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Via Electronic Submission

ExxonMobil Chemical Company
13501 Katy Freeway
Houston, TX 77079-1398
281.870.6113 Telephone
281.588.2522 Facsimile

Susan K. Blevins
Manager
Global Product Stewardship & Regulatory Affairs

ExxonMobil Chemical

September 25, 2008

Administrator
US Environmental Protection Agency
P. O. Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

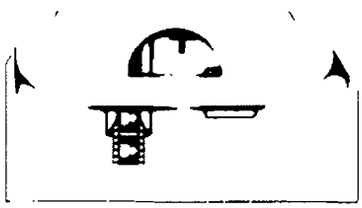
Re: Gases, Petroleum, Extractive, C4-6 Isopentene Rich Reaction Products with Methanol, Ether Fraction, Hydrogenated, Cracked, Isopentene Fraction, CAS No. 108083-44-9 for the HPV Challenge Program (ExxonMobil Chemical Company Registration Number for HPV Challenge Program)

To Whom It May Concern:

ExxonMobil Chemical Company (EMCC) is strongly committed to the chemical industry's Responsible Care® program and takes seriously its commitment to the responsible manufacture, testing, and safe use of its products. Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company committed to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of the Gases, Petroleum, Extractive, C4-6 Isopentene Rich Reaction Products with Methanol, Ether Fraction, Hydrogenated, Cracked, Isopentene Fraction (C4-6 IRRP Fraction), CAS No. 108083-44-9. Although there are no data for the stream, based on its composition, it was determined that data for three constituents can be used to characterize the SIDS endpoints because they comprise a large fraction of the stream and therefore, will define the fate and effects of the stream. The three substances are n-hexane (CAS No. 110-54-3), 2,4-dimethylpentane (CAS No. 108-08-7), and cyclohexane (CAS No. 110-82-7).

With this letter, EMCC submits the test plan and robust study summaries compiled into separate dossiers for the three main constituent substances in the C4-6 IRRP Fraction stream. Sufficient data and information exist to characterize all endpoints in the HPV Program. Therefore, no additional testing is proposed. With the submission of this test plan and dossiers, EMCC has completed its commitment under the HPV Program for the C4-6 IRRP Fraction stream.

Please contact me if you require any further information on the status of EMCC commitments to the U.S. HPV Program.



Sincerely,

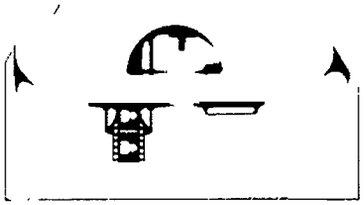
Susan K. Blevins
Global Product Stewardship and Regulatory Affairs Manager
Email: susan.k.blevins@exxonmobil.com

Attachment

Bcc:

EMCC - Houston
R. Brown
C. Fairbrother

EMBSI - Clinton
A. Bachman
R. Davi
T. Parkerton
K. Pavkov
D. Winkelmann



HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN For:

GASES, PETROLEUM, EXTRACTIVE, C4-6 ISOPENTENE RICH REACTION PRODUCTS WITH METHANOL, ETHER FRACTION, HYDROGENATED, CRACKED, ISOPENTENE FRACTION

CAS No. 108083-44-9

Prepared by:

ExxonMobil Chemical Company

September 25, 2008

EXECUTIVE SUMMARY

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company committed to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of Gases, Petroleum, Extractive, C4-6 Isopentene Rich Reaction Products with Methanol, Ether Fraction, Hydrogenated, Cracked, Isopentene Fraction (C4-6 IRRP Fraction), CAS No. 108083-44-9.

Existing data and technical analyses adequately characterize the SIDS endpoints for the C4-6 IRRP Fraction stream and support a screening-level hazard assessment, which informs the public about the SIDS-based hazards of this substance. Sufficient data and information exist to characterize all endpoints in the HPV Program. Therefore, no additional testing is proposed.

The C4-6 IRRP Fraction stream is a complex substance that contains a predominant ether fraction in combination with a larger hydrocarbon fraction. A search for existing studies/information and their review identified adequate data for select constituents to characterize all SIDS endpoints for the stream. Data suggest that the C4-6 IRRP Fraction stream generally presents a low order of hazard for human health and a moderate order of environmental hazard for the predominant groups of constituents as a whole. The predominant constituents of the stream are relatively volatile. Information on their fate in the environment suggests that once in the atmosphere, they will be largely degraded through physical processes at a relatively rapid rate.

TABLE OF CONTENTS

TEST PLAN FOR C4-6 IRRP FRACTION
CAS No. 108083-44-9

I. INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company committed to voluntarily compile a Screening Information Data Set (SIDS) that can be used for an initial hazard assessment of the Gases, Petroleum, Extractive, C4-6 Isopentene Rich Reaction Products with Methanol, Ether Fraction, Hydrogenated, Cracked, Isopentene Fraction (C4-6 IRRP Fraction) stream, CAS No. 108083-44-9. Although there are no data for the stream, based on its composition, it was determined that data for three constituents can be used to characterize the SIDS endpoints because they comprise a large fraction of the stream and therefore, will define the fate and effects of the stream. The three substances are n-hexane (CAS No. 110-54-3), 2,4-dimethylpentane (CAS No. 108-08-7), and cyclohexane (CAS No. 110-82-7).

This assessment includes data for selected physicochemical, environmental fate, and mammalian and environmental effect endpoints identified by the U.S. HPV Program. Procedures to assess the reliability of selected data for inclusion in this test plan were based on guidelines described by Klimisch *et al*. (1997) and identified within the U.S. EPA (1999) document titled *Determining the Adequacy of Existing Data*. The following sections describe the C4-6 IRRP Fraction stream and its manufacturing process, and data used to characterize the various endpoints in the HPV Program. After a review of the existing data, ExxonMobil Chemical Company believes that data needed to adequately assess all SIDS endpoints have been identified and that additional testing is not necessary.

II. CHEMICAL DESCRIPTION, MANUFACTURING PROCESS, AND USE

The C4-6 IRRP Fraction stream is composed of several constituent substances (Table 1). The predominant chemical fractions in this stream are C5 to C8 aliphatic hydrocarbons, which can comprise approximately 90% of the stream. The remaining 10% is made up of olefins (<1%), methoxypentanes or ethers (6%), furans (<1%) and aromatic hydrocarbons (<2%).

In the chemical plant, a mostly C5 stream is brought into the isoamylene unit (IAU) from upstream fractionation. To remove the isoamylene (2-methyl-butene-1 and 2-methyl-butene-2), the stream is run across a catalyst that oxygenates the isoamylene into TAME (tertiary-amyl methyl ether) using methanol. This TAME is then fractionated away from the remaining C5 stream, and decomposed back to isoamylene and methanol and recovered as product. In the first methanol reaction, there are side reactions that occur that cause generation of oxygenates heavier than TAME. These are fractionated off as the IAU light co-product stream. The IAU light co-product stream is then sent back to the refinery for further processing.

Table 1. Percent composition ranges of predominant constituents in the C4-6 IRRP Fraction stream.

C4-6 IRRP Fraction Stream		
Chemical Group	**Constituent**	**Percent Composition**
C5 Aliphatics		
	pentanes	0.6
C6 Aliphatics		
	hexanes	24.5
	hexane	0.1
	cyclohexane	20.8
C7 Aliphatics		
	2,4-dimethylpentane	35.4
	3-methylhexane	0.2
	heptanes	3.1
	heptane	0.1
	dimethylcyclopentane	1.3
	methylcyclohexane	0.3
C8 Aliphatics		
	octanes +	3.6
C6 Olefins		
	2-methyl-1-pentene	0.1
	trans-3-hexene	0.4
	2,3-dimethyl-2-butene	0.3
Methoxypentanes		
	TAME	3.7
	SAME	1.5
Aromatics		
	benzene	1.8
Furans		
	2-methylfuran	1.0

III. TEST PLAN RATIONALE AND DATA SUMMARY

The predominant constituent chemical groups of the C4-6 IRRP Fraction stream include C6 to C7 Aliphatics (9 constituents) at as much as 80% of the stream, these combined constituent fractions, will be responsible for the biological effects exhibited by the stream as a whole. The few remaining chemical groups or individual chemical constituents, that are present at levels between <1% to as much as 4%, will not contribute to a greater adverse biological effect than that resulting from the two major groups. Therefore, data from representative constituents from each of these two groups will be used to characterize the overall biological and fate characteristics of the stream.

The basic strategy of this test plan for characterizing the human health hazards of the C4-6 IRRP Fraction stream is to evaluate data for the major components of the stream. The major chemical components of the stream in the C4-6 IRRP Fraction stream have been tested for human health toxicity endpoints. Available data on these components prove to provide sufficient information to develop scientific judgment-based characterizations of the human health effects of the stream for purposes of satisfying

HPV program requirements. Therefore, no additional human health toxicity testing is proposed. The hazard characterization for the C4-6 IRRP Fraction stream will include the hazards of n-hexane, 2,4-dimethylpentane and cyclohexane.

The environmental fate and effects of the C4-6 IRRP Fraction stream will be characterized by n-hexane, 2,4-dimethylpentane, and cyclohexane. A SIDS dataset exists for cyclohexane. Use of the constituent data to characterize the environmental fate and effects for this stream is supported by calculated results from the ECOSAR computer model (ECOSAR, 2004) using EPI Suite™ (2000) modeled input data. The acute aquatic toxicity data for each of the freshwater fish, daphnid, and green alga endpoints show that the representative constituent fractions are expected to cause effects within a relatively narrow range from 0.2 to 4.5 mg/l.

Additional data for this stream used to characterize the aquatic toxicity endpoints were developed using the ECOSAR computer model (ECOSAR, 2004) provided within EPI Suite™ (2000). This model applies an equation for neutral organics to estimate aquatic toxicity and is therefore considered appropriate to estimate aquatic toxicity for the representative substances. No additional environmental fate and effects testing is proposed.

Data used to characterize the various physicochemical, environmental fate, and environmental and mammalian health endpoints are described below.

A. Physicochemical Data

Calculated and measured n-hexane, 2,4-dimethylpentane, and cyclohexane physicochemical data from the literature are listed in Table 2.

Table 2. Selected physico-chemical properties for three select constituents used to characterize the C4-6 IRRP Fraction stream.

ENDPOINT	Hexane	2,4-Dimethylpentane	Cyclohexane
Melting Point (ºC)	-95.3 (Lide, 2003)	-119.5 (Lide, 2003)	6.6 (Lide, 2003)
Boiling Point (ºC at 1012 hPa)	68.7 (Lide, 2003)	80.4 (Lide, 2003)	80.7 (Lide, 2003)
Density (g/cm^3 at 20°C)	0.659 (Riddick *et al.*, 1986)	0.668 (Riddick *et al.*, 1986)	0.774 (Riddick *et al.*, 1986)
Vapor Pressure (Pa at 25°C)	20,131 (Boublik *et al.*, 1984)	10,586 (Daubert & Danner, 1989)	12,919 (Chao *et al.*, 1983)
Water Solubility (mg/l at 25°C)	9.5 (McAuliffe, 1966)	5.5 (Yalkowsky & Dannenfelser, 1992)	55.0 (McAuliffe, 1966)
Log K_{ow}	3.90 (20°C) (Hansch *et al.*, 1995)	3.63 (25°C) (U.S. EPA, 2000)	3.44 (20°C) (Hansch *et al.*, 1995)

Conclusion

Based on data identified for n-hexane, 2,4-dimethylpentane, and cyclohexane, the C4-6 IRRP Fraction stream will exhibit a melting range between approximately 6.6 to -119°C, a boiling range between approximately 68 to 81°C, a density ranging from approximately 0.6 to 0.8 g/cm^3 at 20°C, and a vapor pressure between approximately 10,500 to 20,100 Pa at 25°C. The predominant constituents of the IRF stream have water solubilities that range from 5.5 to 55 mg/l at 25°C and Log K_{ow} values that range from approximately 3.44 to 3.90.

B. Environmental Fate Data

Biodegradation

Biodegradation of an organic substance by bacteria can provide energy and carbon for microbial growth. This process results in a structural change of an organic substance and can lead to the complete degradation of that substance, producing carbon dioxide and water.

A test procedure used to develop data for substances in this stream was OECD 301F Guideline (Manometric Respirometry Test), which uses a continuously stirred, closed system, measuring oxygen consumption. This method is recommended when assessing the biodegradability of poorly water soluble, volatile constituents like those in this stream. The microbial inocula originated from a domestic wastewater treatment facility and were not acclimated for the test procedures.

Data for heptane was developed following this method and is available to be used as read-across for n-hexane and 2,4-dimethylpentane. Heptane was evaluated in triplicate test systems at a concentration of approximately 45 mg/l, and exhibited 74% biodegradation after 28 days, based on ThOD (ExxonMobil, 1996). Linear and methyl branched C_6 and C_7 hydrocarbon isomers are expected to biodegrade to similar extents because of their similarity in structure and the conservative nature of microbial metabolic processes. In data developed using the Japanese MITI test, for example, n-hexane, at a concentration of 100 mg/l, achieved 100% of its theoretical BOD in 4 weeks using an activated sludge inoculum at 30 mg/l (CITI, 1992).

Additional data for n-heptane was also developed following standard methods for the examination of water and waste water (APHA, 1971). The source of the microbial inoculum used in this study was a silt loam soil and it was not acclimated. The average biodegradation based on theoretical biological oxygen demand for n-heptane on days 2, 5, 10, and 20 was 28, 63, 70, and 70%, respectively (Haines and Alexander, 1974).

Biodegradability of cyclohexane was determined following OECD 301F test guidelines. Cyclohexane was evaluated in triplicate test systems at a concentration of approximately 34 mg/l, and exhibited 77% biodegradation after 28 days, based on ThOD (ExxonMobil, 1995). A lag-phase of about 12 days was observed and the 10-day criteria was fulfilled. The first step of cyclohexane biodegradation is oxidation to cyclohexanol (Verschueren, 1983). Cyclohexanol can clearly be considered as readily biodegradable (CITI, 1992). Overall, it can be concluded that cyclohexane is readily biodegradable in the aquatic environment.

The ether fraction of the stream, which is small (approximately 5%), is not expected to demonstrate significant biodegradation.

Conclusion

Based on data for n-hexane, n-heptane and cyclohexane, the C4-6 IRRP Fraction stream is expected to demonstrate an overall high extent of biodegradation. However, in the environment, the fate of the C4-6 IRRP Fraction stream constituents have the potential to partition primarily to air because the they have relatively high vapor pressures, which suggests that they can volatilize to the air at a rapid rate if released.

Photodegradation – Photolysis

Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric

ozone layer (Harris, 1982a).

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Saturated and unsaturated hydrocarbons like those in the C4-6 IRRP Fraction stream do not absorb light above 290 nm. Therefore, the hydrocarbon constituents of this stream will not exhibit photolytic degradation.

Similarly, the oxygen non-bonding electrons in ethers do not give rise to absorption above 160 nm, which is why pure ether solvents can be used in spectroscopic studies. Consequently, the ether fraction of the C4-6 IRRP Fraction stream is also not subject to photolytic processes in the aqueous environment.

Conclusion

Based on the potential for photolysis of hydrocarbons and ethers, this process is not expected to significantly contribute to the degradation of constituents of the C4-6 IRRP Fraction stream.

Photodegradation – Atmospheric Oxidation

Photodegradation can be measured (US EPA, 1999a) or estimated using an atmospheric oxidation potential (AOP) model accepted by the EPA (US EPA, 1999b). Atmospheric oxidation as a result of hydroxyl radical attack is not direct photochemical degradation, but rather indirect degradation.

The constituents of the C4-6 IRRP Fraction stream have the potential to volatilize to air, based on the vapor pressure of three of the predominant constituents, where they are subject to atmospheric oxidation. In air, C4-6 IRRP Fraction stream constituents can react with photosensitized oxygen in the form of hydroxyl radicals ($^{\bullet}OH$). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (U.S. EPA, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an $^{\bullet}OH$ reaction rate constant and a defined $^{\bullet}OH$ concentration.

n-Hexane has a calculated half-life in air of 23.4 hours or 1.96 days (12-hour day), based on a rate constant of 5.46 x 10^{-12} cm^3/molecule*sec and an $^{\bullet}OH$ concentration of 1.5 x 10^6 $^{\bullet}OH$ /cm^3. 2,4-dimethylpentane has a calculated half-life in air of 18.7 hours or 1.6 days (12-hour day), based on a rate constant of 6.85 x 10^{-12} cm^3/molecule*sec and an $^{\bullet}OH$ concentration of 1.5 x 10^6 $^{\bullet}OH$ /cm^3. Cyclohexane has a calculated half-life in air of 15.1 hours or 1.3 days (12-hour day), based on a rate constant of 8.48 x 10^{-12} cm^3/molecule*sec and an $^{\bullet}OH$ concentration of 1.5 x 10^6 $^{\bullet}OH$ /cm^3. Atkinson (1989) reported experimental $^{\bullet}OH$ rate constants for hexane, 2,4-dimethylpentane, and cyclohexane of 5.61 x 10^{-12} cm^3/molecule*sec, 5.16 x 10^{-12} cm^3/molecule*sec, and 7.49 x 10^{-12} cm^3/molecule*sec, respectively.

Conclusion

Atmospheric oxidation via hydroxyl radical attack can be a significant route of degradation for constituents in the C4-6 IRRP Fraction stream. Based on calculated and experimental values for the three chemicals that are representative of the majority of stream constituents, C4-6 IRRP Fraction stream constituents are expected to have an atmospheric half-life of approximately 2 days or less as a result of indirect photolysis by hydroxyl radical attack.

Stability in Water (Hydrolysis)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Neely, 1985). The lack of a suitable leaving group renders a compound resistant to hydrolysis. Hydrocarbon and ether constituents of the C4-6 IRRP Fraction stream are resistant to hydrolysis because they lack functional groups that are hydrolytically reactive and Harris (1982b) identifies ether groups as generally resistant to hydrolysis.

Conclusion

Hydrolysis will not contribute to the removal from the environment of constituents in the C4-6 IRRP Fraction stream**.**

Chemical Distribution In The Environment (Fugacity Modeling)

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments (*i.e*., air, soil, water, sediment, suspended sediment, and biota). Two widely used fugacity models are the EQC (Equilibrium Criterion) Level I and Level III model (Mackay, 1998a; Mackay, 1998b).

