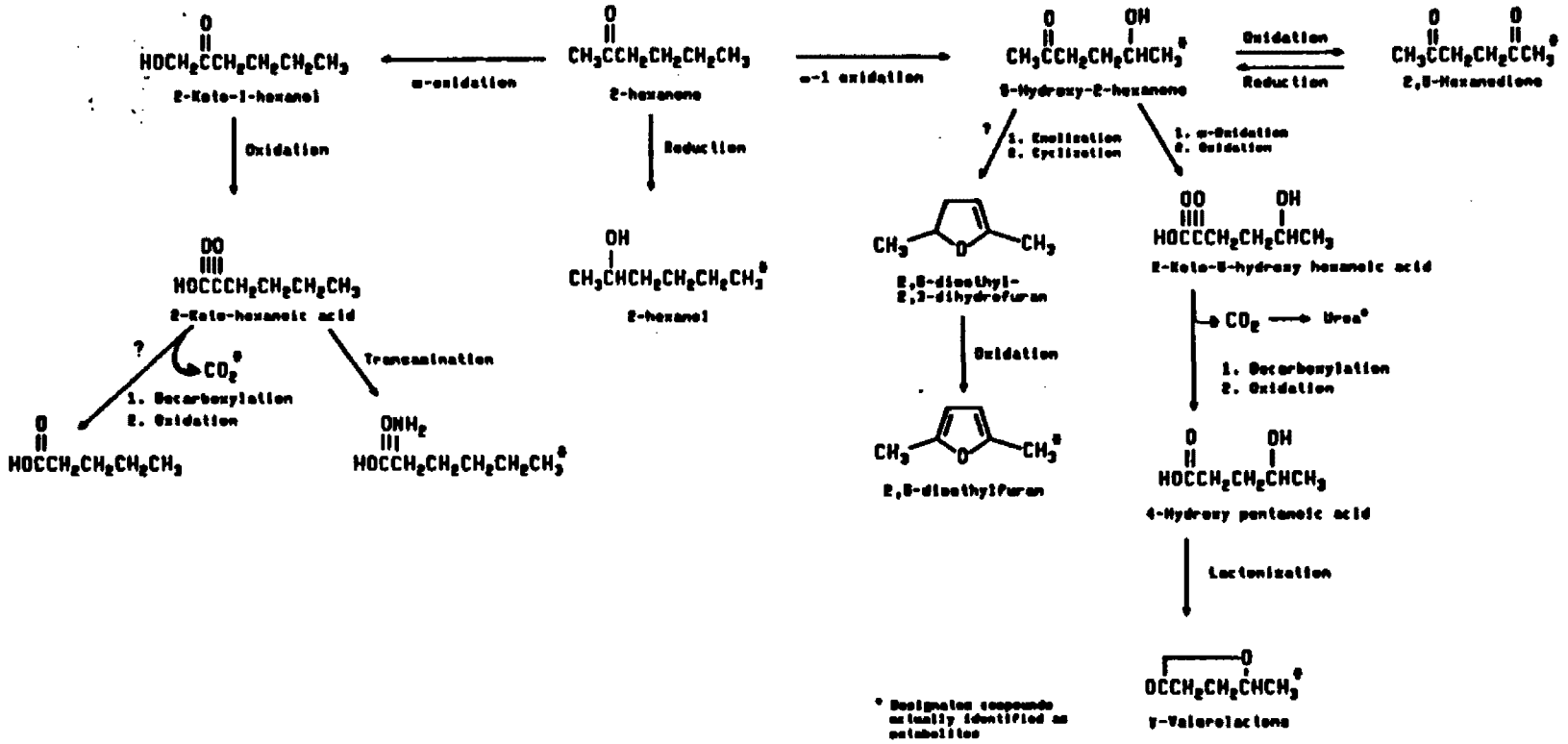

FIGURE 5-1

Proposed Pathway for the Metabolism of [1^{14}-C]2-Hexanone

Source: Divincenzo et al., 1977

alcohol 2-hexanol. Another involves the oxidation of the ω-1 carbon atom to form the hydroxyketone, 5-hydroxy-2-hexanone. The hydroxyketone is further oxidized to 2,5-hexanedione. Presumably, the expired $^{14}CO_2$ is produced by the α-oxidation of (1-^{14}C)-2-hexanone to α-ketohexanoate, followed by decarboxylation to $^{14}CO_2$ and 1-Pentanal. Alternatively, $^{14}CO_2$ could be formed from the decarboxylation of 2-keto-5-hydroxy hexanoic acid that results from the oxidation of 5-hydroxy-2-hexanone. ^{14}C-Norleucine can be formed from the α-oxidation of (1-^{14}C)-2-hexanone to α-ketohexanoate, which in turn can undergo transamination. As shown in Figure 5-1, the formation of 2,5-hexanedione, γ-valerolactone and the cyclic metabolite, 2,5-dimethylfuran, proceeds from 5-hyroxy-2-hexanone. 2-Hexanol, 5-hydroxy-2-hexanone and 2,5-dimethylfuran are excreted as glucuronides. Metabolism of 2-hexanone to CO_2 is considered a detoxification pathway, whereas the formation of 2,5-hexanedione, a neurotoxic metabolite, is regarded as metabolic activation.

5.4. EXCRETION

Two volunteers who ingested a single oral dose of 0.1 mg/kg ^{14}C-2-hexanone excreted ~40% of the total dose as $^{14}CO_2$ in the breath (DiVincenzo et al., 1978). Levels of respiratory $^{14}CO_2$ peaked within 4 hours and declined gradually within 3-5 days. Excretion of radioactivity in the urine within 8 days accounted for 26.3% of the administered dose. The feces were not assayed for radioactivity. The overall recovery of ^{14}C was 65.8%.

Rats administered ^{14}C-2-hexanone (20 or 200 mg/kg) by gavage excreted 44% of the dose in their breath as $^{14}CO_2$ (38%) and as unchanged 2-hexanone (6%) (DiVincenzo et al., 1977). Urinary excretion of radioactivity represented 40% of the total dose, while elimination of radioactivity in

the feces was 1.4%. After 48 hours, 14% of the dose remained in the body, whereas 8% remained after 6 days. The experiments performed with humans and rats indicate that radioactivity derived from (1-^{14}C)-2-hexanone was excreted more completely by rats (DiVincenzo et al., 1977, 1978).

5.5. SUMMARY

2-Hexanone is absorbed readily from the GI tract, the respiratory tract, and through the skin. Respiratory uptake data in humans (DiVincenzo et al., 1978) indicate that ~75-92% of inhaled 2-hexanone was absorbed by the lungs and respiratory mucosa following exposure to 10-100 ppm for 4-7.5 hours. Approximately 65-68% of 2-hexanone vapor was absorbed by the lungs of dogs exposed to 50 or 100 ppm 2-hexanone for 6 hours. A dermal absorption rate of 4.8-8.0 $\mu g/min^{-1}cm^{-2}$ was determined in humans from the analysis of excretion data (DiVincenzo et al., 1978).

Although distribution of radioactivity from administered (1-^{14}C)-2-hexanone appears to be rapid and widespread, the highest concentrations of radioactivity following oral administration of 2-hexanone in rats were detected in the liver and blood (DiVincenzo et al., 1977).

Following absorption, 2-hexanone undergoes extensive metabolism and elimination. 2-Hexanone is metabolized by hepatic cytochrome P-450 oxidases with the formation of 5-hydroxy-2-hexanone and 2,5-hexanedione (DiVincenzo et al., 1977; Couri et al., 1978). The metabolism of 2-hexanone to 2,5-hexanedione is regarded as metabolic activation, since there is evidence that 2,5-hexanone mediates the neurotoxicity and testicular toxicity of 2-hexanone. 2,5-Hexanediol is formed by the oxidation of 2-hexanol or by the reduction of 5-hydroxy-2-hexanone. Urinary metabolites of 2-hexanone include 2,5-hexanedione, 2-hexanol, 5-hydroxy-2-hexanone and 2,5-dimethylfuran. 2-Hexanol, 5-hydroxy-2-hexanone, and 2,5-dimethylfuran are excreted as glucuronides.

Rats administered ^{14}C-2-hexanone by gavage excreted 44% of the dose in the breath as $^{14}CO_2$ (38%) and 2-hexanone (6%) (DiVincenzo et al., 1977). Forty and 1.4% of the dose was excreted in the urine and feces, respectively. About 14% remained in the carcass 48 hours after dosing.

Humans ingesting 0.1 mg/kg of (1-^{14}C)-2-hexanone excreted 40% of the dose in the breath as $^{14}CO_2$ and 26% in urine (DiVincenzo et al., 1978). Excretion of 2-hexanone is less complete in humans than in rats.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Spencer et al. (1975) exposed six rats to 1300 ppm 2-hexanone, 6 hours/day, 5 days/week for 4 months. Three rats served as controls. During each exposure, the rats exhibited slight narcosis after 4 hours and loss of coordination after 5.5 hours. Exposed rats had a slow progressive weight loss beginning on the 73rd day of exposure. In addition, exposed rats developed a pronounced hindlimb foot drop between the third and fourth months of exposure to 2-hexanone. Some of the exposed rats also exhibited severe proximal hindlimb and forelimb weakness. Peripheral and central nerve fiber damage was prominent. Pathological alterations in peripheral nerves included axonal dilatation along with fiber swelling and paranodal myelin retraction. Axonal degeneration was observed in peripheral nerves, spinal cord, medulla oblongata and cerebellum.