The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as percent of chemical partitioned to 6 compartments (air, soil, water, suspended sediment, sediment, biota) within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical may to partition, based on selected physical parameters. The Level III model uses the same physical parameters as the Level I model, but also requires half-life degradation data for the air, soil, water, and sediment compartments, as well as emission parameters for the air, water, and soil compartments.

Results of the Mackay Level I and Level III environmental distribution models for three representative stream constituents are shown in Tables 3 and 4, respectively.

Table 3. Environmental distribution as calculated by the Mackay (1998a) Level I fugacity model for select constituents used to characterize the C4-6 IRRP Fraction stream.

ENVIRONMENTAL COMPARTMENT	HEXANE DISTRIBUTION* (%)	2,4-DIMETHYLPENTANE DISTRIBUTION** (%)	CYCLOHEXANE DISTRIBUTION† (%)
Air	99.97	99.98	99.91
Water	0.02	<0.01	0.03
Soil	0.01	0.01	0.06
Sediment	<0.01	<0.01	<0.01
Suspended Sediment	<0.01	<0.01	<0.01
Biota	<0.01	<0.01	<0.01

* Distribution is based on the following model input parameters for n-Hexane:

Molecular Weight	86.18
Temperature	25° C
Log K_{ow}	3.90
Water Solubility	9.5 g/m^3
Vapor Pressure	20,131 Pa
Melting Point	-95.3° C

** Distribution is based on the following model input parameters for 2,4-dimethylpentane:

Molecular Weight	100.21
Temperature	25° C
Log K_{ow}	3.63
Water Solubility	5.5 g/m^3
Vapor Pressure	10,586 Pa
Melting Point	-119.5° C

† Distribution is based on the following model input parameters for cyclohexane:

Molecular Weight	84.16
Temperature	25° C
Log K_{ow}	3.44
Water Solubility	55.0 g/m^3
Vapor Pressure	12,919 Pa
Melting Point	6.6° C

Table 4. Environmental distribution as calculated by the Mackay (1998b) Level III fugacity model for select constituents used to characterize the C4-6 IRRP Fraction stream.

ENVIRONMENTAL COMPARTMENT	HEXANE DISTRIBUTION* (%)	2,4-DIMETHYLPENTANE DISTRIBUTION** (%)	CYCLOHEXANE DISTRIBUTION† (%)
Air	21.3	20.0	15.8
Water	63.3	70.6	67.3
Soil	4.3	2.8	12.9
Sediment	11.1	6.6	4.0

* Distribution for n-hexane is based on the following model input parameters, reaction half-life in hours as predicted using EPI SuiteTM (2000), and a model default emission rate of 1000 kg/hr into each of the air, water, and soil compartments:

Molecular Weight	86.18	Reaction half-life (hr):	
Temperature	25° C	Air (gaseous)	23.5
Log K_{ow}	3.90	Water (no susp. part.)	360
Water Solubility	9.5 g/m^3	Bulk Soil	720
Vapor Pressure	20,131 Pa	Bulk Sediment	7,200
Melting Point	-95.3° C		

** Distribution for 2,4-dimethylpentane is based on the following model input parameters, reaction half-life in hours as predicted using EPI SuiteTM (2000), and a model default emission rate of 1000 kg/hr into each of the air, water, and soil compartments:

Molecular Weight	100.21	Reaction half-life (hr):	
Temperature	25° C	Air (gaseous)	18.7
Log K_{ow}	3.63	Water (no susp. part.)	360
Water Solubility	5.5 g/m^3	Bulk Soil	720
Vapor Pressure	10,586 Pa	Bulk Sediment	7,200
Melting Point	-119.5° C		

† Distribution for cyclohexane is based on the following model input parameters, reaction half-life in hours as predicted using EPI SuiteTM (2000), and a model default emission rate of 1000 kg/hr into each of the air, water, and soil compartments:

Molecular Weight	84.16	Reaction half-life (hr):	
Temperature	25° C	Air (gaseous)	15.1
Log K_{ow}	3.44	Water (no susp. part.)	360
Water Solubility	55.0 g/m^3	Bulk Soil	720
Vapor Pressure	12,919 Pa	Bulk Sediment	7,200
Melting Point	6.6° C		

Conclusion

Results of the Mackay Level I model suggest that the predominant constituents of the C4-6 IRRP Fraction stream will partition primarily to the air, >99%. These results are largely explained by their vapor pressures. In comparison, the Level III model suggests that the majority of the C4-6 IRRP Fraction stream will partition to the water compartment, approximately 63 to 71%, followed by the air compartment at

approximately 15 to 21%, and soil and sediment compartments at approximately 3 to 13%. These results are explained by the model parameters, but in particular the default emission rates and degradation half-lives.

C. Aquatic Toxicity Data

Data are available to characterize the potential freshwater fish acute, invertebrate acute, and freshwater alga toxicity of the C4-6 IRRP Fraction stream, based on data for three constituents, n-hexane, 2,4-dimethylpentane, and cyclohexane (Tables 5 through 7). n-Hexane demonstrated a measured 48-hour invertebrate (*Daphnia magna*) EC_{50} toxicity value of 2.1 mg/l (TNO, 1986). A 24-hour LC_{50} toxicity value for goldfish (*Carassius auratus*) of 4 mg/l was also reported by Verschueren (1983) using a modified ASTM D1345 test guideline (Shell Chemie, 1975). Two marine invertebrate species, *Chaetogammarus marinus* and *Mysidopsis bahia*, demonstrated 96-hour LC_{50} toxicity values of 0.4 mg/l (TNO, 1986).

The measured n-hexane data were compared with data calculated (Table 5) by the ECOSAR model (2004). This model is considered appropriate to estimate the aquatic toxicity for this class of chemicals. The calculated data compared favorably with the measured data. The calculated freshwater fish acute, invertebrate acute, and freshwater alga toxicity values ranged between 0.9 to 1.3 mg/l.

Table 5. Measured and calculated aquatic toxicity values for n-Hexane

ENDPOINT	MEASURED VALUE (mg/l)	CALCULATED VALUE* (mg/l)
Fish 96-hr LC_{50}	4 (Verschueren, 1983)	1.0
Daphnid 48-hr EC_{50}	2.1 (TNO, 1986)	1.3
Alga 72-hr EbC_{50}	na	na
Alga 96-hr EC_{50}	na	0.9
Alga 72-hr NOEC	na	na
Alga 96-hr ChV**	na	0.3**
Marine Invert. 96-hr LC_{50}	0.4 (TNO, 1986)	0.1

na - not available

* Model input parameters for ECOSAR (2004):

Log K_{ow}	3.90
Water Solubility	9.5 g/m^3
Melting Point	-95.3° C

** ChV (chronic) value

Measured test data was not available for 2,4-dimethylpentane. Measured data for a suitable analog, n-heptane, was used to compare to modeled 2,4-dimethylpentane data. are available for a freshwater invertebrate and two marine invertebrate species (Table 6). n-Heptane demonstrated a 48-hour invertebrate (*Daphnia magna*) EC_{50} toxicity value of 1.5 mg/L (TNO, 1986). Two marine invertebrate species, *Chaetogammarus marinus* and *Mysidopsis bahia*, demonstrated 96-hour LC_{50} toxicity values of 0.2 and 0.1 mg/L, respectively (TNO, 1986).

The measured n-heptane data were compared with data estimated for 2,4-dimethylpentane (Table 6) by the ECOSAR model (2004). As stated previously, this model is considered appropriate to estimate the aquatic toxicity for this class of chemicals. The calculated data compared favorably with the measured data. The calculated freshwater fish acute, invertebrate acute, and freshwater alga toxicity values ranged between 0.2 to 2.6 mg/l.

Table 6. Measured and calculated aquatic toxicity values for 2,4-Dimethylpentane.

ENDPOINT	MEASURED VALUE (mg/l)	CALCULATED VALUE* (mg/l)
Fish 96-hr LC_{50}	na	2.2
Daphnid 48-hr LC_{50}	1.5 (TNO, 1986)	2.6
Alga 96-hr EC_{50}	na	2.0
Alga 96-hr ChV**	na	0.5
Marine Invert. 96-hr LC_{50}	0.2 (TNO, 1986)	0.2

na - not available

* Model input parameters for ECOSAR (2004):
Log K_{ow} 3.63
Water Solubility 5.5 g/m^3
Melting Point -119.5° C

** ChV - chronic value

Measured cyclohexane data are available for a freshwater fish (Table 7). Cyclohexane demonstrated a 96-hour fathead minnow (*Pimephales promelas*) LC_{50} toxicity value of 4.53 mg/l (Geiger, *et.al*., 1987). The study was performed under flow through conditions and the results are based on measured concentrations. An additional study with Rainbow Trout (*Oncorhynchus mykiss*) reported a 96-hour LL_{50} toxicity value of 3.2 mg/l (EMBSI, 2001a). The study was performed under static, no-headspace conditions, with test solutions renewed at 24-hour intervals. Results are based on nominal concentrations of the test substance. Cyclohexane demonstrated a 48-hour invertebrate (*Daphnia magna*) EC_{50} toxicity value of 0.9 mg/l (TNO, 1986). The lowest green alga (*Selenastrum capricornutum*) 72-hour EC_{50} toxicity value was for biomass and measured 3.4 mg/l (EMBSI, 1998). Two marine invertebrate species, *Chaetogammarus marinus* and *Mysidopsis bahia*, demonstrated 96-hour LC_{50} toxicity values of 2.2 mg/l (TNO, 1986). Many other results for cyclohexane are available in the open literature, but most studies were performed in static open systems without analytical monitoring. Due to the high volatility of cyclohexane, they therefore cannot be considered as valid and are not reported here.

The measured cyclohexane data were compared with data calculated (Table 7) by the ECOSAR model (2004). This model is considered appropriate to estimate the aquatic toxicity for this class of chemicals. The calculated data compared favorably with the measured data. The calculated freshwater fish acute, invertebrate acute, and freshwater alga toxicity values ranged between 2.2 to 3.3 mg/l.

Table 7. Measured and calculated aquatic toxicity values for Cyclohexane.

ENDPOINT	MEASURED VALUE (mg/l)	CALCULATED VALUE* (mg/l)
Fish 96-hr LC_{50}	4.53 (Geiger, *et.al*, 1987)	2.8
Daphnid 48-hr LC_{50}	0.9 (TNO, 1986)	3.3
Alga 96-hr EC_{50}	3.4 (EMBSI, 1998)	2.2
Alga 96-hr ChV**	na	0.5
Marine Invert. 96-hr LC_{50}	2.2 (TNO, 1986)	0.3

na - not available

* Model input parameters for ECOSAR (2004):
Log K_{ow} 3.44
Water Solubility 55.0 g/m^3
Melting Point 6.6° C

** ChV - chronic value

Conclusion

The predominant constituent chemical groups of the C4-6 IRRP Fraction stream include C6 Aliphatics (3 constituents), which when combined can comprise approximately 45% of the stream, and C7 Aliphatics (6 constituents), which when combined can comprise approximately 40% of the stream. These combined constituent fractions, which can comprise up to 85% of the stream, will be responsible for the biological effects exhibited by the stream as a whole. The aquatic toxicity data for constituents from this stream are expected to fall within a relatively narrow range regardless of the isomer or mixture of isomers, because the constituent chemicals are neutral organic hydrocarbons whose toxic mode of action is non-polar narcosis (Ramos *et. al*., 1998). The toxic mechanism of short-term toxicity for these chemicals is disruption of biological membrane function (Van Wezel and Opperhuizen, 1995), and the differences between toxicities (i.e., LC/LL_{50}, EC/EL_{50}) can be explained by the differences between the target tissue-partitioning behavior of individual constituent chemicals (Verbruggen *et. al*., 2000).

The existing fish toxicity database for hydrophobic, neutral organic chemicals, which compose the constituents of this stream, supports a critical body residue (CBR) for these chemicals between approximately 2-8 mmol/kg fish (wet weight) (McCarty *et al*., 1991; McCarty and Mackay, 1993). The CBR is the internal concentration of a toxicant that causes mortality. When normalized to lipid content for most organisms, the CBR is approximately 50 µmol/g of lipid (Di Toro *et al*., 2000). Therefore, only hydrocarbon substances with components of sufficient water solubility, such that their molar sum in solution is high enough to produce a total partitioning to the organism of approximately 50 µmol of hydrocarbon per gram of lipid will demonstrate lethality. The C4-6 IRRP Fraction stream is expected to exhibit acute aquatic toxicity in the range from 0.2 to 4.5 mg/l.

D. Mammalian Toxicity Data

Acute Toxicity

Data are available to characterize the potential acute toxicity of the C4-6 IRRP Fraction stream, based on data for cyclohexane, n-hexane, and n-heptane, a suitable analog of 2,4-dimethylpentane. Rat oral LD_{50} values of > 5,000 mg/kg (Phillips Petroleum Company, 1982a), 29,800 mg/kg (Deichmann and Le Blanc, 1943) and 8,000-39,000 mg/kg (Kimura et al., 1971) have been reported for cyclohexane. The oral rat LD50 values for hexane are 28,720 mg/kg, or 15,840 and 29,700 mg/kg for juvenile and adult rats (HSDB, 2005). The dermal LD_{50} value for cyclohexane was >2000 mg/kg (Phillips Petroleum Company, 1982c). The inhalation rat LC_{50} values (4hr) for cyclohexane, n-hexane and n-heptane were >32.88 mg/L (Phillips Petroleum Company, 1982b), 48,000 ppm, and >29 mg/L (HEDSET, 1982), respectively. A 1 hour acute inhalation exposure of rabbits to cyclohexane vapor produced effects on the central nervous system, with exposure-related observations including convulsions, tremors, hyperactivity, rapid respiration, cyanosis and diarrhea; all the animals exposed to 89.6 mg/L died (Treon *et al*., 1943).

In summary, available acute toxicity data on predominant constituents of the C4-6 IRRP Fraction stream demonstrated a low order of acute oral, dermal, and inhalation toxicity. No further testing is proposed.

Genotoxicity

In vitro

Two constituents of the C4-6 IRRP Fraction stream and n-heptane as an analog for 2,4-dimethylpentane have been evaluated in several *in vitro* genotoxicity assays. Cyclohexane, n-hexane and n-heptane were negative in a bacterial reverse gene mutation assay (Ames test) in *Salmonella typhimurium* and/or *Escherichia coli* with and without S-9 metabolic activation (Mortlemans *et al*., 1986; NTP, 1991; Brooks *et al*., 1982). n-Hexane and n-heptane showed no evidence of genotoxic activity in the mammalian chromosomal aberration assays (Daughtrey *et al*., 1994; NTP, 1991; Brooks *et al*., 1982). n-Heptane was also negative in a mitotic gene conversion assay using *Saccharomyces cerevisiae* JD1 (Brooks *et al*., 1982).

Cyclohexane and n-hexane were negative for forward mutations in the mouse lymphoma L5178Y tk+/- assay (API, 1986; Phillips Petroleum Company, 1982g; Hazleton Laboratories, 1992). Similarly, cyclohexane was negative in an *in vitro* sister chromatid exchange test while n-hexane showed a marginally increased incidence of sister chromatid exchanges in chinese hamster ovary cells in the presence of S9 (not dose dependent) (Phillips Petroleum Company, 1982h; NTP, 1991). n-Hexane induced polyploidy in Chinese hamster lung fibroblast cells (Ishidate *et al.*, 1984).

Cyclohexane was also tested in the unscheduled DNA synthesis test at doses of 10^{-2} – 10^{-3} and 10^{-4} M in DMSO (Perocco *et al*., 1983). Human lymphocytes (+ or – S9 mix) were cultured for 4 hours in the presence or absence of cyclohexane. The effects on the DNA synthesis were measured through cellular [^{3}H]TdR uptake. Cyclohexane induced a marked inhibition of [^{3}H]TdR uptake in the S9 mix-lacking cultures while the corresponding cellular viabilities were unaffected. No effect was seen with metabolic activation. The effects seen without metabolic activation were not dose-dependent; solvent controls and negative controls were highly variable. Decrease of the uptake for

the highest dose was within the values of the controls. No conclusion was drawn from this study. DNA synthesis was inhibited in human lymphocytes in the presence of concentrations of n-hexane from 10^{-4} – 10^{-2} M but only at cytotoxic concentrations (Perocco *et al*., 1983).

Cyclohexane was found to be negative when tested alone in the DNA cell binding assay in the groups treated with liver extract or with lysozyme and liver extract. A positive finding (1.6% only) was found in the group treated with cyclohexane + lysozyme at the highest dose (100 uM). This result is considered doubtful because it is a very slight increase and also because this effect is not found in the group minus cyclohexane + lysozyme + liver extract (Kubinsky *et al.*, 1981).

In vivo

In vivo cyclohexane has been studied in a rodent bone marrow cytogenetic assay (American Petroleum Institute, 1982). Groups of 10 male and female Sprague Dawley rats were exposed by inhalation to atmospheres of 0, 97, 307 and 1,042 ppm for 6 hours per day for 5 days (350-1,050 -3,650 mg/m3). Samples of bone marrow cells were taken for cytogenetic analysis 6 hours after completion of the final dose. A positive control, triethyleneamine, showed a significant increase in structural aberration frequency. For cyclohexane a small but statistically significant increase in numerical aberrations was recorded in low and medium dose females, and pooled data at the low dose groups of both sexes. There was no information on general toxicity; no decrease on mitotic index was seen at all the doses tested. However, the authors of the report concluded that the lack of a dose-related response indicated that these increases were not of biological importance. Moreover, the numerical aberrations parameter had often shown great variation in this laboratory, having no statistical significance even for positive controls (numerical data is not available). It can be considered that cyclohexane does not produce chromosomal aberrations under the conditions of this test.

Test for the genotoxic potential of n-hexane *in vivo* have been predominantly negative. No dominant lethal mutations were induced following n-hexane exposure in CD-1 mice (Mast et al., 1988b; Litton Bionetics, 1980). Also n-hexane did not induce chromosomal aberrations and micronuclei in bone marrow cells of B6C3F1 mice injected intraperitoneally (Shelby and Witt, 1995). A slight, but significant, increase in the number of chromosomal mutations induced by n-hexane in albino rat bone marrow cells has been reported (Hazleton Laboratories, 1992). In addition, an *in vivo* bone marrow cytogenetic assay found that male albino rats exposed to 150, 300, and 600 ppm of n-hexane for 5 days experienced a significant increase in chromosomal aberrations at all treatment levels compared with controls (Hazleton Laboratories, 1992). No increase in the incidence of sister chromatid exchanges in *in vivo* mouse bone marrow cells was seen with intraperitoneal doses of 500, 1,000, or 2,000 mg/kg n-hexane. (NTP, 1991). The dosed groups displayed slight increases in chromosomal aberrations, but this increase was not considered to be significant.

In summary, the weight of the evidence for *in vitro* genotoxicity testing of cyclohexane, n-hexane and n-heptane and *in vivo* genotoxicity testing of cyclohexane and n-hexane indicates no strong evidence for genotoxicity. Based on these data on predominant constituents, no additional testing on the C4-6 IRRP Fraction stream is proposed.

Repeated Dose Toxicity

A number of repeated dose toxicity studies have been conducted on cyclohexane, n-hexane, and n-heptane, as a suitable analog for 2,4-dimethylpentane.

Cyclohexane

A two-week repeated dose inhalation range finding study was conducted with Crl CD.BR rats exposed (whole body) to cyclohexane vapor (Haskell Laboratory, 1995). In this study, the rats were exposed to cyclohexane vapor at target concentrations of 0, 3,000, 6,000, and 9,000 ppm. Nine exposures, each lasting 6 hours were performed in total. A slight but significant decrease in body weight gain was observed in males treated with the high dose (9,000 ppm). Only a minimal increase in mitotic index figures in the hepatocytes of males at 6,000 ppm and higher and in females at 9,000 ppm was detected; no other treatment related findings were observed for systemic toxicity. In particular, no modification in absolute and relative liver weights was noted in these studies. Based on these findings, a No Observable Adverse Effect Level (NOAEL) of 3,000 ppm was determined for systemic toxicity. For neurotoxic effects, diminished responses to stimulus were observed from day 2 at 9,000 ppm and from 7 exposures at 6,000 ppm. No effect was observed in a Functional Observational Battery (FOB). A NOAEL of 3,000 ppm was reported for neurotoxic effects in rats. This study served as a range-finding study for a 90 day inhalation toxicity study.

In a 13-week repeated dose toxicity study conducted by Haskell Laboratory, 1996a (Malley *et al*., 2000), CD BR rats (20/sex/group for controls and high concentration and 10/sex/group for intermediary concentration groups) were exposed by whole body inhalation to cyclohexane at target concentrations of 0, 500, 2,000, and 7,000 ppm for 6 hours/day, 5 day/week for 13 weeks (66 exposures). Ten rats per month were allowed a one-month recovery period for control group and 7,000 ppm groups. After 45 and 90 days of exposure, blood and urine were collected for evaluation of clinical pathology parameters. Gross pathology, organ weight, macroscopic and microscopic examinations were performed at the end of the study.

No treatment-related effects were observed on body weight, body weight gain, food consumption, urine analysis and clinical examinations. A slight decrease (not significant) in succinate dehydrogense and lactate dehydrogenase was observed in males and females at 7,000 and 2,000 ppm at both sampling times. In males exposed to 7,000 ppm a slight increase in adrenals weight was observed at the end of the recovery period. This finding was not observed at the end of the 90 day exposure so the relevance and significance is questionable. In the 7,000 ppm group, a statistically significant increase in the relative liver weight with hepatic hypertrophy was observed in males (10/10), concurrent with an increase in the incidence of centrilobular hypertrophy in both sexes (9/10 males and 5/10 females). This finding was partially reversible in the one-month recovery period. For neurological effects, decreases in or absences of response to auditory stimulations were observed with a dose-response relationship from 500 ppm. In the 500 ppm group, there was a decrease in response on treatment days 61, 66, 67 and 68. In the 2,000 ppm group, there was decrease in the response during 16 exposures and no response during 50 exposures. In the 7,000 ppm group, a decreased response was observed in one exposure and no response was observed in

the other 65 exposures. These effects were transient, and as no clinical observations of compromised neurological function were detected they were considered to be due to a reversible sedation caused by cyclohexane. The NOAEL for neurological effects was 500 ppm while the NOAEL for hepatic effects was 2,000 ppm. However, the partially reversible hepatic effects observed in males at 7,000 ppm were slight and may be considered of an adaptive nature.

Additional groups of rats (12/sex/group) were treated in parallel with those of the previous study in order to assess neurotoxicity of cyclohexane in FOB, motor activity and neuropathology tests (Haskell Laboratory 1996c). Neurobehavioral evaluations were conducted prior to exposure and at week 4, 8, and 13. During each evaluation period FOB was performed prior to the motor activity test. At the end of the study, 6 rats/sex/group were selected for neuropathology, the controls and 7,000 ppm tissues selected were examined, and the intermediate dose tissues were saved. Neurological lesions were also assessed by examining sections of the brain, spinal cord, sciatic nerve, gasserian ganglia, cervical and dorsal root fibers and ganglia, cervical and lumbar ventral root fibers and gastrocnemius muscle.

Similar to the main 90 day study described previously, a sedative effect was observed at doses of 2,000 ppm and higher characterized by a decrease in the mean response to an alerting stimulus. This effect was transient since no effects were observed immediately after removal from the exposure chamber. No effects were observed during the FOB and motor activity assessment. Histologically, no treatment-related findings were observed, the only lesions observed being identical in character and severity to those observed in controls. These have already been described as occurring spontaneously in the rat. The NOAEL for neurotoxicity was 500 ppm based on the transient sedative effect observed at 2,000 ppm and higher.

A 13 week inhalation toxicity study (Haskell Laboratory, 1996b; Malley *et al*., 2000) in mice was also performed following a 2-week range finding study in mice. The study was comparable in experimental conditions to that performed on rats. For neurologic effects, a NOAEL of 500 ppm was determined based on signs of sedation observed in animals at 2,000 ppm. The NOAEL for systemic effects was 2,000 ppm based on effects observed in the liver at 7,000 ppm (increase in absolute and relative liver weights).

n-Hexane

A fair number of subchronic inhalation studies with n-hexane have been performed, particularly concerning the neurotoxic potential of n-hexane in rats (Ono *et al.*, 1982; Pryor *et al.*, 1983; Howd *et al.*, 1983; Cavender *et al.*, 1984a,b; Huang, 1989, 1992; Biodynamics, 1978, IRDC, 1992; NTP, 1991). Three of these key studies are described.

The subchronic toxicity of n-hexane is of some concern due to reports of treatment related peripheral neuropathy. A key 13-week inhalation study of n-hexane in male and female rats provided strong evidence for treatment related peripheral neuropathy. (Cavender *et al*. 1984a,b). Male and female F344 rats (15/sex/group) were exposed to n-hexane at 0, 3,000, 6,500, and 10,000 ppm for 6 hours/day, 5 days/week for 13 weeks. There were no n-hexane-related clinical signs of toxicity, effects on food consumption, ophthalmological findings, or changes in neurological function. However, there was a lowering of the urinary pH in high-dose males. There were increased

organ/body weight ratios for liver, kidney, and testis in high-dose males and kidney in mid-dose males. Histopathological examination of the tibial nerves revealed paranodal axonal swelling in mid- and high-dose males. n-Hexane is metabolized to 5-hydroxy-2-hexanone and 2,5-hexanedione *in vivo* (DiVincenzo *et al*., 1976). These two metabolites are believed to be responsible for the neurotoxicities associated with n-hexane exposure. There is evidence to show that 2,5-hexanedione is more persistent in peripheral nerve tissue than the parent n-hexane (Bus *et al*., 1981).

In a 16-week inhalation toxicity study, male Wistar rats (8/group) were exposed to 0, 500, 1,200, or 3,000 ppm n-hexane for 12 hours/day, 7 days/week (Huang *et al.*, 1989). Motor nerve conduction velocity was measured in the tail nerve along with body weight before exposure and after 4, 8, 12, and 16 weeks of exposure. One animal from each group was sacrificed after 16 weeks of exposure for histopathological evaluation of the nerve fibers in the tail. In addition, nerve-specific proteins (i.e. enolase and β-S100), involved in processes such as cell-cell communication, cell growth, intracellular signal transduction, and development and maintenance of the central nervous system, were measured. Statistically significant reductions in body weight gain were observed in a for the mid-dose (at 12 weeks) and high-dose (at 8 weeks) rats. Neurological deficits (i.e. reduction in grip strength and comparative slowness of motion) in mid- and high-dose rats were noted from 12 weeks of exposure. No hind-limb paralysis was observed by the time of sacrifice. A reduction in motor nerve conduction velocity, statistically significant during weeks 8-16, was seen with mid and high-dose rats. In addition increased incidence of paranodal swelling, along with some evidence of demyelination and remyelination was present in the peripheral nerves with 1,200 and 3,000 ppm. These histopathologic findings were most sever in the high-dose group. Dose-dependent biochemical changes included reductions in nervous system-specific proteins, particularly the β-S100 protein in tail nerve fibers which was reduced by approximately 75% at all dose levels. Under the conditions of this study, the NOAEL was 500 ppm based on the neurophysiologic deficits and histopathologic effects seen with 1,200 and 3,000 ppm.

A 13-week inhalation study of n-hexane in mice was conducted in 1991 by the NTP. Groups of 10 mice/sex/group were exposed to 0, 500, 1,000, 4,000, or 10,000 ppm n-hexane 6 hours/day, 5 days per week for the duration of the study. A second group of 10 mice was exposed at 1,000 ppm for 22 hours/day, 5 days/week for the duration of the study. Separate groups of 8 mice/sex/group received identical treatments but were subjected to neurobehavioral tests before the start of dosing then again after 6 and 13 weeks of exposure. Four males and four females were randomly selected from the 0, 1,000 ppm extended duration, and 10,000 ppm exposure groups for histopathological examination of the spinal cord and tibial nerves. Animals were observed daily for signs of clinical toxicity and weighed weekly.

A full necropsy was performed at sacrifice, weights of the major organs were recorded, and histopathological evaluations were carried out at term on a variety of excised organs and tissues. The liver was examined only in the males of all exposure groups. Animals exposed to 10,000 ppm n-hexane exhibited some signs of nasal irritation and all animals survived to term. Relative liver, kidney, and heart weights appeared to be increased compared with controls in exposed females. In addition, females exposed to 10,000 ppm 6 hours/day and 1,000 ppm for 22 hours/day exhibited neurobehavioral deficits with a reduction in locomotor activity. There was an increased incidence of

paranodal axonal swelling in high-dose or extended exposure duration mice. It was concluded that n-hexane caused minimal toxicity to the nervous system and/or respiratory system at 1,000 ppm and above indicating a NOAEL of 500 ppm.

2,4-dimethyl pentane (n-Heptane)

A 26-week inhalation toxicity study with n-heptane was conducted in Sprague-Dawley rats (API, 1980). In this study, the rats (15/sex/group) were exposed by inhalation to 0, 398 and 2,970 ppm n-heptane for 6 hours/day, 5 day/week for 26 weeks. There were no treatment-related deaths during the study. The only treatment-related observations were labored breathing or rapid breathing and slight prostration during the first week of study during exposure only, and anogenital fur staining and dry rales during weekly observations. No significant changes of body weight, hematology or urinalysis for both sexes were detected. Serum alkaline phosphatase was significantly elevated in female high dose rats and slightly elevated in low dose females. All other clinical chemistry values appeared normal with the exception of one male in the high dose group whose serum glutamic pyruvic transaminase and serum alkaline phosphatase levels were markedly elevated when compared to all other male rats on test. Proteinuria, elevated specific gravity and ketones were observed but do not appear to be related to treatment. The effects observed are consistent with acute central nervous system (CNS) depression and generally abated by the second week of the study. Under the conditions of this study, the Low Observed Adverse Effect Level (LOAEL) for acute CNS depression was 2,970 ppm and the NOAEL for systemic toxicity was 2,970 ppm.

In a 30-week inhalation neurotoxicity study, Sprague-Dawley rats (6-9 males/dose group) were exposed by inhalation to air or 1,500 ppm n-heptane for 9 hours/day, 5 days/week for 30 weeks (Frontali *et al.*, 1981). The primary objective of this study was to assess the appearance of polyneuropathy and urinary metabolites in rats following exposure to analytical grade solvents frequently used in Italian shoe factories. Nerve tissue was examined microscopically. None of the animals developed signs of neuropathy. There were no differences in weight gain of rats exposed to n-heptane compared to controls. Differences between mean values for hind limb spreads observed in treated animals and controls were not statistically significant. No histological signs of giant axonal degeneration were noted in rats treated at 1,500 ppm. Under the condition of this test, the NOAEL for repeated dose toxicity was considered to be 1,500 ppm.

In summary, data are available to adequately characterize the repeated dose toxicity of C4-6 IRRP Fraction stream. The C4-6 IRRP Fraction stream is expected to have a low order of repeated dose toxicity although some concern is noted based on evidence for peripheral neuropathy as a result of n-hexane exposure. No further testing is proposed.

Reproductive and Developmental Toxicity

Predominant constituents of the C4-6 IRRP Fraction stream have been evaluated for reproductive and developmental toxicity.

Cyclohexane

A two-generation reproductive toxicity study of inhaled cyclohexane vapor was conducted with CD BR rats (Haskell Laboratory, 1997c) according to OECD and US Environmental Protection Agency guidelines. In this study, weanling F0 rats (30/sex/group) inhaled cyclohexane vapor at 0, 500, 2,000, or 7,000 ppm 5 day/week

and 6 h/day. Exposure duration was 10 weeks before mating until sacrifice of the P1 generation and 11 weeks before mating until sacrifice of the F1 generation. Gravid females were not exposed from day 21 of gestation until day 4 of lactation. From day 5 of lactation until weaning the neonates were potentially exposed by maternal milk; no other exposure was administered. At post partum day 25, thirty F1 animals/sex/dose were chosen to produce the next generation, treatment was continued 11 weeks before mating and during gestation. Fertility parameters were calculated. From 500 ppm, there was an increased incidence of diminished response to a stimulus during exposure, this finding being significant at 2,000 ppm and higher. At 7,000 ppm, major effects were observed on body weight, body weight gain and food efficiency. A decrease in mean body weight was seen with F1 male rats, P1 and F1 females during pre-mating, P1 females throughout gestation, and F1 females during lactation. A decrease in mean body weight gain was observed with F1 male rats and P1 and F1 females during pre-mating; however no reductions were seen for P1 females during gestation, suggesting that the reduction in mean gestation body weight was probably due to pre-existing body weight deficits established during the pre-mating period. The same findings were also seen with the F1 generation. A decrease in mean food efficiency of P1 and F1 females during lactation and a decrease in food consumption of P1 females during lactation were also observed. Effects on reproduction were limited to a decrease in mean pup weight for both the F1 and F2 generations at the high dose which was significant between post partum day 7 and 25 during which time pups were fed only maternal milk indicating the effect is due to cyclohexane via lactation. There was a slight increase in the incidence of pro-static inflammation at 7,000 ppm in P1 and F1 adults, but this was considered incidental due to the lack of severity and the reported common occurrence in rats. There was a slight but significant decrease in the mean percentage of animals born alive in the F1 litters dosed with 7,000 ppm, but given that the value was still in the range of historical controls and that this effect was not dose-related, this was not considered biologically significant.

The NOAEL for adult reproductive toxicity was 2,000 ppm based on decreases in pup body weight observed at 7,000 ppm. The systemic NOAEL for this study was 500 ppm based on sedative effects observed at 2,000 ppm and higher.

In another EPA and OECD guideline study, the developmental toxicity of cyclohexane in rats was tested (Haskell Laboratory, 1997a). As a pilot study, four groups of eight pregnant CDBR rats were exposed whole-body to concentrations of 0, 3,000, 6,000, or 9,000 ppm cyclohexane from gestational day 7 to 16. Dams were sacrificed on day 22 and examined for gross pathologies; implantations and resorptions were counted and their relative positions recorded; fetuses were weighed and examined externally for alterations. Maternal effects were limited to a reduction in overall maternal bodyweight gain, overall food consumption and diminished response of animals to a sound stimulus during exposure to 6,000 ppm and higher. No effects were observed in the pups. The NOAEL was 3,000 ppm for the dams and 9,000 ppm for the pups.

This pilot study served as a range-finding study used to design a more complete study which was carried out during the 90 day inhalation study previously described (Haskell Laboratory, 1997b). Four groups of CD BR rats were exposed whole body to cyclohexane at concentrations of 0, 500, 2,000 or 7,000 ppm from gestational day 7 to 16. Animals were sacrificed on day 22 and examined. Findings were limited to the dams and included a diminished response of the animals to a sound stimulus while in

the chamber during exposure and at 2,000 ppm or higher and reductions in overall body weight gain and food consumption throughout the treatment period. A slight but significant decrease in implantation number with the number of corpora lutea unchanged was seen when compared with controls. This finding was consistent with slight pre-implantation losses and can be considered as not treatment-related since there was no treatment during the pre-implantation period. The NOAEL was 500 ppm for maternal toxicity and 7,000 ppm for developmental toxicity considering the lack of toxic effects noted.

n-Hexane

The developmental toxicity of n-hexane was assessed using timed-pregnant (30 animals per group) and virgin (10 animals per group) Sprague-Dawley rats exposed to 0 (filtered air), 200, 1,000, and 5,000 ppm n-hexane vapor in inhalation chambers for 20 hours per day for a period of 14 consecutive days (Mast, 1987). Spermpositive females were exposed on gestation days (GD) 6-19 and virgins were exposed concurrently for 14 consecutive days. Maternal toxicity, manifested as a reduction in extra-gestational maternal weight gain, was observed at all exposure levels, and was statistically significant for the 5,000 ppm exposure group. Extra-gestational maternal weight gain (calculated from GD 0 to GD 20) relative to control animals was reduced for the 200, 1,000, and 5,000 ppm exposure groups. Cumulative weight gain (CWG) for dams in the 1,000 and 5,000 ppm exposure groups was significantly reduced with respect to controls by GD 20. The CWG for the 5,000 ppm was also significantly reduced with respect to controls by GD 13.

Comparison of n-hexane exposed groups with the control group (0 ppm) indicated that gestational exposure to n-hexane did not result in an increase in the incidence of intrauterine deaths or in the incidence of fetal malformations. A statistically significant reduction in fetal body weight relative to controls was observed for males at the 1,000 and 5,000 ppm exposure levels. Female weights were also reduced with respect to controls for these exposure levels, but the reduction was statistically significant for only the 5,000 ppm group. Gravid uterine weight was also significantly less than controls for the 5,000 ppm exposure groups. A statistically significant increase in the mean percent incidence per litter of reduced ossification of sternebrae 1-4 was observed for the 5,000 ppm group, and was positively correlated with exposure concentration. This increased incidence of reduced ossification in the sternebrae, and the reduction in fetal body weight at the 5,000 ppm level, may have been inter-related manifestations of slight growth retardation.