Mendell et al. (1974) evaluated the neurotoxic effects of 2-hexanone in rats and cats. Four Sprague-Dawley rats and four domestic cats were exposed to 2-hexanone, 24 hours/day, 7 days/week for 12 weeks. The initial exposure concentration of 600 ppm was adjusted to 400 ppm at an unspecified time because of weight loss in the exposed groups. Pair-fed animals were used as controls. Routine recording of the electrical activity of various muscles including supraspinatus, triceps, extensor carpi, deep digital flexors, paraspinals, quadriceps, hamstring, gastrocnemius and anterior tibialis were performed by EMG. Signs of clinical weakness, such as dragging of hind limbs, developed in exposed animals at 5-8 weeks (for cats) and 11-12 weeks (for rats). Pathological changes in exposed cats, as revealed by EMG findings, consisted of abnormal insertional activity with positive waves,

which developed between 4 and 6 weeks. Fibrillation potentials in muscles at rest were evident between 9 and 10 weeks. A decrease in the velocity of ulnar nerve conduction occurred in cats between 7 and 9 weeks. All muscles examined displayed these EMG changes. Histopathological examination of the sciatic nerves of exposed animals revealed a peripheral neuropathy characterized by focal swelling of the axon along the nerve fiber, accumulation of neurofilaments and thinning of the myelin sheath in the area of axonal swelling and denudation of myelin in both species.

Signs of neuropathy were reported in groups of 12 rats that were exposed continuously to 2-hexanone at 225 ppm for $\leq$66 days or 400 ppm for $\leq$42 days (Saida et al., 1976). Paralysis developed in the rats exposed to 225 ppm at 66 days and in the rats exposed to 400 ppm at 42 days. Serial sacrifice of the rats for histopathological examination of the sciatic nerves revealed that the earliest changes were the accumulation of neurofilaments, followed by axonal swelling and thinning of the myelin sheath and eventual denudation of myelin.

Muscular weakness and sciatic nerve axonal hypertrophy and degeneration, along with myelin breakdown, were observed in nine rats exposed to 200 ppm 2-hexanone, 8 hours/day, 5 days/week for 6 weeks (Duckett et al., 1974). There were four control rats; sex and strain of the rats and method of measurement of exposure levels were not specified. Duckett et al. (1979) reported an effect of 2-hexanone on sciatic nerve conduction velocity in rats, but at a lower concentration. Forty Wistar white rats were exposed to 50 ppm 2-hexanone for 6 months, 8 hours/day, 5 days/week. A decrease in MNCV in the exposed group was observed. Demyelination of the sciatic nerve was present in 32 of the rats, with 2 of the rats also showing evidence of axonal hypertrophy. According to the authors, the observed extensive

demyelination and minimal axonal changes differ from the observations in previous studies of 2-hexanone-induced neuropathy, which have described axonal pathology as the primary lesion with secondary demyelination.

Johnson et al. (1977) investigated the behavioral and neurological effects of 2-hexanone in rats and monkeys. Groups of 10 albino male rats (Sprague-Dawley) and 8 male monkeys (Macaca fascicularis) were exposed to 2-hexanone at 0, 100 or 1000 ppm for 6 hours/day, 5 days/week. Exposure to 1000 ppm was terminated after 25 weeks, when rats and monkeys demonstrated a bilateral neuropathy manifested as a hindlimb drag. Five of the monkeys were subjected to histopathological examination; three were maintained without subsequent exposure to evaluate the reversibility of the effects. Exposure to 100 ppm was terminated after 29 weeks (rats) or 41 weeks (monkeys), when (presumably) the exposed animals exhibited hindlimb drag.

The animals were subjected to several neurological tests, including recording of maximum MNCV of the sciatic, tibial and ulnar nerves, absolute refractory period of these nerves and muscle action potentials. In addition, EEG and visual evoked potentials were recorded from monkeys, and exposed rats (number in each group not specified) were trained so that the investigators could evaluate the effects of 2-hexanone on operant behavior. Behavior after exposure was compared with pretreatment performance.

A statistically significant ($p<0.05$) concentration- and duration-related depression in MNCV were observed in the sciatic, tibial and ulnar nerves of the exposed monkeys and rats. Also, a reduction in evoked muscle action potentials was reported that reached statistical significance in monkeys at 1000 ppm. Rats exposed to 1000 ppm 2-hexanone displayed impaired operant behavior after 2 weeks. Exposure to 100 ppm 2-hexanone had no effect on operant behavior. An increase in the latency of visual evoked potentials was observed in monkeys following 4 months of exposure to 1000 ppm. There

were no effects on absolute refractory time or EEG. The three monkeys exposed previously to 1000 ppm and then maintained to evaluate recovery exhibited no change in sciatic, tibial MNCV during the first 2 months of the recovery period. Complete recovery of the MNCV occurred over the next 4-month period. Animals (species not stated) exposed to 100 ppm exhibited complete recovery of sciatictibial MNCV in 2 months.

Johnson et al. (1979) reported no effect on gross histopathology in liver, spleen, kidney, adrenal or brain tissues in rats or monkeys exposed to 100 or 1000 ppm for 29 or 41 weeks, respectively. Neuropathological examination of the sciatic nerves from rats and monkeys in the 1000 ppm group showed axonal swelling and myelin thinning. Monkeys exposed to 100 ppm showed an increase in nonmyelinated fibers and endoneural collagen, and a decrease in large fibers.

Five male rats exposed by inhalation to 700 ppm 2-hexanone, 72 hours/ week for 11 weeks showed a reduction in weight gain with depletion of adipose tissue and marked atrophy of the hindlimb musculature (Katz et al., 1980). The rats were exposed for two 20-hour periods and two 16-hour periods during the work week. A control group of five rats was exposed to conditioned air. A significant depression in testicular weight was also observed. Clinical chemistry and hematological values were similar among exposed and control rats except for a significant reduction in the total white blood cell counts of treated rats. Signs of neuropathy were also evident as early as the second week of exposure.

Allen et al. (1975) reported an outbreak of neuropathy in humans exposed to 2-hexanone in an occupational setting. Screening procedures (questionnaire, EMG and nerve conduction tests) identified 86 individuals affected with toxic neuropathy among 1157 workers in a fabric-printing plant in which 2-hexanone was used as a solvent. The clinical syndrome was presented as an

insidious distal motor and sensory disorder with minimal reflex loss. Severely affected individuals also exhibited moderate weight loss. The time course of the outbreak correlated with exposure to 2-hexanone, which had been introduced as a new solvent ~7 months earlier. Further investigation revealed that symptoms developed in one worker after only 5 weeks of exposure. Levels of 2-hexanone associated with the outbreak were determined to be 9.2-36.0 ppm. Several other chemicals were present in "trace" amounts. An investigation of daily work habits of the employees revealed that at least some of the workers were subjected to dermal as well as inhalation exposure. The condition of the workers improved upon elimination of 2-hexanone from the work environment.

6.1.1.2. **CHRONIC** -- Pertinent data regarding the toxicity of 2-hexanone following chronic inhalation exposure in laboratory animals or humans were not located in the available literature cited in Appendix A.

6.1.2. Oral Exposure.

6.1.2.1. **SUBCHRONIC** -- Krasavage et al. (1980) investigated the neurotoxic effects of 2-hexanone (~96% purity) in rats after oral administration. Groups of five adult male COBS rats were administered 0 or 600 mg/kg/day neat 2-hexanone by gavage, 5 days/week until pronounced hind-limb drag was observed. Controls were treated on the same schedule with distilled water. Exposure to 2-hexanone was terminated at 10 weeks because of hindlimb drag. Treated rats had reduced food consumption and reduced body weights compared with controls. Histopathological examination revealed giant axonal neuropathy and testicular atrophy.

Homan and Maronpot (1978) reported that 1000 mg/kg/day of 2-hexanone administered to female Wistar rats in their drinking water for 120 days produced muscle weakness and atrophy and peripheral neuropathy. Other

effects included a reduction in both food and water consumption, decreased rate of body weight gain and increased relative kidney weight.

Abdel-Rahman et. al. (1978) examined the effects of 2-hexanone, administered in drinking water, on water consumption, body weight, pupillomotor activity and locomotor activity in guinea pigs. Histopathological examination was not performed. Groups of five English short hair guinea pigs (sex not reported) were administered 2-hexanone in their drinking water at concentrations of 0.1 or 0.25% for 24 weeks. On the basis of an average daily water consumption of 60 mℓ/day and an average body weight of ~0.6 kg after 8 weeks of treatment (body weights were recorded only through the 8th week of treatment), dosages were ~0, 100 and 250 mg/kg/day. Exposed guinea pigs gained weight more rapidly than controls. Locomotor activity, measured only in guinea pigs at the 0.25% level at 8 weeks, was marginally ($p<0.1$) depressed. Pupillary response was decreased to about the same degree in both exposed groups (0.57 mm at 0.1% and 0.6 mm at 0.25%) compared with controls (1.06 mm). Statistical analysis was not performed. To determine the time to onset, the experiment was repeated at the 0.25% level. Decreased pupillary response was observed within the first week of treatment, compared with controls ($p<0.001$), and decreased progressively throughout the 5 weeks of exposure.