No major abnormalities were found in any of the fetuses. Variations observed included dilated ureter, renal pelvic cavitation, supernumerary ribs, and reduced skeletal ossifications at several sites. The increase in mean percent incidence per litter of reduced ossification of sternebrae 1-4 was statistically significant for the highest exposure concentration, and the increase was positively correlated with increasing exposure concentration. The NOAEL for developmental toxicity was 200 ppm.

The effect of n-hexane on the male reproductive system when administered via the inhalation route was examined by exposing male Sprague-Dawley rats (12-39/group) to 5,000 ppm n-hexane in either a single 24 hour exposure, repeated 16 hour/day exposures for up to 8 days, or repeated 16 hour/day exposures, 6 hours/day for up to 6

weeks (De Martino *et al.*, 1987). Rats exposed to 5,000 ppm n-hexane displayed some evidence of neuropathy such as paralysis. Focal degeneration of spermatocytes and exfoliation of elongated spermatids was also observed in response to treatment. Early meiotic prophase spermatocytes and transitional spermatocytes as well as those undergoing meiotic metaphase appeared to be more susceptible to the action of n-hexane than pachytene spermatocytes. Rats exposed repeatedly to 5,000 ppm n-hexane over a 6-week period showed complete atrophy of the seminiferous tubules. In addition, a reduction in food consumption and body weight gain accompanied by signs of incipient neuropathy were seen with repeated n-hexane exposure. A wide range of testicular lesion did not complete resolve during a recovery period even though body weights and clinical symptoms improved.

Timed-pregnant (~33 females per group) and virgin (10 females per group) Swiss (CD-1) mice were exposed to 0, 200, 1,000, and 5,000 ppm n-hexane (99.2% purity) vapor in inhalation chambers, 20 h/day, for a period of 12 consecutive days (Mast *et al.*, 1988b). Plug-positive females were exposed on GD 6-17. Maternal body weight at sacrifice (GD 18) and total cumulative weight gain for dams in the 5,000 ppm exposure group were significantly reduced with respect to controls; however, this was due to an exposure correlated reduction in gravid uterine weight, not to a decrease in extragestational gain. An exposure-correlated decrease in the gravid uterine weight to extragestational weight gain ratio (significant for the 5,000 ppm group) occurred in the absence of an effect on placental weight.

Gestational exposure to n-hexane resulted in an increase in the number of resorbed fetuses for all exposure groups relative to the control group; however, the increases were not directly correlated to exposure concentration. The differences were statistically significant for the 200-ppm group with respect to total intrauterine death (early plus late resorptions), and with respect to late resorptions for the 5,000 ppm group. A small, but statistically significant, reduction in female (but not male) fetal body weight relative to the control group was observed at the 5,000 ppm exposure level. There were no exposure-related increases in any individual fetal malformation or variation, nor was there any increase in the incidence of combined malformations or variations.

Gestational exposure of CD-1 mice to n-hexane vapors appeared to cause a degree of concentration-related developmental toxicity in the absence of overt maternal toxicity, but the test material was not found to be teratogenic. This developmental toxicity was manifested as an increase in the number of resorptions per litter for all exposure levels, and as a decrease in the uterine: extra-gestational weight gain ratio at the 5,000 ppm exposure level. Because of the significant increase in the number of resorptions at the 200-ppm exposure level, a NOEL for developmental toxicity was not established for exposure of mice to 200, 1,000, or 5,000 ppm n-hexane vapors.

The available data on predominant constituents of the C4-6 IRRP Fraction stream prove adequate to support a screening level assessment of the reproductive and developmental toxicity of the IRF stream. Furthermore, these data indicate that the C4-6 IRRP Fraction stream is expected to have a low order of reproductive and developmental toxicity.

Conclusion

Mammalian toxicology data on three constituents of the C4-6 IRRP Fraction stream, cyclohexane, n-hexane and n-heptane have shown a low order of acute toxicity by the oral, dermal and inhalation routes of exposure. Repeated exposure to these constituents is not expected to produce target organ toxicity with the exception of n-hexane induced peripheral neuropathy for which some concern is noted. Reproductive and developmental toxicity potential is considered low. The weight of the evidence for *in vitro* and in vivo genotoxicity testing of cyclohexane, n-hexane, and n-heptane indicates no strong evidence for genotoxicity. The available data compiled for predominant constituents prove adequate to support a screening level hazard assessment of the IRF stream. Therefore, no additional human health toxicity testing is proposed.

Table 8. Mammalian toxicity endpoint summary for cyclohexane.

TOXICITY ENDPOINT		RESULTS	REFERENCE
Acute	Inhalation	LC50 > 32.88 mg/L	Phillips Petroleum Company, 1982b
	Oral	LD50 > 5,000 mg/kg	Phillips Petroleum Company, 1982a
	Dermal	LD50 > 2,000 mg/kg	Phillips Petroleum Company, 1982c
Irritation	Skin	Skin irritant	Phillips Petroleum Company, 1982d; Jacobs and Martens, 1987
	Eye	Minimal irritant	Phillips Petroleum Company, 1982e,f
Sensitization		Not a dermal sensitizer	White Eagle Toxicology Labs, 1996; EU Risk Assessment, 2004
Repeated Dose		Rat: NOAEL = 2,000 ppm	Haskell Laboratories, 1996a
Reproductive		NOAEL for Adult Reproductive toxicity = 2,000 ppm NOAEL for Systemic toxicity = 500 ppm	Haskell Laboratories, 1997e
Developmental		NOAEL for maternal toxicity = 500 ppm (rat, mouse) NOAEL developmental toxicity = 7,000 ppm (rat)	Haskell Laboratories, 1997c,d
Neurotoxicity		For FOB and motor activity assessment, very few effects were observed. Cyclohexane did not induce neurobehavioral effects.	TNO, 1998b
Genotoxicity	*In vitro* Ames *Salmonella* assay	Negative	Mortlemans *et al*., 1986
	In vitro chromosome aberration		
	In vivo micronucleus	Negative - Cyclohexane was not clastogenic to rat bone marrow	American Petroleum Institute, 1982

Table 9. Mammalian toxicity endpoint summary for n-hexane.

TOXICITY ENDPOINT		RESULTS	REFERENCE
Acute	Inhalation	LC50 = 48,000 ppm	HEDSET, 1982
	Oral	LD50 = 28,720 mg/kg	HSDB, 2005
	Dermal		
Irritation	Skin	Mild Irritant – Dermal exposure can lead to peripheral neuropathy in humans	Nomiyama *et al*., 1973; Spencer *et al*., 1980 & 1987
	Eye		
Sensitization			
Repeated Dose		Rat: NOAEL = 500 ppm Mouse: NOAEL = 500 ppm	Huang *et al*., 1989; NTP, 1991
Reproductive			
Developmental		NOAEL for maternal toxicity = 200, 1,000 ppm (rat, mouse) NOAEL developmental toxicity = 200 ppm (rat), LOAEL developmental toxicity = 200 ppm (mouse)	Mast *et al*., 1987; 1988
Neurotoxicity		Evidence for peripheral neuropathy	Cavender *et al*., 1984a,b
Genotoxicity	*In vitro* Ames *Salmonella* assay	Negative	NTP, 1991
	In vitro chromosome aberration	Negative	Daughtrey *et al*., 1994; NTP, 1991
	In vivo micronucleus	Negative – n-hexane was not clastogenic to mouse bone marrow Positive – n-hexane was clastogenic to albino rat bone marrow	Shelby and Witt, 1995 Hazleton Laboratories, 1992

Table 10. Mammalian toxicity endpoint summary for 2,4-Dimethylpentane (n-heptane).

TOXICITY ENDPOINT		RESULTS	REFERENCE
Acute	Inhalation	LC50 > 29.29 mg/L	HEDSET, 1982
	Oral		
	Dermal		
Irritation	Skin		
	Eye		
Sensitization			
Repeated Dose		NOAEL = 2,970 ppm (rat)	American Petroleum Institute, 1980
Reproductive			
Developmental			
Neurotoxicity		No signs of neuropathy and no histological evidence of giant axonal degeneration were noted in rats.	Frontali *et al*., 1981
Genotoxicity	*In vitro* Ames *Salmonella* assay	Negative	Brooks *et al*., 1982
	In vitro chromosome aberration	Negative	Brooks *et al*., 1982
	In vivo micronucleus		

IV. TEST PLAN SUMMARY

A search for existing studies/information identified adequate data to characterize all endpoints under the U.S. EPA HPV Program using data from representative constituents of the predominant fractions in the C4-6 IRRP Fraction stream. The three constituents were n-hexane, 2,4-dimethylpentane, and cyclohexane. Adequate data for n-hexane, 2,4-dimethylpentane, and cyclohexane are shown in Table 11.

Table 11. n-hexane, 2,4-dimethylpentane, and cyclohexane data availability and adequacy for endpoints in the HPV Program.

	Mammalian Toxicity						**Environmental Toxicity**			**Environmental Fate**				**Physical/Chemical Properties**					
	Acute Tox.	Genetic Pt. Mut.	Genetic Chrom.	Repeat Dose	Devel.	Repro.	Acute Fish	Acute Invert.	Alga Tox.	Photo-deg.	Hydrol.	Fug.	Biodeg.	Melt. Pt.	Boil. Pt.	Dens.	Vap. Pres.	Water Sol.	K_{ow}
Hexane	**A**	**A**	**A**	**A**	**A**	**A**	**C**	**A/C**	**C**	**T**	**T**	**C**	**A**	**A**	**A**	**A**	**A**	**A**	**A**
2,4-dimethylpentane	**A**	**A**	**A**	**A**	**-**	**-**	**C**	**A/C**	**C**	**T**	**T**	**C**	**-**	**A**	**A**	**A**	**A**	**A**	**A**
Cyclo-hexane	**A**	**A**	**-**	**A**	**A**	**A**	**A/C**	**A/C**	**A/C**	**T**	**T**	**C**	**A**	**A**	**A**	**A**	**A**	**A**	**A**

A Adequate measured data available
C Adequate computer model data available
T Adequate technical discussion available

V. REFERENCES

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I U C L I D

Data Set

Existing Chemical	:	ID: 108-08-7
CAS No.	:	108-08-7
EINECS Name	:	2,4-dimethylpentane
EC No.	:	
TSCA Name	:	2,4-dimethylpentane
Molecular Formula	:	C7H16

Producer related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008

Substance related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008
Status	:	
Memo	:	U.S. EPA - HPV Challenge Program
Printing date	:	30.06.2008
Revision date	:	
Date of last update	:	30.06.2008
Number of pages	:	32
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	**:**	
Substance type	**:**	petroleum product
Physical status	**:**	liquid
Purity	**:**	
Colour	**:**	
Odour	**:**	

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1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= -119.5 °C
Sublimation	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

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2.2 BOILING POINT

Value	:	= 80.4 °C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (13)

2.3 DENSITY

Type	:	density
Value	:	= .668 g/cm³ at 20 °C
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown.
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (16)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 10.59 hPa at 25 °C
Decomposition	:	
Method	:	

Year	:	
GLP	:	no data
Method	:	Method not specified.
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown.
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data were not reviewed for quality, however, the reference is from a peer-reviewed handbook.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (4)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 3.63 at 25 °C
pH value	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Method	:	Calculated values using KOWWIN version 1.67, a subroutine of the computer program EPIWIN version 3.20
Test condition	:	Octanol / Water Partition Coefficient is calculated by the KOWWIN subroutine, which is based on an atom/fragment contribution method of W. Meylan and P. Howard in "Atom/fragment contribution method for estimating octanol-water partition coefficients". 1995. J. Pharm. Sci. 84:83-92.
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPI SuiteTM. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (17)(19)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 5.5 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (20)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .00000000000685 cm³/(molecule*sec)
Degradation	:	= 50 % after 18.7 hour(s)
Deg. product	:	
Method	:	other (calculated): Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20
Year	:	
GLP	:	
Method	:	Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20 Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson under the following conditions: Temperature: 25°C Sensitizer: OH- radical Concentration of Sensitizer: 1.5E6 OH- radicals/cm3
Remark	:	2,4-dimethylpentane has the potential to volatilize to air, based on a relatively high vapor pressure, where it is subject to atmospheric oxidation. In air, 2,4-dimethylpentane can react with photosensitized oxygen in the form of hydroxyl radicals (OH-). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPI SuiteTM, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an OH- reaction rate constant and a defined OH- concentration. Based on a 12-hour day, a rate constant of 6.85 E-12 cm3/molecule*sec, and an OH- concentration of 1.5 E6 OH-/cm3, 2,4-dimethylpentane has a calculated half-life in air of 1. 6 days or 18.7 hours of daylight.
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown.
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (19)

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Method	:	Technical discussion
Remark	:	Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric

ozone layer (Harris, 1982).
An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Saturated and unsaturated hydrocarbons do not absorb light above 290 nm. Consequently, 2,4-dimethylpentane is not subject to photolytic processes in the aqueous environment.

Test substance : CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
03.07.2008 (9)(21)

3.1.2 STABILITY IN WATER

Type :
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other: Technical discussion
Year :
GLP : no data
Result : Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Gould, 1959). The lack of a suitable leaving group renders a compound resistant to hydrolysis. Heptane is resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive and Harris (1982) identifies hydrocarbons as generally resistant to hydrolysis. Therefore, hydrolysis will not contribute to the removal of 2,4-dimethylpentane from the environment.
Test substance : CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
03.07.2008 (7)(10)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type :
Media : other: air - biota - sediment(s) - soil - water
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)

Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Calculation according Mackay, Level I
Year :
Remark : The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment.

Physicochemical input values for the model were calculated using the EPIWIN Estimation v 3.20 program. Measured input values were also used where available and obtained from the EPIWIN database. Distribution data from the equilibrium model provide basic information on the potential partitioning behavior of chemicals between selected environmental compartments (i.e., air, water, soil, sediment, suspended sediment, biota).

Physicochemical data used in the calculation:

Parameter	Value w/ Units
Molecular Weight	100.21
Temperature	25° C
Log Kow	3.63
Water Solubility	5.5 g/m3
Vapor Pressure	10,586 Pa
Melting Point	-119.5° C

Result : Using the Mackay Level I calculation, the following distribution is predicted for heptane:

%Distribution	Compartment
99.98	Air
<0.01	Water
0.01	Soil
<0.01	Sediment
<0.01	Suspended Sediment
<0.01	Biota

Test substance : CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.
Flag : Critical study for SIDS endpoint
03.07.2008 (14)

Type : fugacity model level III
Media : other
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Level III simulation using the Mackay Multimedia Environmental Model (Mackay, 2001)
Year :
Method : The EQC Level III model is a steady state model that is useful for determining how the medium of release affects environmental fate. Level III fugacity allows non-equilibrium conditions to exist between connected media as steady state, and illustrate important transport and transformation processes.

Physicochemical input values for the model were calculated using the EPIWIN Estimation v 3.20 program. Measured input values were also

used where available and obtained from the EPIWIN database. Distribution data from the equilibrium model provide basic information on the potential partitioning behavior of chemicals between selected environmental compartments (i.e., air, water, soil, and sediment).

Input values used:
Molecular mass = 100.21 g/mol
Water solubility = 5.5 g/m^3
Vapour pressure = 10,586 Pa
log Kow = 3.63
Melting point = -119.5 deg C

Degradation half-lives:

Air - 18.7 hrs
Water - 360 hrs
Soil - 720 hrs
Sediment - 7200 hrs

Environmental Properties (EQC standard environment)
Dimensions (all defaults)
Densities (all defaults)
Organic carbon & Advection (all defaults)
Transport Velocities (all defaults)

Emission and Inflows (defaults used)
Air 1000 kg/hr
Water 1000 kg/hr
Soil 1000 kg/hr
Sediment 0 kg/hr

Result : Output:

	Mass%	Emissions(kg/hr)
Air	20.0	1000
Water	70.6	1000
Soil	2.8	1000
Sediment	6.6	0

Test substance : CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Conclusion : The majority of 2,4-dimethylpentane is calculated to partition into the water phase, with smaller but significant amounts into air, soil, and sediment based on the modeling parameters used in this calculation. 2,4-dimethylpentane is considered to be a Type 1 chemical with potential to partition into all environmental compartments.
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.
Flag : Critical study for SIDS endpoint
03.07.2008 (15)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Contact time : 28 day(s)

Degradation : 74 (±) % after 28 day(s)
Result : other: readily biodegradable
Deg. product :
Method : OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year : 1996
GLP : yes
Result : Test material was readily biodegradable. Half-life was reached by day 10. By day 28, 74% degradation of the test material was observed. 10% biodegradation was achieved on day 4.
By day 10, >60% biodegradation of positive control was observed, which met the guideline requirement. No excursions from the protocol were noted.
Biodegradation was based on oxygen consumption and the theoretical oxygen demand of the test material as calculated using results of an elemental analysis of the test material.

Sample	% Degradation* (day 28)	Mean % Degradation (day 28)
Test Material	72.5, 74.0, 76.8	74.4
Na Benzoate	88.7, 88.9	88.8

* replicate data

Test condition : Non acclimated activated sludge and test medium were combined prior to test material addition. Test medium consisted of glass distilled water and mineral salts (Phosphate buffer, Ferric chloride, Magnesium sulfate, Calcium chloride).
Test vessels were 1L glass flasks placed in a waterbath and electronically monitored for oxygen consumption.
Test material was tested in triplicate, controls and blanks were tested in duplicate.
Test material concentration was approximately 45 mg/L. Sodium benzoate (positive control) concentration was 50mg/L.
Test temperature was 22 +/- 1 Deg C.
All test vessels were stirred constantly for 28 days using magnetic stir bars and plates.
Test substance : CAS #142-82-5; heptane; 99% pure.
Conclusion : Heptane is readily biodegradable.
Reliability : (1) valid without restrictions

30.06.2008 (8)

Type : aerobic
Inoculum : other: soil, non-adapted
Contact time : 20 day(s)
Degradation : 70 (±) % after 20 day(s)
Result : other: readily biodegradable
Deg. product :
Method : other: Standard Methods for the Examination of Water and Waste Water
Year : 1971
GLP : no
Result : 70% degradation was measured after 20 days incubation with an unacclimated inoculum.
% Biodegradation of test substance after days:
2 days = 28 %
5 days = 63 %
10 days = 70 %
20 days = 70 %
Test condition : American Public Health Association, Standard Methods for the Examination of Water and Waste Water, using 1.0 mg/l of test substance. Biodegradation was determined by measuring biological oxygen demand

(BOD). Each 300 ml BOD bottle received 1.0 mg of heptane, 1.0 ml of a 1:10 suspension Hudson-Collamer silt loam soil in distilled water, and a mineral salts solution prepared as described in the test method. Bottles were incubated in the dark at 25C. The test substance was obtained from Aldrich Chemical Co.