A significant reduction in body weight was observed at all dose levels in male rats that were administered 2-hexanone at concentrations of 0.25, 0.5 and 1.0% in the drinking water for 10-13 months (Krasavage et al., 1979). Assuming an average water intake of 0.14 ℓ/kg/day (U.S. EPA, 1986b), the estimated doses are 350, 700 and 1400 mg/kg/day. The authors reported that morphologic changes observed were similar for those of other reports for this chemical.

6.1.2.2. CHRONIC -- Perinent data regarding the toxicity of 2-hexanone following chronic oral exposure were not located in the available literature cited in Appendix A.

6.1.3. Other Relevant Information. Table 6-1 summarizes the results of the acute lethal exposure to 2-hexanone derived from several animal studies. The oral LD_{50} data indicate that rats and mice are nearly equally sensitive to the acute toxicity of 2-hexanone. The dermal LD_{50} data in rabbits suggest that absorption occurs readily by this route.

Schrenk et al. (1936) examined the acute toxicity of 2-hexanone in guinea pigs following exposure to 2-hexanone vapors at concentrations of 0, 1000, 2300, 6500 or 20000 ppm for $\leq$810 minutes. Nasal irritation occurred within the first minute at all levels of exposure. Eye irritation and lacrimation occurred in all groups within 30 minutes. Incoordination was observed at 5-10 minutes at 20,000 ppm, at 20-30 minutes at 6500 ppm and at 90 minutes at 2300 ppm. Narcosis was observed at 20-30 minutes at 2000 ppm and at 90-120 minutes at 6500 ppm. Dyspnea and gasping were noted at 30-60 minutes at 20,000 ppm and at 240-540 minutes at 6500 ppm. Guinea pigs exhibited narcosis after a 20- to 30-minute exposure to 20,000 ppm vapor.

Lethality occurred at 20,000 ppm at 70 minutes and at 6500 ppm at 540 minutes. Apparently, death was due to narcosis rather than to irritation of the lungs. Autopsy examinination of animals that died during exposure revealed slight congestion of the brain, and moderately marked congestion of the lungs, kidneys and liver. No gross pathology was observed in guinea pigs exposed to 2200 ppm vapor for 90 and 270 minutes, or to 1000 ppm for 810 minutes. Volunteers exposed for a few minutes to 1000 ppm 2-hexanone vapor experienced moderate eye and nasal irritation.

Specht et al. (1940) reported acute toxicity of 2-hexanone in guinea pigs. Ten female guinea pigs exposed by inhalation to 6000 ppm for $\leq$525

TABLE 6-1

Acute Lethal Toxicity of 2-Hexanone

Species	Route	Result	Reference
Rat	oral	LD_{50} 2590 mg/kg	NIOSH, 1989
Mouse	oral	LD_{50} 2430 mg/kg	NIOSH, 1989
Rat	inhalation	8000 ppm lethal to 6/6 in 4 hours	NIOSH, 1989
Rat	inhalation	4000 ppm lethal to 0/6 in 4 hours	Smyth et al., 1954
Guinea pig	inhalation	6000 ppm lethal to all animals by 9 hours	Specht et al., 1940
Rabbit	dermal	LD_{50} 4800 mg/kg	NIOSH, 1989

minutes displayed symptoms of narcosis, depressed body temperature, reduced heart and respiratory rate, loss of corneal reflex and eye and upper respiratory tract irritation. Seven guinea pigs died between 100 and 525 minutes. Spencer and Schaumberg (1977) observed clinical, gross and microscopic evidence of neuropathy in 11 young, adult Sprague-Dawley rats exposed continuously by inhalation to 600 ppm 2-hexanone for 3.5 days. Sixteen age- and weight-matched rats served as controls.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of 2-hexanone following inhalation exposure were not located in the available literature cited in Appendix A.

6.2.2. Oral. Pertinent data regarding the carcinogenicity of 2-hexanone following oral exposure were not located in the available literature cited in Appendix A.

6.2.3. Other Relevant Information. Other relevant information regarding the carcinogenicity of 2-hexanone were not located in the available literature cited in Appendix A.

6.3. MUTAGENICITY

Pertinent data regarding the mutagenicity of 2-hexanone were not located in the available literature cited in Appendix A.

6.4. DEVELOPMENTAL TOXICITY

There are relatively few data regarding the capacity for 2-hexanone to produce developmental toxicity. Peters et al. (1981) examined the effects of 2-hexanone on postnatal development and behavior in rats following chronic inhalation exposure. Groups of 25 pregnant F344 rats were exposed to 500, 1000 or 2000 ppm 2-hexanone for 6 hours/day throughout the 21 days of gestation. Control groups were established for each of the exposed groups. Rats in the 2000 ppm group were pair-fed since exposure at this

concentration was associated with a reduction in maternal food consumption. Behavioral, neurological, liver function, clinical pathological, organ weight and histopathological evaluations of the offspring were performed at various times until the offspring were 20 months old. Behavioral tests included righting reflex, inclined screen performance, food maze behavior, open-field behavior, activity wheel behavior, endurance swim test and avoidance conditioning.

2-Hexanone exposure reduced maternal weight gain by 10 and 14% at the 1000 and 2000 ppm levels, respectively. Exposure to 2000 ppm resulted in muscular incoordination and weakness by exposure day 20. Reduced number and weight of live offspring were reported at 2000 ppm. These effects were not reported in the 500 ppm group, which -- because of problems in the experiment -- was terminated before the offspring were 3 weeks of age. There were no consistent treatment-related alterations in survival, organ weights or histopathological appearance of several major organs and tissues. Organs examined were adrenals, brain, heart, kidney, liver, lung, ovaries, pituitary, pancreas, prostate, seminal vesicles, spleen, testis, thymus, thyroid and uterus. Pentobarbital-induced sleeping time (evaluated only in offspring of the 2000 ppm group) was increased in prenatally exposed males and decreased in prenatally exposed females.

Alterations in several of the behavioral tests (inclined screen, food maze behavior, open field, activity wheel) were detected following exposure to 1000 and 2000 ppm of 2-hexanone. The results of some of the tests suggest that 2-hexanone exposure is associated with hyperactivity in young but not in aged rats. Further, the authors noted that exposure of pregnant rats caused a lifelong dose-dependent reduction in the growth of male and female offspring.

Using inhalation chambers, Tyl et al. (1987) exposed pregnant F344 rats and CD-1 mice to the 2-hexanone vapors. The exposures occurred on gestation days 6 through 15 and at concentrations of 0, 300, 1000 or 3000 ppm. Rats were sacrificed on gestational day 21 and mice on gestational day 18. There was no evidence of a treatment-related effect at 300 or 1000 ppm in either mice or rats.

Rats exposed to 3000 ppm, observed through gestation day 15, demonstrated maternal toxicity (decreased body weight, reduced body weight gain, and decreased food consumption). These effects were directly related to the exposure and returned to normal during the postexposure period (gestation days 15-21). At the time of the scheduled sacrifice, dams exposed to 3000 ppm had a statistically significant increase in relative kidney weight; there were no other treatment-related findings.

Alterations in developmental parameters in rat fetuses that demonstrated statistically significant effects were limited to a reduction in fetal weight and a reduction in skeletal ossification. These effects were only seen in the group exposed to 3000 ppm. There were no statistically significant changes in the external, visceral, skeletal or total malformations in any of the exposed groups relative to the controls.

Similarly, mice were found to have maternal toxicity after exposure to 3000 ppm, specifically, the death of three pregnant dams on gestation day 6. At the time of the scheduled sacrifice, observations of maternal toxicity were limited to dams exposed to 3000 ppm. These animals had statistically significant increases in absolute and relative liver weight; there were no other treatment-related findings.

Relative to the controls, developmental toxicity in mice was limited to groups exposed to 3000 ppm. This included statistically significant increases in the number of dead fetuses, significant reduction in fetal body

weight per litter and reductions in skeletal ossification. As with the exposed rats, there were no statistically significant changes in the external, visceral, skeletal or total malformations in any of the exposed groups relative to the controls.

6.5. OTHER REPRODUCTIVE EFFECTS

As noted in Sections 6.1.1.1. and 6.1.2.1., respectively, following inhalation exposure to the 2-hexanone (700 ppm, 72 hours/week for 11 weeks) Katz et al. (1980) observed a significant depression in testicular weight and Krasavage et al. (1980) found that exposure by gavage (600 mg/kg/day, 5 days/week for up to 11 weeks) produced a testicular atrophy. Similar to the neuropathy, the production of the 2,5-hexanedione metabolite appears to be an integral feature of the biochemical mechanism leading to the effect.

The testicular effects have been evaluated by directly administering the 2,5-hexanedione to test animals. The mechanism of action for the effect appears to be an alteration of the biochemistry (principally lipid metabolism) of the testis (Gillies et al., 1981; Boekelheide, 1987). Another ramification of exposure appears to be attributable to a direct action on the Sertoli cells (Chapin et al., 1982) by inducing a biochemical dysfunction of the systems associated with microtubule assembly (Boekelheide, 1987). Further, this effect is dependent on the dose rate and is independent of the total dose (Boekelheide and Eveleth, 1988). Curiously, this is the direct opposite of the dynamics associated with the 2,5-hexanedione induced injury of the nervous system (Krasavage et al., 1980).

6.6. SUMMARY

Acute inhalation exposure of animals or humans to high concentrations of 2-hexanone vapor causes an almost immediate irritation to the eyes and nose (Schrenk et al., 1936). In guinea pigs, exposure to 6500-20,000 ppm

resulted in ataxia, narcosis and death (Schrenk et al., 1936). The cause of death in guinea pigs was attributed to narcosis. Congestion of the lungs, kidneys and liver was found during autopsy examination. In humans, exposure to 1000 ppm for a few minutes resulted in moderate ocular and nasal irritation (Schrenk et al., 1936).

Results of subchronic inhalation animal studies indicate that 2-hexanone neurotoxicity is characterized by the development of peripheral neuropathy (Mendell et al., 1974; Spencer et al., 1975; Saida et al., 1976; Johnson et al., 1977). Neuropathological features of peripheral nerve damage include giant axonal swellings and axonal degeneration. Peripheral nerve damage is associated with hindlimb drag and weakness of the forelimbs and hindlimbs in rats, monkeys and cats. Electrodiagnostic studies reveal accompanying abnormalities in EMG and MNCV (Johnson et al., 1977; Duckett et al., 1979). A marked depression in testicular weight was noted by one investigator (Katz, 1980).

Behavioral studies revealed alterations in rats exposed to levels associated with histopathological evidence of peripheral neuropathy (Johnson et al., 1977). Intermittent exposure to 50 ppm, the lowest concentration tested in animal inhalation studies, was associated with decreased MNCV and extensive nerve demyelination in rats (Duckett et al., 1979). Clinical signs of neuropathy have been documented in humans exposed to 2-hexanone in the work environment at concentrations as low as 9.2-36.0 ppm (Allen et al., 1975).

Several oral gavage and drinking water studies indicate that the effects of oral exposure to 2-Hexanone are similar to those associated with inhalation exposure (Krasavage et al., 1979, 1980; Homan and Maronpot, 1978; Abdel-Rahman et al., 1978). Generally, large doses were administered to

produce the typical neurological syndrome. In one study, testicular atrophy was observed in rats treated by gavage at 600 mg/kg/day for 10 weeks (Krasavage et al., 1980). The oral studies were not performed at dosages sufficiently low to identify thresholds for neuropathy.

Testicular effects have been studied in greater detail by administering 2,5-hexanedione directly to test animals. Alterations are observed in the biochemistry of lipid metabolism and microtubule assembly (Gillies et al., 1981; Boekelheide, 1987). These effects appear to be dependent on the dose rate and are independent of the total dose (Boekelheide and Eveleth, 1988).

Data were not located regarding the carcinogenicity of 2-hexanone to animals or humans exposed by any route. No data were located regarding the mutagenicity of 2-hexanone in prokaryotic or eukaryotic test systems. In a teratogenicity study in pregnant rats, a decrease in maternal weight gain was observed at 1000 or 2000 ppm 2-hexanone for 6 hours/day throughout gestation (Peters et al., 1981). A reduction in the number and weight of live offspring was detected in rats exposed to 2000 ppm 2-hexanone. Post-natal behavioral changes were observed in both the 1000 and 2000 ppm groups.

These results were corroborated by Tyl et al. (1987) who found a decrease in maternal weights in mice and rats only after exposure to 3000 ppm of 2-hexanone during days 6-15 of gestation. Evidence of developmental toxicity was only observed in the group exposed to 3000 ppm and was limited to increased incidence of dead fetuses (only seen in mice), reduced fetal body weight per litter, and reductions in skeletal ossification (mice and rats). There was no evidence of a dose-dependent increase in developmental toxicity, at 300 or 1000 ppm in either species.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The current ACGIH (1988) recommended TWA-TLV for 2-hexanone is 5 ppm (20 mg/m^3). ACGIH (1988) does not recommend a STEL for 2-hexanone. These recommendations are based largely on the inhalation and oral studies in animals that associate peripheral neuropathy with exposure to the compound (ACGIH, 1986). OSHA (1989) lists transitional limits for 2-hexanone of 100 ppm (410 mg/m^3) and final rule limits of 5 ppm (20 mg/m^3), identical to the ACGIH (1988) recommendation.

7.2. AQUATIC

Guidelines and standards to protect aquatic life from exposure to 2-hexanone were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of 2-hexanone to animals or humans following inhalation exposure were not located in the available literature cited in Appendix A.

8.1.2. Oral. Pertinent data regarding the carcinogenicity of 2-hexanone to animals or humans following oral exposure were not located in the available literature cited in Appendix A.

8.1.3. Other Routes. Pertinent data regarding the carcinogenicity of 2-hexanone following other routes of exposure were not located in the available literature cited in Appendix A.

8.1.4. Weight of Evidence. The lack of data regarding the carcinogenicity of 2-hexanone in humans or animals is the basis for assigning 2-hexanone to U.S. EPA Group D -- not classifiable as to human carcinogenicity, using the U.S. EPA (1986c) classification scheme.

8.1.5. Quantitative Risk Estimates. The lack of positive carcinogenicity data for 2-hexanone precludes quantitative estimation of carcinogenic risk.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURE (SUBCHRONIC) -- Several studies have demonstrated the development of peripheral neuropathy in rats, cats and monkeys following inhalation exposure to 2-hexanone (Mendell et al., 1974; Spencer et al., 1975; Saida et al., 1976; Spencer and Schaumberg, 1977; Johnson et al., 1977, 1979; Duckett et al., 1974, 1979). CNS effects, progressive weight loss and a pronounced hindlimb foot drop were noted in rats (Rec. #3) exposed to 1300 ppm 2-hexanone, 6 hours/day, 5 days/week for 4 months (Spencer et al., 1975). Mendell et al. (1974) reported altered

electrical activity of muscles, hindlimb drag and histopathological evidence of severe neuropathy in cats (Rec. #5) and rats (Rec. #4) exposed continuously to 400 ppm. Saida et al. (1976) reported paralysis in rats exposed continuously to 400 ppm for 42 days or to 225 ppm for 66 days (Rec. #15). Johnson et al. (1977) exposed rats and monkeys 6 hours/day, 5 days/week to 1000 ppm for 25 weeks or to 100 ppm for 29 weeks (rats, Rec. #2) or 41 weeks (monkeys, Rec. #1), when exposures were terminated because hindlimb drag was evident. MNCV in the sciatic, tibial and ulnar nerves were decreased in a generally concentration- and duration-related manner. Exposure to 1000 ppm 6 hours/day 5 days/week for 25 weeks had no effect on the histopathological morphology of liver, spleen, kidney, adrenal or brain tissues in rats or monkeys, indicating that peripheral neuropathy is the critical effect of repeated exposure to lower levels of 2-hexanone. Because gross impairment of neurological function was observed by Spencer et al. (1975) at 1300 ppm, by Mendell et al. (1974) at 400 ppm, by Saida et al. (1976) at 225 and 400 ppm and by Johnson et al. (1977) at 1000 and 100 ppm, these studies define FELs but do not define LOAELs for peripheral neuropathy.

Duckett et al. (1979) reported a reduction in MNCV, along with extensive demyelination of the sciatic nerve, in rats subjected to 50 ppm 2-hexanone 8 hours/day, 5 days/week for 6 months (Rec. #8). The data were available only in an abstract, however, and were reported in insufficient detail to determine whether the observed effects define a FEL or a LOAEL. Therefore, it is inappropriate to use this study as the basis of an RfD.

Allen et al. (1975) reported an outbreak of neuropathy in humans exposed to 2-hexanone in an occupational setting. The clinical symptoms correlated with exposure to 2-hexanone on a time course basis; 2-hexanone was introduced as a new solvent ~7 months before symptoms were reported. Concentrations of 9.2-36.0 ppm were quantified in the workroom atmosphere. However,

it appears that some of the workers also had skin contact with liquid 2-hexanone, so that both dermal and inhalation exposure may have been involved. Trace amounts of other chemicals were also present in the workroom air. These data are not appropriate for deriving an RfD for inhalation exposure because a threshold for neuropathy in humans was not identified, the workers were exposed simultaneously to a number of chemicals and mixed routes of exposure were involved. The data are sufficient, however, to suggest that neuropathy in humans may occur at or below levels associated with neuropathy in laboratory animals.

The available data, therefore, are insufficient for derivation of an RfD for subchronic inhalation exposure to 2-hexanone. It is recommended that a well-designed inhalation study be performed with groups of rats exposed continuously to 2-hexanone at concentrations <50 ppm. Because of the insidious and progressive nature of the neurologic syndrome associated with this chemical, the study duration should be at least 6 months. Several behavioral and neurological variables should be evaluated.