Test substance : CAS #142-82-5; heptane; 99% pure.
Conclusion : Heptane is readily biodegradable.
Reliability : (2) valid with restrictions
A standard test method was used. The study was conducted prior to GLP.

30.06.2008 (8)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other: see remark
Exposure period : at 25 °C
Concentration :
BCF : = 125
Elimination :
Method : other: calculation
Year :
GLP : no
Remark : A log bioconcentration factor (BCF) of 2.097 is calculated (BCF = 125). With respect to a log Kow = 3.63, which was used to calculate the BCF, 2,4-dimethylpentane in the aquatic environment is expected to have a low potential to bioaccumulate.
Test substance : CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag : Critical study for SIDS endpoint

03.07.2008 (19)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	
Species	:	other: fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 2.2
Method	:	other: ECOSAR version 0.99h, US EPA
Year	:	
GLP	:	
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 96-hr LC50 for fish = 2.2 mg/L
Test condition	:	Experimental water solubility = 5.5 mg/l @ 25°C (Yalkowsky and Dannenfelser, 1992), log Kow = 3.63 @ 25°C (USEPA, 2000), and melting point = -119.5°C (Lide et al., 1997-1998) were entered into the program. Class: Neutral organics
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

03.07.2008 (5)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	other: Daphnia
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	= 2.6
Method	:	other: ECOSAR version 0.99h, US EPA

Year	:	
GLP	:	
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 48-hr LC50 for a daphnid = 2.6 mg/L
Test condition	:	Experimental water solubility = 5.5 mg/l @ 25°C (Yalkowsky and Dannenfelser, 1992), log Kow = 3.63 @ 25°C (USEPA, 2000), and melting point = -119.5°C (Lide et al., 1997-1998) were entered into the program. Class: Neutral organics
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

03.07.2008 (5)

Type	:	static
Species	:	other: Daphnia
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 1.5
Method	:	other: based on discussions in GESAMP/MARPOL meetings held in 1973
Year	:	
GLP	:	no data
Method	:	Individual treatment concentrations were prepared by mixing the test substance in freshwater for 24 hours in a conical flask. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were 250 ml conical flasks with 25 daphnids per flask. Two replicates of each treatment level and control were evaluated. Organisms supplied by testing lab; age = <24 hours old; parents age = approximately 21 days old. Statistical method: Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-

119.).

Result : 48-hr EC50 for a daphnid = 0.423 mg/L

Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C.

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 0.32 to 10 mg/L. Only the following analytical data were reported:

Nominal Conc. (mg/L)	Initial Measured Conc. (mg/L)	48-hr Measured Conc. (mg/L)
0.32	0.04	Not Determined
1.0	0.04	Not Determined
3.2	0.5	Not Determined
5.6	2.1	1.7
10	2.2	Not Determined

Test substance : CAS #142-82-5; heptane

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline, OECD 202, and used acceptable methods to prepare exposure solutions.

Flag : Critical study for SIDS endpoint

03.07.2008 (18)

Type : semistatic

Species : other: Gammarid (Chaetogammarus marinus)

Exposure period : 96 hour(s)

Unit : mg/l

LC50 : = .2

Method : other: Static Gammarid Acute Toxicity Test

Year :

GLP : no data

Method : Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours.

Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; length = 5 mm.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).

Result : 96-hr LC50 for a gammarid = 0.2 mg/L

Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 15 Deg C. Natural seawater was used with a salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 0.32 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Only the following analytical data were reported:

Nominal Conc. (mg/L)	Initial Measured Conc. (mg/L)
0.32	0.003
1.0	0.07
3.2	0.2
5.6	Not Determined
10	Not Determined

Test substance : CAS #142-82-5; heptane
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.
Flag : Critical study for SIDS endpoint
03.07.2008 (18)

Type : semistatic
Species : other: mysid shrimp (Mysidopsis bahia)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = .1
Method : other: Static Gammarid Acute Toxicity Test
Year :
GLP : no data
Method : Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours.

Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; test organisms were approximately 4 weeks old, with lengths of approximately 6 mm.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result : 96-hr LC50 for a gammarid = 0.1 mg/L
Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C. Natural seawater was used with a salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 0.32 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Only the following analytical data were reported:

Nominal Conc. (mg/L)	Initial Measured Conc. (mg/L)
0.32	0.003
1.0	0.07
3.2	0.2
5.6	Not Determined
10	Not Determined

Test substance : CAS #142-82-5; heptane

Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.
Flag	:	Critical study for SIDS endpoint

03.07.2008 (18)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Green Alga
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	= 2.0
ChV	:	= 0.5
Method	:	other: ECOSAR version 0.99h, US EPA
Year	:	
GLP	:	
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 96-hr EC50 for a green alga = 2.0 mg/L Calculated 96-hr ChV for a green alga = 0.5 mg/L
Test condition	:	Experimental water solubility = 5.5 mg/l @ 25°C (Yalkowsky and Dannenfelser, 1992), log Kow = 3.63 @ 25°C (USEPA, 2000), and melting point = -119.5°C (Lide et al., 1997-1998) were entered into the program. Class: Neutral organics
Test substance	:	CAS #108-08-7; 2,4-dimethylpentane; purity is unknown
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

03.07.2008 (5)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	other terrestrial plant: Lactuca sativa Ravel R2
Endpoint	:	other: growth
Exposure period	:	day(s)
Unit	:	mg/l
Method	:	other
Year	:	
GLP	:	no
Test substance	:	n-Heptane; CAS #142-82-5; >/= 95% pure
Result	:	Soil Test Results Test 1 (lab 1): Days 7 and 14 EC50 = >1000 mg/kg soil (dry weight), based on nominal concentrations. No effects at the highest concentration tested. Test 2 (lab 2): Days 7 and 14 EC50 = >1000 mg/kg soil (dry weight), based on nominal concentrations. No effects at the highest concentration tested. Nutrient Solution Test Results Test 1 (lab 1): Day 16 or 21 EC50 = 1.7 (1.4-2.0) mg/L, based on measured concentrations (value is below water solubility). Test 2 (lab 2): Day 16 or 21 EC50 = 47 (38-65) mg/L, based on measured concentrations (value exceeds water solubility).
Test condition	:	Testing occurred in two labs. Two tests were conducted in soil (one at each lab) and two tests in a nutrient solution (one at each lab). In both soil tests, lettuce seeds (Lactuca sativa) were germinated in soil obtained from an orchard. The characteristics of the soil collected for the first study were: pH = 7.5; organic matter content = 1.4%; clay content = 12%. The characteristics of the soil collected for the second study were: pH = 7.5; organic matter content = 1.8%; clay content = 24%. Test soil was sieved, 4 mm, prior to use. The nutrient solution composition was as follows: 3.73 mM Ca(NO3); 4.40 mM KNO3; 0.97 mM KH2PO4; 1.92 mM MgSO4; 0.89 mM K2SO4; trace elements and FeEDTA (per Steiner A, 1968. Soilless culture. Proceedings, Sixth Colloquium of the International Potash Institute, Florence, Italy, pp. 342-341.). Soil Experiments Test substances were dissolved in acetone and/or mixed with a small amount of quartz sand, which was then mixed through the test soil to obtain a uniform distribution of test substance through the soil sample. A nominal concentration of 1000 mg/kg soil was tested. Test substance concentrations in dry soil were spaced by a factor of 3.2. Controls and at least 3 test concentrations were run in duplicate. Soil was brought to 25 to 30% moisture content, which was equivalent to approximately 80% water holding capacity. Test systems were covered

with glass plates until germination occurred to prevent moisture loss. After germination, the plates were removed and moisture loss was control by adding demineralized water back to the soil.

Five seedlings from each replicate test system were selected for the test and allowed to grow. Seedlings were sampled on days 7 and 14 by cutting them at soil level and measuring fresh weight. Soil water content and pH were measured at experimental initiation and termination.

Heptane was analyzed in soil at test initiation and termination by solvent extraction and GC/FID and/or GC/ECD. Measured concentrations in soil for test substances ranged from 70 to 150% of nominal concentrations. Specific results for heptane were not given.

Nutrient Solution Experiment

Test substances were dissolved in tributylalcohol and added to the nutrient solution. Seeds were placed on plastic trays, which contained perlite that was saturated with nutrient solution. The trays were covered with glass plates to reduce volatile loss during germination. After germination, seedlings were transferred to containers filled with nutrient solution and test substance. Solutions were renewed 3 times a week. Duplicate containers were used for each test concentration. Test concentrations were spaced by a factor of 3.2. Shoots were harvested on either day 16 or 21 and fresh weights determined. Oxygen content and pH were measured at solution renewal.

Heptane was analyzed in nutrient solution at test initiation and termination by solvent extraction and GC/FID and/or GC/ECD. Measured concentrations in solution for heptane were <50% of nominal concentrations. Specific results for heptane were not given. The volatility of heptane was suspected to have contributed to the loss in solution.

Statistics

EC50 values were determined based only on harvested shoots and calculated by applying a logistic model (per Haanstra et al., 1985. The use of sigmoidal dose response curves in soil ecotoxicological research. Plant Soil 82, 293-297.)

Reliability : (2) valid with restrictions
Although a specific standard guideline was not used, the test method generally followed standard test procedures, however, less specific analytical information was provided than is desirable.

07.07.2008 (12)

Species : other terrestrial plant: Daucus carota L. cv. Early Horn
Endpoint : other: leaf damage, electrolyte loss
Exposure period : 0 day(s)
Unit : mg/l
Method : other
Year :
GLP : no
Test substance : n-Heptane; CAS #142-82-5; >99.5% pure
Result : The rate at which electrolytes were lost from carrot leaves exposed to n-heptane was 34 min-1 x E4. The rate at which electrolytes were lost from untreated leaves was 12 min-1 x E4. The effects on cell membrane permeability as indicated by conductance agreed with the known susceptibility of different plant species towards hydrocarbons applied in the liquid state. The effect on the final conductance values and electrolyte concentration was similar for the hydrocarbons tested.

Electrolyte loss from leaves exposed to a liquid hydrocarbon solvent

coating is explained as resulting from the destruction of plant cell membrane permeability and the release of internal cell electrolytes.

Test condition : Carrot plants, Daucus carota, were grown in a nutrient solution under controlled temperatures of 23 deg C during the day and 13 deg C during the night. The plants used were 3 to 5 weeks old. 5 g, fresh weight, of leaves were selected at random from the plants. 2 ml of test material was added to abaxial leaf surfaces by dropwise application so as to cover them as evenly as possible. This quantity represented an excess when compared to the lipid content of the plant cells. The leaves were immediately immersed in 100 ml of deionized water at 25 deg C in a glass flask. The leakage of salts from the leaves was inferred from changes in conductance across a dip-type bright platinum electrode inserted into the water over a period of 6 to 7 hours. The flasks were sealed with parafilm and the contents shaken before each reading. Data are based on 3 replicates.

A final conductance value representing the total electrolytes released from the leaves was taken after the suspensions were boiled.

Reliability : (4) not assignable
There is insufficient documentation on the samples and results to rate this study for reliability. The relevance of the method of exposure and adding the test substance to the abaxial surface of the leaf to mimic the effect of applying agrochemical sprays is not clear.

07.07.2008 (2)

Species : other terrestrial plant: Helianthus annuus
Endpoint : other: leaf damage, electrolyte loss
Exposure period : 0 day(s)
Unit : mg/l
Method : other
Year :
GLP : no
Test substance : n-Heptane; CAS #142-82-5; >99.5% pure
Result : The rate at which electrolytes were lost from sunflower leaves exposed to n-heptane was 160 min-1 x E4. The rate at which electrolytes were lost from untreated leaves was 16 min-1 x E4. A second study with n-heptane resulted in a rate of 170 min-1 x E4. The rate at which electrolytes were lost from untreated leaves in the second study was 17 min-1 x E4. The effects on cell membrane permeability as indicated by conductance agreed with the known susceptibility of different plant species towards hydrocarbons applied in the liquid state. The effect on the final conductance values and electrolyte concentration was similar for the hydrocarbons tested.

Electrolyte loss from leaves exposed to a liquid hydrocarbon solvent coating is explained as resulting from the destruction of plant cell membrane permeability and the release of internal cell electrolytes.

Test condition : Sunflower plants, Helianthus annuus, were grown in a nutrient solution under controlled temperatures of 23 deg C during the day and 13 deg C during the night. The plants used were 3 to 5 weeks old. 5 g, fresh weight, of leaves were selected at random from the plants. 2 ml of test material was added to abaxial leaf surfaces by dropwise application so as to cover them as evenly as possible. This quantity represented an excess when compared to the lipid content of the plant cells. The leaves were immediately immersed in 100 ml of deionized water at 25 deg C in a glass flask. The leakage of salts from the leaves was inferred from changes in conductance across a dip-type bright platinum electrode inserted into the water over a period of 6 to 7 hours. The flasks were sealed with parafilm and the contents shaken before each reading. Data are based on 3 replicates.

A final conductance value representing the total electrolytes released from

the leaves was taken after the suspensions were boiled.

Reliability : (4) not assignable
There is insufficient documentation on the samples and results to rate this study for reliability. The relevance of the method of exposure and adding the test substance to the abaxial surface of the leaf to mimic the effect of applying agrochemical sprays is not clear.

07.07.2008 (2)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> 29.29 mg/l
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	29.29 mg/L (17940 ppm)
Exposure time	:	4 hour(s)
Method	:	other: Similar to OECD guideline 403
Year	:	1982
GLP	:	
Test substance	:	other TS: n-Heptane (CAS # 142-82-5)
Remark	:	Animals were exposed to n-heptane vapor for 4 hours at a concentration of 29.29 mg/L (nominal) or 17937.5 ppm (mean analytical).
Result	:	There was no mortality during the course of the study. A slight reduction of mean male body weights was noted on day 2 post exposure but males recovered by day 4. All animals appeared normal throughout the study and at terminal necropsy with the exception of one female observed with enlarged mandibular lymph nodes on the right side.
Conclusion	:	n-Heptane has a low order of toxicity by the inhalation route of exposure.
Reliability	:	(2) valid with restrictions

07.07.2008 (11)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation

Exposure period	:	6 hours/day
Frequency of treatm.	:	5 days/week for 26 weeks
Post exposure period	:	2-week post exposure recovery period
Doses	:	0, 500, 2000 and 4000 ppm
Control group	:	yes
NOAEL	:	= 2970 ppm
Method	:	other: similar to OECD guideline 413
Year	:	1980
GLP	:	
Test substance	:	other TS: n-Heptane (CAS # 142-82-5)
Remark	:	Animals were exposed to 0, 398 or 2970 ppm n-heptane. Type: 26-week inhalation toxicity study Number of animals: 15/sex/dose group
Result	:	There were no treatment-related deaths during the study. The only treatment-related observations were labored breathing or rapid breathing and slight prostration during the first week of study during exposure only, and anogenital fur and dry rales during weekly observations. The in chamber signs were generally more numerous and severe in the higher dose group and appeared to abate by the second week of the study. No treatment-related effects were observed for body weight, hematology or urinalysis. Serum alkaline phosphatase was significantly elevated in female high dose rats and slightly elevated in low dose females. All other clinical chemistry values appeared normal with the exception of one male high level rat whose serum glutamic pyruvic transaminase and serum alkaline phosphatase levels were markedly elevated when compared to all other male rats on test. Proteinuria, elevated specific gravity and ketones were observed but do not appear to be related to treatment.
Conclusion	:	The effects observed are consistent with acute CNS depression and generally abated by the second week of study. Under the conditions of this study, the LOAEL for acute CNS depression is 2,970 ppm and the NOAEL for systemic toxicity is 2,970 ppm.
Reliability	:	(2) valid with restrictions

08.07.2008 (1)

Type	:	
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	9 hours/day
Frequency of treatm.	:	5 days/week for 7, 14 or 30 weeks
Post exposure period	:	None. Animals were sacrificed at 7, 14 or 30 weeks.
Doses	:	0, 1500 ppm
Control group	:	other: yes, omitted the second air flow
NOAEL	:	> 1500 - ppm
Method	:	other: none specified
Year	:	1981
GLP	:	
Test substance	:	other TS: n-Heptane (CAS # 142-82-5)
Remark	:	Only males and one dose group were used. The primary objective of this study was to assess the appearance of polyneuropathy and urinary metabolites in rats following exposure to analytical grade solvents frequently used in Italian shoe factories. Nerve tissue was examined microscopically. Body weights were analyzed by a two-way analysis of variance and Student's t test for the comparison of two slopes. Type: 30-week inhalation neurotoxicity study Number of animals: 6-9 males/dose group
Result	:	None of the animals developed signs of neuropathy. There were no differences in weight gain of rats (30 weeks) compared to controls.

Differences between mean values for hindlimb spreads observed in treated animals and controls were not statistically significant. However, authors note that in their hands, the test employed turned out to be scarcely effective due to high individual variability. No histological signs of giant axonal degeneration were noted in rats treated at 1500 ppm (30 weeks).

Conclusion : Under the conditions of this test, inhalation of n-heptane at 1500 ppm did not induce neuropathy in rats.

Reliability : (2) valid with restrictions

08.07.2008 (6)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay
System of testing : Salmonella typhimurium and Escherichia coli
Test concentration : Doses ranging from 3.91 to 250 ug/ml
Cycotoxic concentr. : 500 µg/ml
Metabolic activation : with and without
Result : negative
Method : other: No specific method or guideline was noted.
Year : 1982
GLP :
Test substance : other TS: heptane (CAS # 142-82-5)
Remark : GLP: Quality assurance statement
Strains tested: Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, TA1538; Escherichia coli strains WP2, WP uvr A

Test substance concentrations: 3.91, 7.81, 15.6, 31.3, 62.5, 125, 250 mg/ml

Metabolic activation: With and without (S9 fraction mix of livers from Aroclor 1254 pretreated rats)

Vehicle: Tween 80/ethanol

Positive Controls: benzo[a]pyrene, 4-nitroquinoline-N-oxide, sodium azide, neutral red, potassium dichromate.

Cytotoxicity study: A toxicity screening test conducted prior to the full assay indicated cytotoxicity at 500 mg/ml with and without metabolic activation.