8.2.1.2. CHRONIC EXPOSURE -- No data regarding the chronic inhalation effects of 2-hexanone are available. In the absence of sufficient subchronic data, an RfD cannot be derived for chronic inhalation exposure to 2-hexanone.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURE -- In a 90-day gavage study, 5 rats (Rec. #4) were administered 600 mg/kg/day 2-hexanone, 5 days/week (Krasavage et al., 1980). Peripheral neuropathy, paralysis, decrease in weight gain and testicular atrophy were observed. Because paralysis represents a gross impairment of neurologic function, the 600 mg/kg/day dosage is considered a FEL rather than a LOAEL. Homan and Maronpot (1978)

reported that 1000 mg/kg/day of 2-hexanone administered to rats in their drinking water for 120 days produced muscle weakness and atrophy and peripheral neuropathy (Rec. #2). This study was available only as a brief abstract.

Abdel-Rahman et al. (1978) treated groups of five guinea pigs with 2-hexanone in their drinking water at doses of 100 (Rec. #3) and 250 mg/kg/day. Decreased locomotor activity was noted at the 250 mg/kg/day level at 8 weeks. Pupillary response was decreased at both dosage levels. In addition, a significant increase in body weight was observed at both dosages. This study was too limited in scope (histopathological examination was not performed), however, to be considered for RfD derivation.

Krasavage et al. (1979) administered 2-hexanone to rats at doses of 350 mg/kg/day (Rec. #1), 700 mg/kg/day and 1400 mg/kg/day in the drinking water for 10-13 months. A significant reduction in body weight occurred at all dose levels. Typical clincal signs of neuropathy were noted in rats exposed at the two highest doses. All treated groups of rats exhibited morphological signs typical for the compound. This study was available only in an abstract, however, and was too briefly reported to evaluate the effects at the lowest dosage; hence, the study cannot serve as the basis of an RfD.

The available subchronic oral data, while demonstrating that neurological effects are the critical effects of oral exposure to 2-hexanone, are insufficient to serve at the basis for quantitative risk assessment. Oral studies designed to evaluate peripheral neuropathy in rats at dosages $\leq$350 mg/kg/day should be initiated. Because of the insidious and progressive nature of the neurologic syndrome, exposures should continue for at least 6 months.

8.2.2.2. **CHRONIC EXPOSURE** -- Studies of chronic oral exposure to 2-hexanone were not available. In the absence of sufficient subchronic data, an RfD cannot be derived for chronic oral exposure to 2-hexanone.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of 2-hexanone was discussed in Chapter 6 and dose-response data considered for CS derivation are summarized in Table 9-1. Since no chronic toxicity data are available, subchronic data were considered. A finding common to both the inhalation and oral studies [except for the developmental toxicity study by Peters et al., 1981)] is peripheral neuropathy, which was frequently accompanied by muscular weakness, paralysis, hindlimb drag and histopathological evidence of axonal degeneration. The occupational study by Allen et al. (1975), in which neuropathy was reported in workers who experienced both inhalation and dermal exposure, is not included in Table 9-1. In the study by Peters et al. (1981), exposure to 1000 and 2000 ppm of 2-hexanone (6 hours/day through gestation) produced a 10 and 14% weight loss, respectively. In addition, at 1000 ppm there was a decrease in body weights and behavioral effects in male offspring; at 2000 ppm there was a decrease in the number of live pups, a decrease in the body weights of all offspring and behavioral alterations.

Besides typical signs of 2-hexanone-induced neuropathy, Krasavage et al. (1980) found testicular atrophy and a decrease in weight gain in rats administered 600 mg/kg/day 2-hexanone by gavage, 5 days/week for 90 days. In a 24-week drinking water study limited to evaluation of reflexes and behavior in guinea pigs, 100 mg/kg/day resulted in impaired pupillary reflex (Abdel-Rahman et al., 1978).

Table 9-2 presents CSs and RQs derived for the lowest human equivalent dosages associated with each of the effects compiled in Table 9-1. Because of the insidious and progressive nature of the syndrome, neuropathy was assigned an RV_e of 8. The fetotoxic effects reported by Peters et al.

TABLE 9-1

Toxicity Summary for 2-Hexanone

Route	Species/ Strain	Sex	No. at Start	Average Body Weight	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[a] (mg/kg/day)	Response	Reference
Inhalation	rat/NR	NR	6	0.35[b]	air	NR	1300 ppm (5325 mg/m³), 6 hours/day, 5 days/ week for 4 months	606.0[c]	10.4[d]	Hindlimb footdrop, neuropathy	Spencer et al., 1975
Inhalation	rat/Sprague-Dawley	NR	4	0.35[b]	air	NR	400 ppm (1639 mg/m³), 24 hours/day, 7 days/ week for 12 weeks	1044.0[c]	17.9[d]	Hindlimb dragging, neuropathy	Mendell et al., 1974
Inhalation	cat/NR	NR	4	3.0[e]	air	NR	400 ppm (1639 mg/m³), 24 hours/day, 7 days/ week for 12 weeks	656[c]	23.0[d]	Hindlimb dragging, neuropathy	Mendell et al., 1974
Inhalation	rat/NR	NR	9	0.35[b]	air	NR	200 ppm (819 mg/m³), 8 hours/day, 5 days/ week for 6 weeks	124.0[c]	2.12[d]	Muscular weakness, neuropathy	Duckett et al., 1974
Inhalation	rat/Wistar	NR	40	0.35[b]	air	NR	50 ppm (205 mg/m³), 8 hours/day, 5 days/ week for 6 months	31.1[c]	0.53[d]	Decreased nerve conduction, extensive demyelination	Duckett et al., 1979
Inhalation	rat/Sprague-Dawley	NR	12	0.35[b]	air	NR	225 ppm (922 mg/m³), 24 hours/day, 7 days/ week for ≤66 days	587[c]	10.0[d]	Paralysis, neuropathy	Saida et al., 1976
Inhalation	rat/Sprague-Dawley	M	10	0.35	air	≥97%	100 ppm (410 mg/m³), 6 hours/day, 5 days/ week for 29 weeks	46.6[c]	0.92[d]	Neuropathy, hindlimb drag	Johnson et al., 1977, 1979
Inhalation	monkey/ Macaca fascicularis	M	8	4.2	air	≥97%	100 ppm (410 mg/m³), 6 hours/day, 5 days/ week for 41 weeks	49.4[c]	1.93[d]	Neuropathy, hindlimb drag	Johnson et al., 1977, 1979
Inhalation	rat/NR	M	5	0.35[b]	air	96.1%	700 ppm (2868 mg/m³), 72 hours/week for 11 weeks	783.0[c]	13.4[d]	Neuropathy, weight loss, decreased testicular weight	Katz et al., 1980
Inhalation	rat/F344	F	25	0.150	air	NR	1000 ppm (4097 mg/m³), 6 hours/day for 21 consecutive days of gestation	1522.55[c]	196.69	Decreased growth of male offspring	Peters et al., 1981

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Body Weight	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[a] (mg/kg/day)	Response	Reference
Oral/gavage	rat/Sprague-Dawley	M	5	0.35	neat	~96%	600 mg/kg/day, 5 days/ week for 10 weeks	429	7.34[d]	Neuropathy, paralysis, testicular atrophy, decreased weight gain	Krasavage et al., 1980
Oral/drinking water	rat/Wistar	F	NR	0.35[b]	water	NR	1000 mg/kg/day for 120 days in drinking water	1000	17.1[d]	Neuropathy, muscle weakness and atrophy	Homan and Maronpot, 1978
Oral/drinking water	guinea pig/ NR	NR	NR	0.60	water	NR	0.1% in drinking water for 24 weeks (1000 ppm)	333	6.8[d]	Pupillary reflex impairment	Abdel-Rahman et al., 1978
Oral/drinking water	rat/Sprague-Dawley	M	NR	0.35[b]	water	NR	0.25% in drinking water for 10-13 months (2500 ppm)	350	6.0[d]	Neuropathy	Krasavage et al., 1979

[a]Calculated by multiplying the animal transformed dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg)

[b]Reference rat body weight (U.S. EPA, 1980)

[c]Calculated by multiplying the concentration in air by the number of hours/day, number of days/week of study by the animal inhalation rate [0.223 m^3/day for rats (U.S. EPA, 1980), 1.2 m^3/day for cats and 5.4 m^3/day for monkeys (U.S. EPA, 1986b)] dividing by the reference animal body weight, and assuming 100% absorption (DiVincenzo et al., 1978).

[d]An uncertainty factor of 10 was applied to expand from subchronic to chronic exposure.

[e]Reference cat body weight (U.S. EPA, 1986b)

NR = Not reported

TABLE 9-2

Composite Scores for 2-Hexanone

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Inhalation	rat	46.6	55.83	2.8	Neuropathy and hindlimb drag	8	23.04	100	Johnson et al., 1977, 1979
Inhalation	rat	1522.55	13,741.96	1	Decreased growth of male offspring	8	8	1000	Peters et al., 1981
Oral	rat	429	514	1.4	Testicular atrophy, neuropathy, decreased body weight	8	11.2	1000	Krasavage et al., 1980
Oral	guinea pig	333	477.5	1.4	Impaired pupillary reflex	7	10.4	1000	Abdel-Rahman et al., 1978

(1981) were also assigned an RV_e of 8. The impaired pupillary reflex reported in guinea pigs (Abdel-Rahman et al., 1978) was assigned an RV_e of 7. The highest CS calculated, 22.4 associated with neuropathy in rats exposed by inhalation (Johnson et al., 1977, 1979), was selected as most stringently representing the chronic toxicity of 2-hexanone. The CS of 22.4 and its corresponding RQ of 100 are presented in Table 9-3.