The cultures were incubated at 37°C for 48-72 hours in a sealed container before the revertant colonies were counted. Pre-incubation method was used to limit evaporation of test material.

Result : The addition of heptane at amounts up to 250 mg per ml to cultures of Escherichia coli WP2 and WP2 uvr A, Salmonella typhimurium TA 1535, TA 1537, TA 1538, TA 98, and TA 100 did not lead to an increase in the reverse gene mutation frequency in any of these strains, either in the presence or in the absence of rat liver S9 fraction. In one assay with Escherichia coli WP2 in the presence of S9 fraction a greater than 2.5 fold increase over control values was seen at 15.6 and 31.3 mg per ml. This increase was not dose-related nor repeated in replicate assays and was therefore not considered to be a compound-related effect.

Conclusion : Under the conditions of this study, the test material was not mutagenic.

Reliability : (1) valid without restriction

08.07.2008 (3)

Type : other: Mitotic gene conversion assay
System of testing : Yeast
Test concentration : Doses ranging from 0.01 to 5.0 mg/ml

Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: No specific method or guideline was noted
Year	:	1982
GLP	:	
Test substance	:	other TS: heptane (CAS # 142-82-5)
Remark	:	GLP: Quality assurance statement Strains tested: Saccharomyces cerevisiae JD1 Test substance concentrations: 0.01, 0.1, 0.5, 1.0, 5.0 mg/ml Metabolic activation: With and without (S9 fraction mix of livers from Aroclor 1254 pretreated rats) Vehicle: Tween 80/ethanol Positive Controls: 4-nitroquinoline-N-oxide, cyclophosphamide After 18-hour incubation at 30°C the cultures were placed onto the appropriate culture media for the selection of prototrophic colonies. After three days incubation at 30°C the numbers of prototrophic colonies were counted.
Result	:	Exposure of Saccharomyces cerevisiae JD1 to heptane at concentrations up to 5.0 mg/ml did not result in a consistent increase in the rate of mitotic gene conversion, either in the presence or in the absence of rat liver S9 fraction.
Conclusion	:	Under the conditions of this study, the test material was not genotoxic.
Reliability	:	(1) valid without restriction

08.07.2008 (3)

Type	:	other: Chromosome aberration assay
System of testing	:	Rat Liver (RL4) cells
Test concentration	:	2.5, 5, 10 ug/ml
Cycotoxic concentr.	:	20 ug/ml (100% cytotoxicity), 10 ug/ml (0% cytotoxicity)
Metabolic activation	:	
Result	:	negative
Method	:	other: No specific method or guideline was noted
Year	:	1982
GLP	:	
Test substance	:	other TS: heptane (CAS # 142-82-5)
Remark	:	GLP: Quality assurance statement Vehicle: Tween 80/ethanol Positive Controls: 7,12-Dimethylbenzanthracene (DMBA) Cultured rat liver cells were grown and treated on glass microscopic slides contained in 100-ml volume glass Leighton tubes. After 22-hour exposure to test compound or vehicle, colcemid was added to each culture. After further 2 hours, the slides were removed, subjected to hypotonic treatment followed by fixation (methanol:acetic acid, 3:1) and stained with Giemsa. The preparations were randomly coded and 100 cells from each culture were analyzed microscopically.
Result	:	In one culture exposed to 10 mg/ml of heptane a total of 7 chromatid gaps were seen; this increased the frequency to 0.024 gaps per cell which, although greater than the vehicle control frequency, was not accompanied by an increase in any other type of aberration and is not considered to be a compound-related effect. Thus there was no significant or dose-related increase of chromosome damage in any of the culture exposed to heptane. Cultures exposed to the positive control material, DMBA, showed a marked increase in the frequency of chromosome damage.
Conclusion	:	Under the conditions of this study, the test material was not clastogenc.

Reliability : (2) valid with restrictions
08.07.2008 (3)

5.6 GENETIC TOXICITY ‘IN VIVO‘

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

IUCLID

Data Set

Existing Chemical	:	ID: 110-54-3
CAS No.	:	110-54-3
EINECS Name	:	hexane
EC No.	:	203-777-6
TSCA Name	:	Hexane
Molecular Formula	:	C6H14

Producer related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008

Substance related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008
Status	:	
Memo	:	U.S. EPA - HPV Challenge Program
Printing date	:	12.08.2008
Revision date	:	
Date of last update	:	12.08.2008
Number of pages	:	36
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	**:**	
Substance type	**:**	petroleum product
Physical status	**:**	liquid
Purity	**:**	
Colour	**:**	
Odour	**:**	

30.06.2008

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= -95.3 °C
Sublimation	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (20)

2.2 BOILING POINT

Value	:	= 68.7 °C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (20)

2.3 DENSITY

Type	:	density
Value	:	= .659 g/cm³ at 20 °C
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (31)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 20.13 hPa at 25 °C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Method	:	Method not specified.
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data were not reviewed for quality, however, the reference is from a peer-reviewed handbook.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (6)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 3.9 at 20 °C
pH value	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions The value cited by the author is a recommended value based on a review of data retrieved from the literature. This robust summary has a reliability rating of 2 because there is insufficient information available on the method.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (11)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 9.5 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 20 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	other TS: hexane; (CAS #110-54-3)
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are from a peer-reviewed journal.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (38)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .00000000000546 cm³/(molecule*sec)
Degradation	:	= 50 % after 23.4 hour(s)
Deg. product	:	
Method	:	other (calculated): Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20
Year	:	
GLP	:	
Test substance	:	other TS: hexane; (CAS #110-54-3)
Method	:	Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20 Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson under the following conditions: Temperature: 25°C Sensitizer: OH- radical Concentration of Sensitizer: 1.5E6 OH- radicals/cm3
Remark	:	Hexane has the potential to volatilize to air, based on a relatively high vapor pressure, where it is subject to atmospheric oxidation. In air, hexane can react with photosensitized oxygen in the form of hydroxyl radicals (OH-). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPI SuiteTM, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an OH- reaction rate constant and a defined OH- concentration. Based on a 12-hour day, a rate constant of 5.46 E-12 cm3/molecule*sec, and an OH- concentration of 1.5 E6 OH-/cm3, hexane has a calculated half-life in air of 1.96 days or 23.4 hours of daylight.
Test substance	:	CAS #110-54-3; hexane; purity is unknown.
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint
30.06.2008		(37)

Deg. product	:	
Method	:	
Year	:	
GLP	:	
Method	:	Technical discussion
Remark	:	Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and

wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982).
An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Saturated and unsaturated hydrocarbons do not absorb light above 290 nm. Consequently, hexane is not subject to photolytic processes in the aqueous environment.

Test substance : CAS #110-54-3; hexane
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
30.06.2008 (13) (39)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other: Technical discussion
Year :
GLP : no data
Test substance : other TS: hexane; (CAS #110-54-3)
Result : Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Gould, 1959). The lack of a suitable leaving group renders a compound resistant to hydrolysis. Hexane is resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive and Harris (1982) identifies hydrocarbons as generally resistant to hydrolysis. Therefore, hydrolysis will not contribute to the removal of hexane from the environment.
Test substance : CAS #110-54-3; hexane
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
30.06.2008 (11) (14)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type :
Media : other: air - biota - sediment(s) - soil - water
Air : % (Fugacity Model Level I)

Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Calculation according Mackay, Level I
Year :
Remark : The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment.

Physicochemical input values for the model were calculated using the EPIWIN Estimation v 3.20 program. Measured input values were also used where available and obtained from the EPIWIN database. Distribution data from the equilibrium model provide basic information on the potential partitioning behavior of chemicals between selected environmental compartments (i.e., air, water, soil, sediment, suspended sediment, biota).

Physicochemical data used in the calculation:

Parameter	Value w/ Units
Molecular Weight	86.18
Temperature	25° C
Log Kow	3.90
Water Solubility	9.5 g/m3
Vapor Pressure	20,131 Pa
Melting Point	-95.3° C

Result : Using the Mackay Level I calculation, the following distribution is predicted for heptane:

%Distribution	Compartment
99.97	Air
0.02	Water
0.01	Soil
<0.01	Sediment
<0.01	Suspended Sediment
<0.01	Biota

Test substance : CAS #110-54-3; hexane
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.
Flag : Critical study for SIDS endpoint
30.06.2008 (22)

Type : fugacity model level III
Media : other
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: Level III simulation using the Mackay Multimedia Environmental Model (Mackay, 2001)
Year :
Method : Level III simulation using the Mackay Multimedia Environmental Model (Mackay, 2001). Mass balances are calculated for the four bulk media of air (gas + aerosol), water (solution + suspended sediment + biota), soil, (solids + air + water), and sediment (solids + pore water). Equilibrium exists within, but not between media. Physical-chemical properties are used to quantify a chemical's behavior in an evaluative environment. Three types of chemicals are treated in this model: chemicals that partition into all media

(Type 1), non volatile chemicals (Type 2), and chemicals with zero, or near-zero, solubility (Type 3). The model cannot treat ionizing or speciating substances. The Level III model assumes a simple, evaluative environment with user-defined volumes and densities for the following homogeneous environmental media (or compartments): air, water, soil, sediment, suspended sediment, fish and aerosols.

This model provides a description of a chemical's fate including the important degradation and advection losses and the intermedia transport processes. The distribution of the chemical between media depends on how the chemical enters the system, e.g. to air, to water, or to both. This mode of entry also affects persistence or residence time.

The rates of intermedia transport are controlled by a series of 12 transport velocities. Reaction half-lives are requested for all 7 media. The advective residence time selected for air also applies to aerosols and the residence time for water applies to suspended sediment and fish. The advective residence time of aerosols, suspended sediment and fish cannot be specified independently of the air and water residence times.

Result : Output:

	Mass%	Emissions(kg/hr)
Air	21.3	1000
Water	63.3	1000
Soil	4.3	1000
Sediment	11.1	0

Test condition : Physicochemical data used in the calculation:

Parameter	Value w/ Units
Molecular Weight	86.18
Temperature	25° C
Log Kow	3.90
Water Solubility	9.5 g/m3
Vapor Pressure	20,131 Pa
Melting Point	-95.3° C

Reaction Half Lives in hours as predicted using EPI SuiteTM:

Air (gaseous)	23.5
Water (no susp. part.)	360
Bulk Soil	720
Bulk Sediment	7200

Environmental Properties (EQC standard environment)
Dimensions (all defaults)
Densities (all defaults)
Organic carbon & Advection (all defaults)
Transport Velocities (all defaults)

Emission and Inflows (defaults used)
Air 1000 kg/hr
Water 1000 kg/hr
Soil 1000 kg/hr
Sediment 0 kg/hr

Test substance : CAS #110-54-3; hexane

Conclusion : The majority of hexane is calculated to partition into the water phase, with smaller but significant amounts into air, soil, and sediment based on the modeling parameters used in this calculation. Hexane is considered to be a Type 1 chemical with potential to partition into all environmental compartments.

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.

Flag : Critical study for SIDS endpoint
30.06.2008 (23)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Contact time : 28 day(s)
Degradation : 74 (±) % after 28 day(s)
Result : other: readily biodegradable
Deg. product :
Method : OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year : 1996
GLP : yes
Test substance : other TS: heptane; (CAS #142-82-5)
Result : Test material was readily biodegradable. Half-life was reached by day 10. By day 28, 74% degradation of the test material was observed. 10% biodegradation was achieved on day 4.
By day 10, >60% biodegradation of positive control was observed, which met the guideline requirement. No excursions from the protocol were noted.
Biodegradation was based on oxygen consumption and the theoretical oxygen demand of the test material as calculated using results of an elemental analysis of the test material.

Sample	% Degradation* (day 28)	Mean % Degradation (day 28)
Test Material	72.5, 74.0, 76.8	74.4
Na Benzoate	88.7, 88.9	88.8

* replicate data

Test condition : Non acclimated activated sludge and test medium were combined prior to test material addition. Test medium consisted of glass distilled water and mineral salts (Phosphate buffer, Ferric chloride, Magnesium sulfate, Calcium chloride).
Test vessels were 1L glass flasks placed in a waterbath and electronically monitored for oxygen consumption.
Test material was tested in triplicate, controls and blanks were tested in duplicate.
Test material concentration was approximately 45 mg/L. Sodium benzoate (positive control) concentration was 50mg/L.
Test temperature was 22 +/- 1 Deg C.
All test vessels were stirred constantly for 28 days using magnetic stir bars and plates.
Test substance : CAS #142-82-5; heptane; 99% pure.
Conclusion : Heptane is readily biodegradable.
Reliability : (1) valid without restrictions

30.06.2008 (10)

Type : aerobic

Inoculum	:	other: soil, non-adapted
Contact time	:	20 day(s)
Degradation	:	70 (±) % after 20 day(s)
Result	:	other: readily biodegradable
Deg. product	:	
Method	:	other: Standard Methods for the Examination of Water and Waste Water
Year	:	1971
GLP	:	no
Test substance	:	other TS: heptane; (CAS #142-82-5)
Result	:	70% degradation was measured after 20 days incubation with an unacclimated inoculum. % Biodegradation of test substance after days: 2 days = 28 % 5 days = 63 % 10 days = 70 % 20 days = 70 %
Test condition	:	American Public Health Association, Standard Methods for the Examination of Water and Waste Water, using 1.0 mg/l of test substance. Biodegradation was determined by measuring biological oxygen demand (BOD). Each 300 ml BOD bottle received 1.0 mg of heptane, 1.0 ml of a 1:10 suspension Hudson-Collamer silt loam soil in distilled water, and a mineral salts solution prepared as described in the test method. Bottles were incubated in the dark at 25C. The test substance was obtained from Aldrich Chemical Co.
Test substance	:	CAS #142-82-5; heptane; 99% pure.
Conclusion	:	Heptane is readily biodegradable.
Reliability	:	(2) valid with restrictions A standard test method was used. The study was conducted prior to GLP.

30.06.2008 (12)

Type	:	aerobic
Inoculum	:	activated sludge
Contact time	:	28 day(s)
Degradation	:	= 100 (±) % after 28 day(s)
Result	:	Readily biodegradable
Deg. product	:	
Method	:	other: Modified MITI test (Comparable to OECD 301C)
Year	:	1992
GLP	:	no data
Test substance	:	CAS No. 110-54-3; hexane
Test condition	:	Concentration of the test substance was 100 mg/l, with a concentration of inoculum of 30 mg/l. The source of the inoculum was non-acclimated activated sludge.Results of the study were based on BOD.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Reliability	:	(2) valid with restrictions The study was performed following acceptable guidlines, however, the data were not retrieved an reviewed for quality.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (5)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species	:	other: see remark
Exposure period	:	at 25 °C
Concentration	:	
BCF	:	= 200

Elimination	:	
Method	:	other: calculation
Year	:	
GLP	:	no
Test substance	:	other TS: hexane; (CAS #110-54-3)
Remark	:	A log bioconcentration factor (BCF) of 2.30 is calculated (BCF = 200). With respect to a log Kow = 3.90, which was used to calculate the BCF, hexane in the aquatic environment is expected to have a low potential to bioaccumulate.
Test substance	:	CAS #110-54-3; hexane
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (37)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	
Species	:	other: fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 1.0
Method	:	other: ECOSAR version 0.99h, US EPA
Year	:	
GLP	:	
Test substance	:	other TS: hexane; (CAS #110-54-3)
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 96-hr LC50 for fish = 1.0 mg/L
Test condition	:	Experimental water solubility = 9.5 mg/l @ 25°C (McAuliffe, 1996), log Kow = 3.90 @ 20°C (Hansch, et.al, 1995), and melting point = -95.3°C (Lide et al., 2003) were entered into the program. Class: Neutral organics
Test substance	:	CAS #110-54-3; hexane
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

30.06.2008 (8)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	other: Daphnia
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 2.1

Method	:	other: based on discussions in GESAMP/MARPOL meetings held in 1973
Year	:	
GLP	:	no data
Method	:	Individual treatment concentrations were prepared by mixing the test substance in freshwater for 24 hours in a conical flask. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were 250 ml conical flasks with 25 daphnids per flask. Two replicates of each treatment level and control were evaluated. Organisms supplied by testing lab; age = <24 hours old; parents age = approximately 21 days old. Statistical method: Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result	:	48-hr EC50 for a daphnid = 2.1 mg/L
Test condition	:	Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C. Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 1.0 to 10 mg/L.
Test substance	:	CAS #110-54-3; hexane
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline, OECD 202, and used acceptable methods to prepare exposure solutions.
Flag	:	Critical study for SIDS endpoint

30.06.2008 (36)

Type	:	semistatic
Species	:	other: Gammarid (Chaetogammarus marinus)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= .4
Method	:	other: Static Gammarid Acute Toxicity Test
Year	:	
GLP	:	no data
Method	:	Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours. Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; length = 5 mm. Statistical method: Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result	:	96-hr LC50 for a gammarid = 0.4 mg/L
Test condition	:	Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 15 Deg C. Natural seawater was used with a

salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 1.0 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Test substance : CAS #110-54-3; hexane
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.
Flag : Critical study for SIDS endpoint
30.06.2008 (36)

Type : semistatic
Species : other: mysid shrimp (Mysidopsis bahia)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = .4
Method : other: Static Gammarid Acute Toxicity Test
Year :
GLP : no data
Method : Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours.

Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; test organisms were approximately 4 weeks old, with lengths of approximately 6 mm.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result : 96-hr LC50 for a mysid = 0.4 mg/L
Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C. Natural seawater was used with a salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 0.32 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Test substance : CAS #110-54-3; hexane
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.
Flag : Critical study for SIDS endpoint

30.06.2008 (36)

Type	:	
Species	:	other: Daphnia
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	= 1.3
Method	:	other: ECOSAR version 0.99h, US EPA
Year	:	
GLP	:	
Test substance	:	other TS: hexane; (CAS #110-54-3)
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 48-hr LC50 for a dahpnid = 1.3 mg/L
Test condition	:	Experimental water solubility = 9.5 mg/l @ 25°C (McAuliffe, 1996), log Kow = 3.90 @ 20°C (Hansch, et.al, 1995), and melting point = -95.3°C (Lide et al., 2003) were entered into the program. Class: Neutral organics
Test substance	:	CAS #110-54-3; hexane
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

30.06.2008 (8)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Green Alga
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	= .9
ChV	:	= .3
Method	:	other: ECOSAR version 0.99h, US EPA
Year	:	

GLP	:	
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 96-hr EC50 for a green alga = 0.9 mg/L Calculated 96-hr ChV for a green alga = 0.3 mg/L
Test condition	:	Experimental water solubility = 9.5 mg/l @ 25°C (McAuliffe, 1996), log Kow = 3.90 @ 20°C (Hansch, et.al, 1995), and melting point = -95.3°C (Lide et al., 2003) were entered into the program. Class: Neutral organics
Test substance	:	CAS #110-54-3; hexane
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are calculated and not measured.

30.06.2008 (8)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	28,720 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Year	:	
GLP	:	
Remark	:	
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Conclusion	:	Hexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

21.07.2008 (17)

Type	:	LD50
Value	:	=15,840 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	no data
Year	:	
GLP	:	
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Conclusion	:	Hexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

21.07.2008 (17)

Type	:	LD50
Value	:	29,700 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	1970
GLP	:	pre-GLP
Remark	:	The oral LD50 in a 14-day old rat was 29,700 mg/kg. Symptoms included depressive effect on the central nervous system, salivation and soft faeces.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Conclusion	:	Hexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions

Original study not retrieved and reviewed. Data from reliable peer-reviewed source.

Flag : Critical study for SIDS endpoint

21.07.2008 (19)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	48,000 ppm
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	no data
Vehicle	:	other: none
Doses	:	1000 to 64000 ppm
Exposure time	:	4 hour(s)
Method	:	other: Similar to OECD guideline 403
Year	:	
GLP	:	
Remark	:	Animals were exposed to n-heptane vapor for 4 hours at concentrations of 1000 to 64000 ppm.
Conclusion	:	n-Hexane has a low order of toxicity by the inhalation route of exposure.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.

21.07.2008 (16)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	humans
Sex	:	no data
Number of animals	:	
Duration of study	:	
Doses	:	
Method	:	no data
Year	:	1973
GLP	:	pre-GLP
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Result	:	Mild irritant
Remark	:	Dermal exposure can lead to peripheral neuropathy in humans.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

22.07.2008 (29)(34)(35)

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Number of animals	:	15/sex/group
Strain	:	F344
Route of admin.	:	inhalation
Exposure period	:	6 hours/day
Frequency of treatm.	:	5 days/week for 13 weeks
Doses	:	0, 3000, 6500 and 10000 ppm
Control group	:	yes
Method	:	no data
Year	:	1984
GLP	:	
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Result	:	There were no n-hexane-related clinical signs of toxicity, effects on food consumption, ophthalmological findings, or changes in neurological function. However, there was a lowering of the urinary pH in high-dose males. There were increased organ/body weight ratios for liver, kidney, and testis in high-dose males and kidney in mid-dose males. Histopathological examination of the tibial nerves revealed paranodal axonal swelling in mid- and high-dose males.
Remark	:	n-Hexane is metabolized to 5-hydroxy-2-hexanone and 2,5-hexanedione *in vivo* (DiVincenzo *et al*., 1976). These two metabolites are believed to be responsible for the neurotoxicities associated with n-hexane exposure. There is evidence to show that 2,5-hexanedione is more persistent in peripheral nerve tissue than the parent n-hexane (Bus *et al*., 1981).
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.

08.08.2008 (3)(4)

Type	:	
Species	:	rat
Sex	:	male
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	12 hours/day
Frequency of treatm.	:	7 days/week for 16 weeks
Doses	:	0, 500, 1200, 3000 ppm
Control group	:	yes,
NOAEL	:	500 ppm
Method	:	other: none specified
Year	:	1989
GLP	:	no data
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Remark	:	Motor nerve conduction velocity was measured in the tail nerve along with body weight before exposure and after 4, 8, 12, and 16 weeks of exposure. One animal from each group was sacrificed after 16 weeks of exposure for histopathological evaluation of the nerve fibers in the tail. In addition, nerve-specific proteins (i.e. enolase and β-S100), involved in processes such as cell-cell communication, cell growth, intracellular signal transduction, and development and maintenance of the central nervous system, were measured.

Result	:	Statistically significant reductions in body weight gain were observed in a for the mid-dose (at 12 weeks) and high-dose (at 8 weeks) rats. Neurological deficits (i.e. reduction in grip strength and comparative slowness of motion) in mid- and high-dose rats were noted from 12 weeks of exposure. No hind-limb paralysis was observed by the time of sacrifice. A reduction in motor nerve conduction velocity, statistically significant during weeks 8-16, was seen with mid and high-dose rats. In addition increased incidence of paranodal swelling, along with some evidence of demyelination and remyelination was present in the peripheral nerves with 1,200 and 3,000 ppm. These histopathologic findings were most sever in the high-dose group. Dose-dependent biochemical changes included reductions in nervous system-specific proteins, particularly the β-S100 protein in tail nerve fibers which was reduced by approximately 75% at all dose levels.
Conclusion	:	Under the conditions of this study, the NOAEL was 500 ppm based on the neurophysiologic deficits and histopathologic effects seen with 1,200 and 3,000 ppm.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.

08.08.2008 (18)

Type	:	
Species	:	mouse
Sex	:	male /female
Number of animals	:	10/sex/group
Strain	:	B6C3F1
Route of admin.	:	inhalation
Exposure period	:	6 hours/day
Frequency of treatm.	:	5 days/week for 13 weeks
Doses	:	0, 500, 1000, 4000, 10000 ppm
Control group	:	yes,
NOAEL	:	500 - ppm
Method	:	other: none specified
Year	:	1991
GLP	:	no data
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Remark	:	Groups of 10 mice/sex/group were exposed to 0, 500, 1,000, 4,000, or 10,000 ppm n-hexane 6 hours/day, 5 days per week for the duration of the study. A second group of 10 mice was exposed at 1,000 ppm for 22 hours/day, 5 days/week for the duration of the study. Separate groups of 8 mice/sex/group received identical treatments but were subjected to neurobehavioral tests before the start of dosing then again after 6 and 13 weeks of exposure. Four males and four females were randomly selected from the 0, 1,000 ppm extended duration, and 10,000 ppm exposure groups for histopathological examination of the spinal cord and tibial nerves. Animals were observed daily for signs of clinical toxicity and weighed weekly.
Result	:	A full necropsy was performed at sacrifice, weights of the major organs were recorded, and histopathological evaluations were carried out at term on a variety of excised organs and tissues. The liver was examined only in the males of all exposure groups. Animals exposed to 10,000 ppm n-hexane exhibited some signs of nasal irritation and all animals survived to term. Relative liver, kidney, and heart weights appeared to be increased compared with controls in exposed females. In addition, females exposed to 10,000 ppm 6 hours/day and 1,000 ppm for 22 hours/day exhibited neurobehavioral deficits with a reduction in locomotor activity. There was an increased incidence of paranodal axonal swelling in high-dose or

extended exposure duration mice.

Conclusion	:	It was concluded that n-hexane caused minimal toxicity to the nervous system and/or respiratory system at 1,000 ppm and above indicating a NOAEL of 500 ppm.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.

08.11.2008 (28)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Test species/strain: Salmonella typhimurium TA100, TA1535, TA97, TA98, TA1537
Test concentration	:	0, 0.001, 0.0033, 0.010, 0.033, 0.10, and 0.333 mg/plate
Cytotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	no data
Year	:	1986
GLP	:	no data
Test Method	:	*Salmonella typhimurium* (TA1535, TA1537, TA97, TA98 and TA100) were incubated with and without metabolic activation. Two metabolic activation systems were used, one with S9 rats livers and the other with Syrian hamster livers. Doses of hexane ranged from 0 to 0.333 mg/plate.
Result	:	The highest negative dose tested in any Salmonella typhimurium strain was 0.333 mg/plate. Some cultures exhibited slight clearing of the background bacterial lawn at the two highest doses tested. Genotoxic effects: With metabolic activation: negative Without metabolic activation: negative
Test substance	:	CAS No. 110-54-3; hexane
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

22.07.2008 (27)(28)

Type	:	Mouse Lymphoma Assay
System of testing	:	L5178Y mouse lymphoma cells (TK locus)
Test concentration	:	40 to 180 µg/ml
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	Method equivalent to current guidelines
Year	:	1980
GLP	:	no data
Method	:	The ability of n-hexane to induce specific locus mutations at the TK locus in cultured L5178Y mouse lymphoma cells was evaluated in the presence and absence of Aroclor-induced rat liver S9 metabolic activation. Based on preliminary toxicity tests, 8 non-activated cultures were treated with 80, 90, 100, 110, 120, 130, 140, or 150 µg/ml which produced a range of 0 to 140% total growth. Eight activated cultures were treated with 40, 60, 80, 100, 120, 140, 160, or 180 µg/ml which produced a range of 0 to 22% total growth. The method used was equivalent to the guidelines.

Result	:	None of the non-activated or activated cultures produced mutant frequencies significantly greater than the solvent controls.
Test substance	:	CAS No. 110-54-3; n-hexane
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

11.08.2008 (15)

Type	:	Sister Chromatid Exchange Test
System of testing	:	Mouse bone marrow cells
Test concentration	:	500, 1000, 2000 mg/kg
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	Method equivalent to current guidelines
Year	:	1982
GLP	:	no data
Remark	:	No increase in the incidence of sister chromatid exchanges in *in vivo* mouse bone marrow cells was seen with intraperitoneal doses of 500, 1,000, or 2,000 mg/kg n-hexane.
Result	:	The dosed groups displayed slight increases in chromosomal aberrations, but this increase was not considered to be significant.
Test substance	:	CAS No. 110-54-3; hexane
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

12.08.2008 (28)

Type	:	Unscheduled DNA synthesis
System of testing	:	Human lymphocytes
Test concentration	:	0.1 to 10 mM cyclohexane
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	Method equivalent to current guidelines
Year	:	1983
GLP	:	no data
Remark	:	Human lymphocytes (+ or – S9 mix) were cultured for 4 hours in the presence or absence of hexane. The effects on the DNA synthesis were measured through cellular [^{3}H]TdR uptake.
Result	:	DNA synthesis was inhibited in human lymphocytes in the presence of concentrations of n-hexane from 10^{-4} – 10^{-2} M but only at cytotoxic concentrations
Test substance	:	CAS No. 110-54-3; hexane
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

22.07.2008 (30)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus

Species	:	mouse
Strain	:	B6C3F1
Sex	:	no data
Route of admin.	:	Intraperitoneal injection
Result	:	negative
Doses	:	
Method	:	
Year	:	
GLP	:	no data
Remark	:	
Result	:	n-Hexane did not induce chromosomal aberrations and micronuclei in bone marrow cells of B6C3F1 mice injected intraperitoneally.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

22.07.2008 (32)

Type	:	Cytogenetic Assay
Species	:	rat
Strain	:	Sprague Dawley
Sex	:	Male/female
Number of animals	:	10 per sex
Route of admin.	:	inhalation
Exposure period	:	6 hours/day for 5 days
Doses	:	0, 150, 300, 600 ppm
Method	:	other: not specified
Year	:	
GLP	:	no data
Remark	:	
Result	:	A slight, but significant, increase in the number of chromosomal mutations induced by n-hexane in albino rat bone marrow cells was reported. In addition, an in vivo bone marrow cytogenetic assay found that male albino rats exposed to 150, 300, and 600 ppm of n-hexane for 5-days experienced a significant increase in chromosomal aberrations at all treatment levels compared with controls.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

22.07.2008 (15)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Type	:	Developmental toxicity
Species	:	rat
Sex	:	female
Number of animals	:	30/group
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	14 days
Frequency of treatm.	:	20 hours/day

Doses	:	0, 200, 1000, or 5000 ppm
Control group	:	yes
Method	:	no data
Year	:	1987
GLP	:	no data
Method	:	The developmental toxicity of n-hexane was assessed using timed-pregnant (30 animals per group) and virgin (10 animals per group) Sprague-Dawley rats exposed to 0 (filtered air), 200, 1,000, and 5,000 ppm n-hexane vapor in inhalation chambers for 20 hours per day for a period of 14 consecutive days (Mast, 1987). Spermpositive females were exposed on gestation days (GD) 6-19 and virgins were exposed concurrently for 14 consecutive days.
Result	:	Maternal toxicity, manifested as a reduction in extra-gestational maternal weight gain, was observed at all exposure levels, and was statistically significant for the 5,000 ppm exposure group. Extra-gestational maternal weight gain (calculated from GD 0 to GD 20) relative to control animals was reduced for the 200, 1,000, and 5,000 ppm exposure groups. Cumulative weight gain (CWG) for dams in the 1,000 and 5,000 ppm exposure groups was significantly reduced with respect to controls by GD 20. The CWG for the 5,000 ppm was also significantly reduced with respect to controls by GD 13. Comparison of n-hexane exposed groups with the control group (0 ppm) indicated that gestational exposure to n-hexane did not result in an increase in the incidence of intrauterine deaths or in the incidence of fetal malformations. A statistically significant reduction in fetal body weight relative to controls was observed for males at the 1,000 and 5,000 ppm exposure levels. Female weights were also reduced with respect to controls for these exposure levels, but the reduction was statistically significant for only the 5,000 ppm group. Gravid uterine weight was also significantly less than controls for the 5,000 ppm exposure groups. A statistically significant increase in the mean percent incidence per litter of reduced ossification of sternebrae 1-4 was observed for the 5,000 ppm group, and was positively correlated with exposure concentration. This increased incidence of reduced ossification in the sternebrae, and the reduction in fetal body weight at the 5,000 ppm level, may have been inter-related manifestations of slight growth retardation. No major abnormalities were found in any of the fetuses. Variations observed included dilated ureter, renal pelvic cavitation, supernumerary ribs, and reduced skeletal ossifications at several sites. The increase in mean percent incidence per litter of reduced ossification of sternebrae 1-4 was statistically significant for the highest exposure concentration, and the increase was positively correlated with increasing exposure concentration.
Conclusion	:	The NOAEL for developmental toxicity was 200 ppm.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

18.07.2008 (24)

Type	:	
Species	:	rat
Sex	:	male
Number of animals	:	12 to 39/group
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	24 hours

Frequency of treatm.	:	single
Doses	:	5000 ppm
Control group	:	yes
Method	:	no data
Year	:	1987
GLP	:	no data
Method	:	The effect of n-hexane on the male reproductive system when administered via the inhalation route was examined by exposing male Sprague-Dawley rats (12-39/group) to 5,000 ppm n-hexane in either a single 24 hour exposure, repeated 16 hour/day exposures for up to 8 days, or repeated 16 hour/day exposures, 6 hours/day for up to 6 weeks.
Result	:	Rats exposed to 5,000 ppm n-hexane displayed some evidence of neuropathy such as paralysis. Focal degeneration of spermatocytes and exfoliation of elongated spermatids was also observed in response to treatment. Early meiotic prophase spermatocytes and transitional spermatocytes as well as those undergoing meiotic metaphase appeared to be more susceptible to the action of n-hexane than pachytene spermatocytes. Rats exposed repeatedly to 5,000 ppm n-hexane over a 6-week period showed complete atrophy of the seminiferous tubules. In addition, a reduction in food consumption and body weight gain accompanied by signs of incipient neuropathy were seen with repeated n-hexane exposure. A wide range of testicular lesion did not complete resolve during a recovery period even though body weights and clinical symptoms improved.
Test substance	:	CAS No. 110-54-3; hexane; purity is unknown
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag	:	Critical study for SIDS endpoint

11.08.2008 (7)

Type	:	
Species	:	mouse
Sex	:	female
Number of animals	:	33/group
Strain	:	CD-1
Route of admin.	:	inhalation
Exposure period	:	14 days
Frequency of treatm.	:	20 hours/day
Doses	:	0, 200, 1000, or 5000 ppm
Control group	:	yes
Method	:	no data
Year	:	1988
GLP	:	no data
Method	:	Timed-pregnant (~33 females per group) and virgin (10 females per group) Swiss (CD-1) mice were exposed to 0, 200, 1,000, and 5,000 ppm n-hexane (99.2% purity) vapor in inhalation chambers, 20 h/day, for a period of 12 consecutive days. Plug-positive females were exposed on GD 6-17.
Result	:	Maternal body weight at sacrifice (GD 18) and total cumulative weight gain for dams in the 5,000 ppm exposure group were significantly reduced with respect to controls; however, this was due to an exposure correlated reduction in gravid uterine weight, not to a decrease in extragestational gain. An exposure-correlated decrease in the gravid uterine weight to extragestational weight gain ratio (significant for the 5,000 ppm group) occurred in the absence of an effect on placental weight. Gestational exposure to n-hexane resulted in an increase in the number of resorbed fetuses for all exposure groups relative to the control group; however, the increases were not directly correlated to exposure

concentration. The differences were statistically significant for the 200-ppm group with respect to total intrauterine death (early plus late resorptions), and with respect to late resorptions for the 5,000 ppm group. A small, but statistically significant, reduction in female (but not male) fetal body weight relative to the control group was observed at the 5,000 ppm exposure level. There were no exposure-related increases in any individual fetal malformation or variation, nor was there any increase in the incidence of combined malformations or variations.

Gestational exposure of CD-1 mice to n-hexane vapors appeared to cause a degree of concentration-related developmental toxicity in the absence of overt maternal toxicity, but the test material was not found to be teratogenic. This developmental toxicity was manifested as an increase in the number of resorptions per litter for all exposure levels, and as a decrease in the uterine: extra-gestational weight gain ratio at the 5,000 ppm exposure level. Because of the significant increase in the number of resorptions at the 200-ppm exposure level, a NOEL for developmental toxicity was not established for exposure of mice to 200, 1,000, or 5,000 ppm n-hexane vapors.

Conclusion : The LOAEL for developmental toxicity (in mice) was 200 ppm.

Test substance : CAS No. 110-54-3; hexane; purity 99.2%
Reliability : (2) valid with restrictions
Original study not retrieved and reviewed. Data from reliable peer-reviewed source.
Flag : Critical study for SIDS endpoint
11.08.2008 (26)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D

Data Set

Existing Chemical	:	ID: 110-82-7
CAS No.	:	110-82-7
EINECS Name	:	Cyclohexane
EC No.	:	203-806-2
TSCA Name	:	Cyclohexane
Molecular Formula	:	C6H12
IUPAC Name	:	Cyclohexane

Producer related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008

Substance related part

Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	30.06.2008
Status	:	
Memo	:	U.S. EPA - HPV Challenge Program
Printing date	:	30.06.2008
Revision date	:	
Date of last update	:	30.06.2008
Number of pages	:	41
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	petroleum product
Physical status	:	liquid
Purity	:	
Colour	:	
Odour	:	

01.07.2008

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 6.6 °C
Sublimation	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (27)

2.2 BOILING POINT

Value	:	= 80.7 °C at 1013 hPa
Decomposition	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (27)

2.3 DENSITY

Type	:	density
Value	:	= .774 g/cm³ at 20 °C
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (43)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 12.9 hPa at 25 °C
Decomposition	:	
Method	:	other (measured): not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (4)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 3.44 at 20 °C
pH value	:	
Method	:	other (measured): not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite. This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (14)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 55 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: not specified
Year	:	
GLP	:	no data
Test substance	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions Data supplied by the experimental database associated with EPISuite.