9.2. BASED ON CARCINOGENICITY

No data were located regarding the carcinogenicity of 2-hexanone in humans or animals, and the compound was placed in EPA Group D. Hazard ranking based on carcinogenicity is not possible for EPA Group D substances; therefore, an RQ based on carcinogenicity cannot be assigned.

TABLE 9-3

2-HEXANONE

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Species:	rat
Dose*:	23.3
Duration:	29 weeks
Effect:	peripheral neuropathy and hindlimb drag
RV_d:	3.3
RV_e:	8
CS:	26.7
RQ:	100
Reference:	Johnson et al., 1977, 1979

*Equivalent human dose

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in May, 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyons, France.

Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA 600/6-84-010. NTIS PB84-243906. SRI International, Menlo Park, CA.

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Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

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USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Summary Table for 2-Hexanone

	Species	Exposure	Effect	RfD or q_1*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ND	ID
Chronic	ID	ID	ID	ND	ID
Carcinogenicity	ID	ID	ID	ND	ID
Oral Exposure					
Subchronic	ID	ID	ID	ND	ID
Chronic	ID	ID	ID	ND	ID
Carcinogenicity	ID	ID	ID	ND	ID
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		100			Johnson et al., 1977, 1979
Based on Carcinogenicity:		ID			ID

ID = Insufficient data; ND = not derived

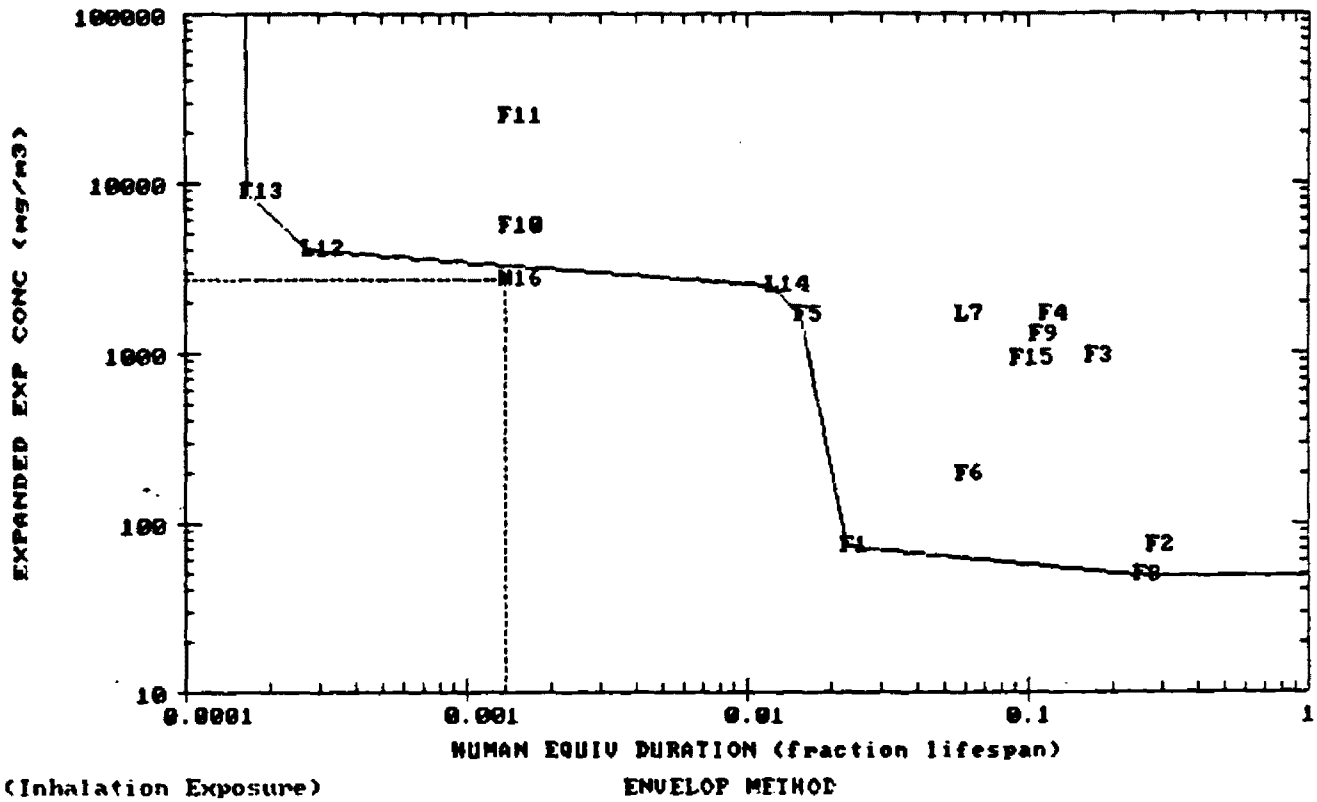
APPENDIX C

DOSE/DURATION RESPONSE GRAPHS FOR EXPOSURE TO 2-HEXANONE

C.1. DISCUSSION

Dose/duration-response graphs for inhalation and oral exposure to 2-hexanone generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1988) developed under contract to ECAO-Cincinnati are presented in Figures C-1, C-2 and C-3. Data used to generate these graphs are presented in Section C.2. In the generation of these figures, all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. For inhalation exposure the ordinate expresses concentration in either of two ways. In Figure C-1 the experimental concentration expressed as mg/m^3 was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week) and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In Figure C-2, the expanded experimental concentration was multiplied by the cube root of the ratio of the animal: human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975) to estimate an equivalent human or scaled concentration [scaled conc (mg/m^3). For oral exposure the ordinate expresses dosage as human equivalent dose. The animal dosage in mg/kg/day is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate (Mantel and Schneiderman, 1975). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human.]

The boundary for adverse effects (solid line) is drawn by identifying the lowest adverse effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this point an infinite

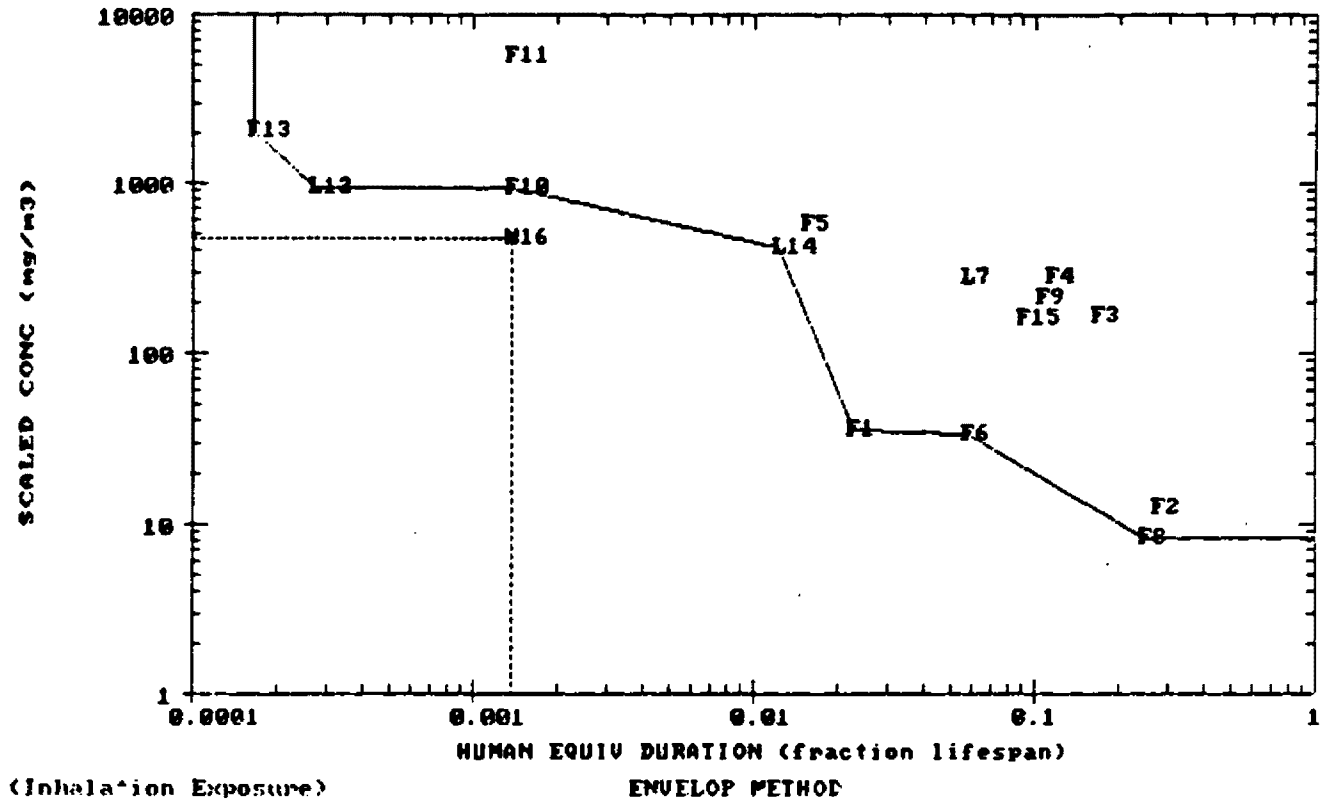


Key: F = FEL
L = LOAEL
N = NOAEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-1

Dose/Duration Response Graph for Inhalation Exposure to 2-Hexanone, Expanded Experimental Concentration

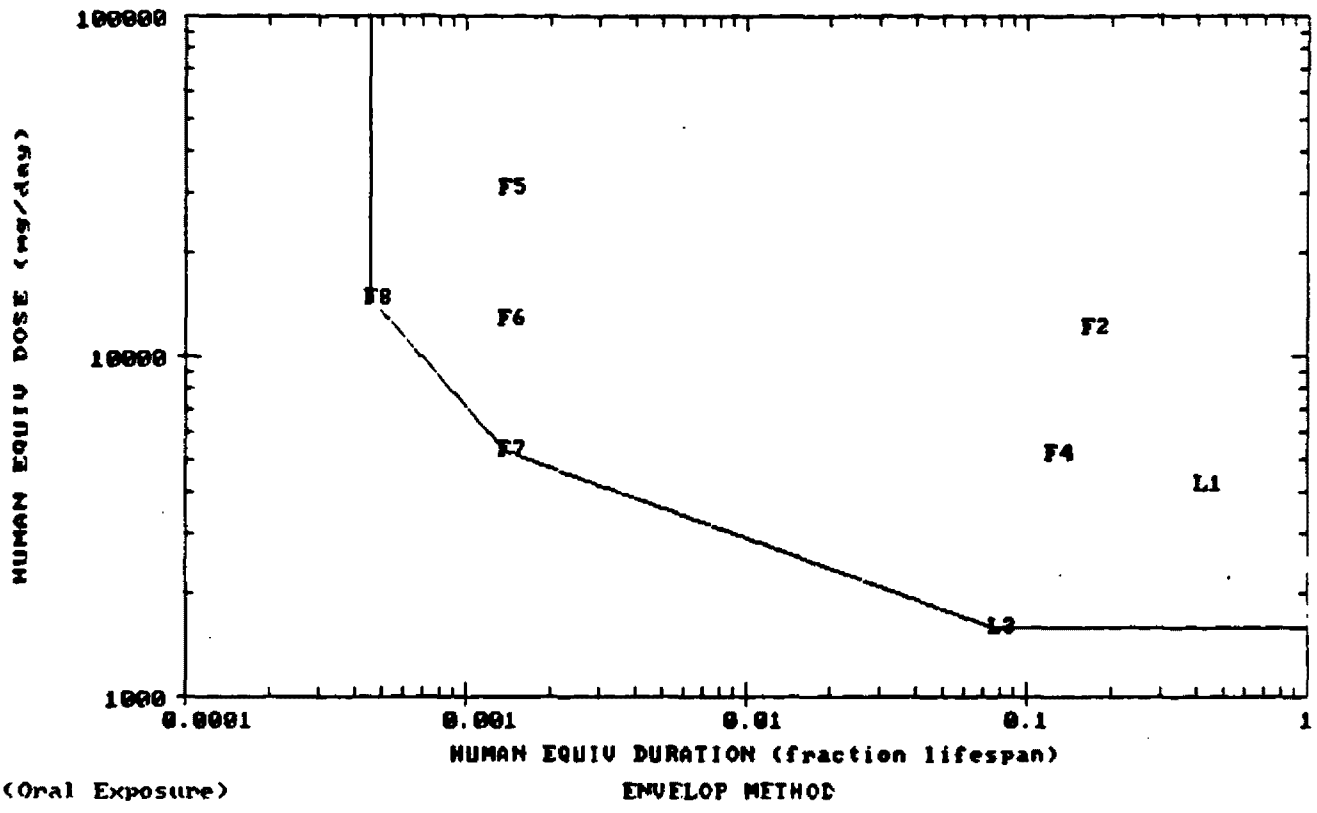


Key: F = FEL
L = LOAEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-2

Dose/Duration Response Graph for Inhalation Exposure to 2-Hexanone, Scaled Concentration



Key: F = FEL
L = LOAEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-3

Dose/Duration Response Graph for Inhalation Exposure to 2-Hexanone, Envelope Method

line is extended upward parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point a line is extended to the right parallel to the duration axis. The region of adverse effects lies above the adverse effects boundary.

Using the envelope method, the boundary for no-adverse effects (dashed line) is drawn by identifying the highest no adverse effects dose or concentration. From this point a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next lower or equal no-adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line is dropped parallel to the dose or concentration axis to the duration axis. The no-adverse effects region lies below the no-adverse effects boundary. At either ends of the graph between the Adverse Effects and no-adverse effects boundaries are regions of ambiguity. The area (if any) resulting from intersection of the adverse effects and no-adverse effects boundaries is defined as the region of contradiction.

In the censored data method, all no adverse effect points located in the region of contradiction are dropped from consideration and the no-adverse effect boundary is redrawn so that it does not intersect the adverse effects boundary and no region of contradiction is generated. This method results in the most conservative definition of the no-adverse effects region.

Figures C-1 and C-2 present dose/duration-response graphs for inhalation exposure drawn by the envelope method. Figure C-1 presents results using an expanded experimental concentration. The adverse effects boundary is

defined by several experimental points (Recs. #1, 5, 8) associated with peripheral neuropathy (Johnson et al., 1977, 1979; Mendell et al., 1974; Duckett et al., 1979) in the rat, cat and monkey. The adverse effects boundary also includes studies that reported eye and upper respiratory tract irritation (Rec. #12) and mortality (Rec. #13) in acutely exposed guinea pigs (Schrenk et al., 1936; Specht et al., 1940). The only nonadverse effect point (Rec. #16) was a NOEL for lethality in rats (Smyth et al., 1954).

Figure C-2 presents the graph redrawn so that the data are expressed as scaled concentration. Scaling excluded from the adverse effects boundary a FEL for peripheral neuropathy in cats (Rec. #5) but included a FEL (Rec. #6) for neuropathy in rats (Duckett et al., 1974) and a FEL (Rec. #10) for mortality in rats (Smyth et al., 1954).

Figure C-3 presents the dose/duration-response graph generated by the envelope method for oral exposure. The adverse effects boundary is defined by lethality data in guinea pigs (Rec. #8) and mice (Rec. #7) and a LOAEL (Rec. #3) for impaired pupillary response in guinea pigs (NIOSH, 1979; Abdel-Rahman et al., 1978). There were no nonadverse points to plot; therefore, only an adverse effects region and a region of ambiguity are defined.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

Inhalation Exposure

Chemical Name: 2-Hexanone
CAS Number: 591-78-6
Document Title: Health and Environmental Effects Document on 2-Hexanone
Document Number: pending
Document Date: pending
Document Type: HEED

RECORD #1:

Species:	Monkeys	Dose:	73.0
Sex:	Male	Duration Exposure:	41.0 weeks
Effect:	FEL	Duration Observation:	41.0 weeks
Route:	Inhalation		

Number Exposed:	8
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 100 ppm (410 mg/m³), range: 100 or 1000 ppm 6 hours/day, 5 days/week; decreased motor nerve conduction velocity, hindlimb drag.

Citation: Johnson et al., 1977, 1979

RECORD #2:

Species:	Rats	Dose:	73.0
Sex:	Male	Duration Exposure:	29.0 weeks
Effect:	FEL	Duration Observation:	29.0 weeks
Route:	Inhalation		

Number Exposed:	10
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 100 ppm (410 mg/m³), range: 100 or 1000 ppm 6 hours/day, 5 days/week; decreased motor nerve conduction velocity, hindlimb drag.

Citation: Johnson et al., 1977, 1979

RECORD #3:

Species:	Rats	Dose:	951.0
Sex:	NR	Duration Exposure:	4.0 months
Effect:	FEL	Duration Observation:	4.0 months
Route:	Inhalation		

Number Exposed:	6	6	6
Number Responses:	NR	NR	NR
Type of Effect:	NEURP	NEURP	WGTDC
Site of Effect:	PNS	CNS	BODY
Severity Effect:	8	8	3

Comment: 1300 ppm (5325 mg/m³) 6 hours/day, 5 days/week; hindlimb drop, PNS and CNS nerve fiber damage, loss of body weight.

Citation: Spencer et al., 1975

RECORD #4:

Species:	Rats	Dose:	1639.0
Sex:	NR	Duration Exposure:	12.0 weeks
Effect:	FEL	Duration Observation:	12.0 weeks
Route:	Inhalation		

Number Exposed:	4
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 400 ppm (1639 mg/m^3) continuous; hindlimb drag and giant axonal swelling.

Citation: Mendell et al., 1974

RECORD #5:

Species:	Cats	Dose:	1639.0
Sex:	NR	Duration Exposure:	12.0 weeks
Effect:	FEL	Duration Observation:	12.0 weeks
Route:	Inhalation		

Number Exposed:	4
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 400 ppm (1639 mg/m^3); hindlimb drag, axonal swelling, altered EMG.

Citation: Mendell et al., 1974

RECORD #6:

Species:	Rats	Dose:	195.0
Sex:	NR	Duration Exposure:	6.0 weeks
Effect:	FEL	Duration Observation:	6.0 weeks
Route:	Inhalation		

Number Exposed:	9
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 200 ppm (819 mg/m^3) 8 hours/day, 5 days/week; peripheral neuropathy (hindlimb drag), axonal degeneration.

Citation: Duckett et al., 1974

RECORD #7:

Species:	Rats	Dose:	1639.0
Sex:	NR	Duration Exposure:	6.0 weeks
Effect:	LOAEL	Duration Observation:	6.0 weeks
Route:	Inhalation		

Number Exposed:	12
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	7

Comment: 400 ppm (1639 mg/m³) continuous; paralysis, axonal degeneration, demyelination.

Citation: Saida et al., 1976

RECORD #8:

Species:	Rats	Dose:	49.0
Sex:	NR	Duration Exposure:	6.0 months
Effect:	FEL	Duration Observation:	6.0 months
Route:	Inhalation		

Number Exposed:	40
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 50 ppm (205 mg/m³) 8 hours/day, 5 days/week; decreased motor nerve conduction velocity, 32/40 rats had demyelination of sciatic nerve, 2/40 had axonal degeneration.

Citation: Duckett et al., 1979

RECORD #9:

Species:	Rats	Dose:	1229.0
Sex:	Male	Duration Exposure:	11.0 weeks
Effect:	FEL	Duration Observation:	11.0 weeks
Route:	Inhalation		

Number Exposed:	15	15	15
Number Responses:	NR	NR	NR
Type of Effect:	NEURP	WGTDC	WGTDC
Site of Effect:	PNS	TESTE	BODY
Severity Effect:	8	4	4

Comment: 700 ppm (2868 mg/m³) 72 hours/168 hours; decreased body weight gain, depletion of adipose tissue and atrophy of hind-limb musculature. A significant depression in testicular weight was noted.

Citation: Katz et al., 1980

RECORD #10:

Species:	Rats	Dose:	5462.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Inhalation		

Number Exposed:	6
Number Responses:	6
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: 8000 ppm (32,772 mg/m³) for 4 hours; lethal to 6/6.

Citation: Smyth et al., 1954

RECORD #11:

Species:	Guinea pigs	Dose:	24579.0
Sex:	NR	Duration Exposure:	3.0 days
Effect:	FEL	Duration Observation:	3.0 days
Route:	Inhalation		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: 6000 ppm (24579 mg/m³); lethal to all animals by 72 hours of exposure.

Citation: Specht, 1940

RECORD #12:

Species:	Guinea pigs	Dose:	4097.0
Sex:	NR	Duration Exposure:	0.6 days
Effect:	LOAEL	Duration Observation:	0.6 days
Route:	Inhalation		

Number Exposed:	NR	NR
Number Responses:	NR	NR
Type of Effect:	IRRIT	IRRIT
Site of Effect:	EYE	NASAL
Severity Effect:	9	9

Comment: 1000 ppm (4097 mg/m³) for up to 810 minutes (range 1000, 2300, 6500 or 20,000 ppm); nasal and ocular irritation; mortality at 6500 ppm.

Citation: Schrenk et al., 1936

RECORD #13:

Species:	Guinea pigs	Dose:	8909.0
Sex:	NR	Duration Exposure:	0.4 days
Effect:	FEL	Duration Observation:	0.4 days
Route:	Inhalation		

Number Exposed:	10
Number Responses:	7
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: 6000 ppm (24,579 mg/m³) up to 525 minutes.

Citation: Specht et al., 1940

RECORD #14:

Species:	Rats	Dose:	2458.0
Sex:	NR	Duration Exposure:	9.0 days
Effect:	LOAEL	Duration Observation:	9.0 days
Route:	Inhalation		

Number Exposed:	11
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 600 ppm (2458 mg/m³) continuous; neuropathological

Citation: Spencer and Schaumberg, 1977

RECORD #15:

Species:	Rats	Dose:	922.0
Sex:	NR	Duration Exposure:	66.0 days
Effect:	FEL	Duration Observation:	66.0 days
Route:	Inhalation		

Number Exposed:	12
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 225 ppm (922 mg/m³) continuous; paralysis, axonal degeneration, demyelination.

Citation: Saida et al., 1976

RECORD #16:

Species:	Rats	Dose:	2731.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	NOEL	Duration Observation:	1.0 days
Route:	Inhalation		

Number Exposed:	6
Number Responses:	0
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: 4000 ppm (16386 mg/m^3) for 4 hours; no lethality.

Citation: Smyth et al., 1954

Oral Exposure

Chemical Name: 2-Hexanone
CAS Number: 591-78-6
Document Title: Health and Environmental Effects Document on 2-Hexanone
Number: pending
Document Date: pending
Document Type: HEED

RECORD #1:

Species:	Rats	Dose:	350.0
Sex:	Male	Duration Exposure:	10.0 months
Effect:	LOAEL	Duration Observation:	10.0 months
Route:	Water		

Number Exposed:	NR	NR
Number Responses:	NR	NR
Type of Effect:	NEURP	WGTDC
Site of Effect:	PNS	BODY
Severity Effect:	8	3

Comment: 0.25% (range: 0.25, 0.5, 1.0%); 350, 700 and 1400 mg/kg/day. Decreased body weight at all doses. Signs of neuropathy at the two highest dose levels, morphologic changes at all doses.

Citation: Krasavage et al., 1979

RECORD #2:

Species:	Rats	Dose:	1000.0
Sex:	Female	Duration Exposure:	120.0 days
Effect:	FEL	Duration Observation:	120.0 days
Route:	Water		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	NEURP
Site of Effect:	PNS
Severity Effect:	8

Comment: 1000 mg/kg/day; continuous for 120 days; muscle weakness and atrophy, neuropathology.

Citation: Homan and Maronpot (1978)

RECORD #3:

Species:	Guinea pigs	Dose:	100.0
Sex:	NR	Duration Exposure:	24.0 weeks
Effect:	LOAEL	Duration Observation:	24.0 weeks
Route:	Water		

Number Exposed:	5	5
Number Responses:	NR	NR
Type of Effect:	FUNP	WGTIN
Site of Effect:	EYE	BODY
Severity Effect:	7	3

Comment: 0.1% (range: 0.1, 0.25%, doses 100, 250 mg/kg/day) estimated from data provided; impaired pupillary response, altered locomotor activity measured only at 0.25%.

Citation: Abdel-Rahman et al. (1978)

RECORD #4:

Species:	Rats	Dose:	429.0
Sex:	Male	Duration Exposure:	90.0 days
Effect:	FEL	Duration Observation:	90.0 days
Route:	Gavage		

Number Exposed:	5	5	5
Number Responses:	NR	NR	NR
Type of Effect:	NEURP	ATROP	WGTDC
Site of Effect:	PNS	TESTE	BODY
Severity Effect:	8	4	4

Comment: 600 ppm (2458 mg/m^3); 5 days/week; severe hindleg footdrop, paralysis, and decrease in weight gain, and testicular atrophy were reported.

Citation: Krasavage et al., 1980

RECORD #5:

Species:	Rats	Dose:	2590.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	10

Comment: LD_{50} value, details not provided.

Citation: Smyth et al., 1954

RECORD #6:

Species:	Mice	Dose:	2430.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	10

Comment: LD_{50} value, details not provided.

Citation: NIOSH, 1989

RECORD #7:

Species:	Mice	Dose:	1000.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	10

Comment: LD_{LO} value, details not provided.

Citation: NIOSH, 1979

RECORD #8:

Species:	Guinea pigs	Dose:	914.0
Sex:	NR	Duration Exposure:	1.0 days
Effect:	FEL	Duration Observation:	1.0 days
Route:	Oral (NOS)		

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	NR
Severity Effect:	10

Comment: LD_{LO} value, details not provided.

Citation: NIOSH, 1979

NR = Not reported

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 10

SUBJECT: Health and Environmental Effects Document for **2-Hexanone**

FROM: William H. Farland, Ph.D.
Director
Office of Health and Environmental
Assessment (RD-689)

TO: Matthew Straus
Chief, Waste Characterization Branch
Office of Solid Waste (WH-562B)

I am forwarding copies of the Health and Environmental Effects Document for **2-Hexanone** (ECAO-Cin-G068).

The HEEDs support listings under RCRA, as well as provide health-related limits and goals for emergency and remedial actions under CERCLA. These documents represent scientific summaries of the pertinent available data on the environmental fate and mammalian and aquatic toxicity of each chemical at an extramural effort of about $10K. The attached document has been reviewed within OHEA, by staff in OPP and OTS, and by two external scientists.

Should you wish to see any of the files related to the development of the HEEDs, please call Chris DeRosa at FTS: 684-7531.

Attachment

DATE: 6/12/90

ROUTE SLIP

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