This robust summary has a reliability rating of 2 because the data was not reviewed for quality, however, the reference is associated with a peer-reviewed publication.

Flag : Critical study for SIDS endpoint
01.07.2008 (30)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .00000000000848 cm³/(molecule*sec)
Degradation	:	= 50 % after 15.1 hour(s)
Deg. product	:	
Method	:	other (calculated): Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20
Year	:	
GLP	:	
Test substance	:	

Method	:	Calculated values using AOPWIN version 1.92, a subroutine of the computer program EPI SuiteTM version 3.20 Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson under the following conditions: Temperature: 25°C Sensitizer: OH- radical Concentration of Sensitizer: 1.5E6 OH- radicals/cm3
Remark	:	Cyclohexane has the potential to volatilize to air, based on a relatively high vapor pressure, where it is subject to atmospheric oxidation. In air, cyclohexane can react with photosensitized oxygen in the form of hydroxyl radicals (OH-). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPI SuiteTM, 2000) calculates a chemical half-life for a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated), based on an OH- reaction rate constant and a defined OH- concentration. Based on a 12-hour day, a rate constant of 8.48 E-12 cm3/molecule*sec, and an OH- concentration of 1.5 E6 OH-/cm3, cyclohexane has a calculated half-life in air of 1.3 days or 15.1 hours of daylight.
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (46)

Type	:	water
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Test condition	:	Direct photochemical degradation occurs through the absorbance of solar radiation by a chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range.

Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982).

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Saturated and unsaturated hydrocarbons do not absorb light above 290 nm. Consequently, cyclohexane is not subject to photolytic processes in the aqueous environment.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
01.07.2008 (15)(48)

3.1.2 STABILITY IN WATER

Deg. product :
Method : other: Technical Discussion
Year :
GLP : no data
Test substance :

Result : Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with leaving groups that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Gould, 1959). The lack of a suitable leaving group renders a compound resistant to hydrolysis. Cyclohexane is resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive and Harris (1982) identifies hydrocarbons as generally resistant to hydrolysis. Therefore, hydrolysis will not contribute to the removal of cyclohexane from the environment.
Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability of 2 because it is a technical discussion and not a study.
Flag : Critical study for SIDS endpoint
01.07.2008 (13)(16)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level I
Media : other: air - biota - sediment(s) - soil - water
Air : % (Fugacity Model Level I)

Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: Calculation according Mackay, Level I
Year	:	2003

Method : The EQC Level I is a steady state, equilibrium model that utilizes the input of basic chemical properties including molecular weight, vapor pressure, and water solubility to calculate distribution within a standardized regional environment.

Physicochemical input values for the model were calculated using the EPIWIN Estimation v 3.20 program. Measured input values were also used where available and obtained from the EPIWIN database. Distribution data from the equilibrium model provide basic information on the potential partitioning behavior of chemicals between selected environmental compartments (i.e., air, water, soil, sediment, suspended sediment, biota).

Input values used:
Molecular mass = 84.16 g/mol
Water solubility = 55 g/m^3
Vapour pressure = 12,919 Pa
log Kow = 3.44
Melting point = 6.6 deg C

Result :

Air - 99.91%
Water - 0.03%
Soil - 0.06%
Sediment - <0.01%
Suspended Sed - <0.01%
Biota - <0.01%

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.

01.07.2008 (28)

Type	:	fugacity model level III
Media	:	other: air - sediment(s) - soil - water
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: Calculation according Mackay, Level III
Year	:	2003

Method : The EQC Level III model is a steady state model that is useful for determining how the medium of release affects environmental fate. Level III fugacity allows non-equilibrium conditions to exist between connected media as steady state, and illustrate important transport and transformation processes.

Physicochemical input values for the model were calculated using the EPIWIN Estimation v 3.20 program. Measured input values were also used where available and obtained from the EPIWIN database. Distribution data from the equilibrium model provide basic information on the potential partitioning behavior of chemicals between selected environmental compartments (i.e., air, water, soil, and sediment).

Input values used:

Molecular mass = 84.16 g/mol
Water solubility = 55 g/m^3
Vapour pressure = 12,919 Pa
log Kow = 3.44
Melting point = 6.6 deg C

Degradation half-lives:

Air - 15.1 hrs
Water - 360 hrs
Soil - 720 hrs
Sediment - 7200 hrs

Environmental Properties (EQC standard environment)
Dimensions (all defaults)
Densities (all defaults)
Organic carbon & Advection (all defaults)
Transport Velocities (all defaults)

Emission and Inflows (defaults used)
Air 1000 kg/hr
Water 1000 kg/hr
Soil 1000 kg/hr
Sediment 0 kg/hr

Result : Output:

	Mass%	Emissions(kg/hr)
Air	15.8	1000
Water	67.3	1000
Soil	12.9	1000
Sediment	4.0	0

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag : Critical study for SIDS endpoint
01.07.2008 (28)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Contact time : 28 day(s)
Degradation : 77 (±) % after 28 day(s)
Result : other: readily biodegradable
Deg. product :
Method : OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year : 1995
GLP : yes
Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown

Result : Test material was readily biodegradable. Half-life was reached by day 20. By day 28, 77% degradation of the test material was observed. 10% biodegradation was achieved on day 13.
By day 2, >60% biodegradation of positive control was observed, which met the guideline requirement. No excursions from the protocol were noted.
Biodegradation was based on oxygen consumption and the theoretical oxygen demand of the test material as calculated using results of an elemental analysis of the test material.

Sample	% Degradation* (day 28)	Mean % Degradation (day 28)
Test Material	79.8, 70.7, 80.2	76.9
Na Benzoate	91.0, 90.4	90.7

* replicate data

Test condition : Non acclimated activated sludge and test medium were combined prior to test material addition. Test medium consisted of glass distilled water and mineral salts (Phosphate buffer, Ferric chloride, Magnesium sulfate, Calcium chloride).
Test vessels were 1L glass flasks placed in a waterbath and electronically monitored for oxygen consumption.
Test material was tested in triplicate, controls and blanks were tested in duplicate.
Test material concentration was approximately 34 mg/L. Sodium benzoate (positive control) concentration was 50mg/L.
Test temperature was 22 +/- 1 Deg C.
All test vessels were stirred constantly for 28 days using magnetic stir bars and plates.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown.

Conclusion : Cyclohexane is readily biodegradable.

Reliability : (1) valid without restrictions

01.07.2008 (9)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other: see remark

Exposure period : at 25 °C

Concentration :

BCF : = 89

Elimination :

Method : other: calculation

Year :

GLP : no

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown

Remark : A log bioconcentration factor (BCF) of 1.95 is calculated (BCF = 89). With respect to a log Kow = 3.44, which was used to calculate the BCF, cyclohexane in the aquatic environment is expected to have a low potential to bioaccumulate.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated and not measured.

Flag : Critical study for SIDS endpoint

01.07.2008 (43)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : Flow Through Acute Fish Toxicity Test
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : 4.53 measured/nominal
Limit test :
Analytical monitoring : no data
Method :
Year : 1987
GLP : no data
Statistical Method : Trimmed Spearrman Karber Method
Test Conditions : Treatment solutions were prepared by diluting a 37.9mg/L stock solution. Nominal cyclohexane treatment levels were 1.62, 3.24, 4.86, 6.48, 8.10 mg/L, which measured 2.00, 3.53, 4.84, 6.96 and 8.86mg/L, respectively.

Control/dilution water was EPA Duluth laboratory water.
Ten fish were tested per treatment. Treatment volume = 250ml.

Test parameters were as follows: temperature = 25.2 Deg C (s.d. 0.14); dissolved oxygen (DO) = 7.2 mg/L (s.d. 0.38); pH = 7.5 (s.d. 0.10); fish age = 30 days old; fish mean wt. = 0.119 g; fish mean length = 20.5 mm; fish loading = 0.1190 g/L/day. Temperature, DO, and pH data from the treatment solutions were only provided as mean values with standard deviations.

Organism supplier was U.S. EPA Environmental Research Lab, Duluth, MN, USA.

Results : 96-hour LC50 = 4.53 mg/L (95% CI 3.96 to 5.18) based upon measured concentrations

Analytical method used was Gas-Liquid Chromatography.

Measured Conc. (mg/L)	Fish Total Mortality (@ 24, 48, 72, 96 hrs)*
Control	0, 0, 0, 0
2.00	0, 0, 0, 0
3.52	1, 1, 1, 1
4.84	0, 2, 3, 6
6.96	10, 10, 10, 10
8.86	10, 10, 10, 10

* 10 fish added at test initiation

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Conclusion : 96-hour LC50 = 4.53 mg/L (95% CI 3.96 to 5.18) based upon measured concentrations
Reliability : (1) valid without restrictions
Although a standard method was not cited, the testing procedures followed generally accepted fish acute toxicity guideline methods and sufficient information on testing method and conditions was available to rate this study as "reliable without restriction".
Flag : Critical study for SIDS endpoint
01.07.2008 (12)

Type :
Species : other: freshwater fish
Exposure period : 96 hour(s)

Unit	:	mg/l
LC50	:	= 2.8 calculated
Method	:	other: ECOSAR Computer Model
Year	:	
GLP	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Method	:	ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound. To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Result	:	Calculated 96-hr LC50 for fish = 2.8 mg/L
Test condition	:	Experimental water solubility = 55.0 mg/l @ 25°C (McAuliffe, 1966), log Kow = 3.44 @ 20°C (Hansch, et.al, 1995), and melting point = 6.6°C (Lide, 2003) were entered into the program. Class: Neutral organics
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag	:	Critical study for SIDS endpoint

01.07.2008 (3)

Type	:	Fish Acute Toxicity Test
Species	:	Oncorhynchus mykiss (Fish, fresh water, marine)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	3.2 measured/nominal
Limit test	:	no
Analytical monitoring	:	no
Method	:	OECD 203 Fish Acute Toxicity Test
Year	:	2000
GLP	:	yes
Statistical Method	:	Binomial Method
Test Conditions	:	Individual Water Accomodated Fractions (WAF's) were prepared for each test treatment. The test substance was added volumetrically, via a syringe, to 19L of dilution water in a 20L glass carboy. The solutions were mixed for

24 hours at a vortex of </= 10% of the total depth. The test solutions were pumped from each mixing vessel into three replicates of 4.5L in 4.0L glass aspirator bottles (no headspace). Five fish were added to each test replicate and the replicates sealed. Daily renewals were performed by removing ~80% of the test solution through the port at the bottom and refilling with fresh solution.

Test temperature was 14.5 Deg C., Lighting was 16 hours light : 8 hours dark with 562 to 728 Lux during full daylight periods.
Dissolved Oxygen at initiation ranged from 8.6 to 8.9 mg/L and from 7.1 to 8.1 mg/L in "old" solutions prior to renewals. The pH was ranged from 7.5 to 7.8 during the study. Fish were not fed during the study. Water hardness ranged from 92 to 96 mg/L as $CaCO_3$.

Fish Mean Wt.= 0.213g. Mean Total length = 3.1cm, Test Loading = 0.24 g of fish/L.

Results : LL50 = 3.2mg/L (CI 1.0 to 10.0), based upon nominal loading levels.

Nominal Conc.	% Mortality @ 96 hr.
Control	0
1 mg/L	0
10 mg/L	10
100 mg/L	10

Dissolved oxygen levels dropped below 60% of saturation in some of the treatments on Days 1 through 4 of the test. Since no mortality occurred in these treatments, the deviations are not believed to have affected the outcome of the study.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
No analytical monitoring of test concentrations was performed.

01.07.2008 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 3.3 calculated
Method : other: ECOSAR Computer Model
Year :
GLP :
Test condition : ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be

calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound.

To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Result : Calculated 48-hr LC50 for a dahpnid = 3.3 mg/L
Test condition : Experimental water solubility = 55.0 mg/l @ 25°C (McAuliffe, 1966), log Kow = 3.44 @ 20°C (Hansch, et.al, 1995), and melting point = 6.6°C (Lide, 2003) were entered into the program.
Class: Neutral organics
Reliability : (2) valid with restrictions
The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.
Flag : Critical study for SIDS endpoint
08.07.2008 (3)

Type : static
Species : other: Daphnia
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 0.9
Method : other: based on discussions in GESAMP/MARPOL meetings held in 1973
Year :
GLP : no data
Method : Individual treatment concentrations were prepared by mixing the test substance in freshwater for 24 hours in a conical flask. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were 250 ml conical flasks with 25 daphnids per flask. Two replicates of each treatment level and control were evaluated.

Organisms supplied by testing lab; age = <24 hours old; parents age = approximately 21 days old.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result : 48-hr EC50 for a daphnid = 0.9 mg/L
Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C.

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 1.0 to 10 mg/L.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient

information in the report to suggest that the testing procedure generally followed an acceptable test guideline, OECD 202, and used acceptable methods to prepare exposure solutions.

Flag : Critical study for SIDS endpoint
30.06.2008 (44)

Type : semistatic
Species : other: Gammarid (Chaetogammarus marinus)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 2.2
Method : other: Static Gammarid Acute Toxicity Test
Year :
GLP : no data
Method : Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours.

Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; length = 5 mm.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).
Result : 96-hr LC50 for a gammarid = 2.2 mg/L
Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 15 Deg C. Natural seawater was used with a salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 1.0 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.

Flag : Critical study for SIDS endpoint
30.06.2008 (44)

Type : semistatic
Species : other: mysid shrimp (Mysidopsis bahia)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 2.2
Method : other: Static Gammarid Acute Toxicity Test
Year :
GLP : no data
Method : Individual treatment solutions were prepared by mixing the test substance in freshwater for 24 hours in conical flasks. The flask was almost completely filled with solution. After mixing, the treatment solutions were

allowed to settle for 24 hours. The aqueous solution was then drained through a stopcock at the base of the flask and tested. Test vessels were scintillation vials almost filled with approximately 20 ml of test solution and one organism per vial. Ten organisms were tested per treatment level. Organisms were transferred into fresh control and test solutions every 24 hours up to 96 hours.

Organisms supplied by testing lab, grown in natural seawater with a salinity of 2.8%; test organisms were approximately 4 weeks old, with lengths of approximately 6 mm.
Statistical method:
Parametric model developed by Kooijman (Kooijman, S.A.L.M. 1981. Parametric analyses of mortality rate in bio-assays. Water Res., 15:107-119.).

Result : 96-hr LC50 for a mysid = 2.2 mg/L

Test condition : Dissolved oxygen was >50% saturation during the study. The pH was 7.5 to 8.3. Temperature was 20 Deg C. Natural seawater was used with a salinity of 2.8%

Analytical method used was Gas Chromatography with Flame Ionization Detection (GC-FID). Nominal treatment levels ranged from 0.32 to 10 mg/L. Test solutions were analyzed only upon test initiation.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because there is less raw data and information on the testing procedure than is desirable in order to rate this study for reliability at a level higher than 2. There is sufficient information in the report to suggest that the testing procedure generally followed an acceptable test guideline and used acceptable methods to prepare exposure solutions.

Flag : Critical study for SIDS endpoint

30.06.2008 (44)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae: Pseudokirchneriella subcapitata

Endpoint :

Exposure period : 72 hour(s)

Unit : mg/l

EC50 : = 3.4 measured

Method : OECD 201 - Alga, Growth Inhibition Test

Year : 1998

GLP : yes

Statistical Method : Proc regression procedure of SAS, Anova procedure of SAS for NOEC

Test condition :

Individual test treatment solutions were prepared as Water Accommodated Fractions (WAFs). Test material was added to algal media via syringe in 2.0L aspirator bottles. The bottles were completely filled, no headspace. The mixing vessels were sealed with Teflon-covered stoppers and mixed on magnetic stir plates with teflon coated stir bars for 23.5 hours at room temperature. After mixing the solutions were allowed to settle for one hour and the WAF was removed from the bottom of the mixing vessel via the port and used for testing. Test vessels were 125ml glass Erlenmeyer flasks with approximately 140 ml of treatment solution and inoculated with algae. Test vessels were completely filled and sealed with glass stoppers. Samples were taken daily for cell counts. Six replicates were prepared for each treatment level. The initial algal concentration was 1.0×10^4 cells/ml. All test replicates were placed on a shaker table at 100 oscillations per minute

during the study. Biomass was calculated as the area under the growth curve.
Nominal loading levels were 0.5, 1.4, 3.9, 11, and 31 mg/L

Test temperature was 24.6 Deg. C. Lighting was continuous at approximately 4200 Lux. The pH was 7.5 to 7.6 at test initiation and ranged from 8.4 to 8.7 at test termination.

Test treatments were analyzed by GC-FID. Measured values on Day 0 were 0.085, 0.719, 0.952, 2.940 and 4.425 mg/L. The test material was not detected in the control.

Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Result : 72-hr EC50 for a green alga = 3.4 mg/L
72-hr NOEC for a green alga = 0.952 mg/L
Reliability : (1) valid without restrictions

Flag : Critical study for SIDS endpoint
02.07.2008 (10)

Species : other algae: Pseudokirchneriella subcapitata
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 2.2 calculated
ChV : = 0.5 calculated
Method : other: ECOSAR Computer Model
Year :
GLP :
Test condition : ECOSAR version 0.99h, U.S. EPA. The structure-activity relationships (SARs) presented in this program are used to predict the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. Most SAR calculations in the ECOSAR Class Program are based upon the octanol/water partition coefficient (Kow). SARs have been used by the U.S. Environmental Protection Agency since 1981 to predict the aquatic toxicity of new industrial chemicals in the absence of test data. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures, e.g., phenols. Using the measured aquatic toxicity values and estimated Kow values, regression equations can be developed for a class of chemicals. Toxicity values for new chemicals may then be calculated by inserting the estimated Kow into the regression equation and correcting the resultant value for the molecular weight of the compound.

To date, over 150 SARs have been developed for more than 50 chemical classes. These chemical classes range from the very large, e.g., neutral organics, to the very small, e.g., aromatic diazoniums. Some chemical classes have only one SAR, such as acid chlorides, for which only a fish 96-hour LC50 has been developed. The class with the greatest number of SARs is the neutral organics, which has SARs ranging from acute and chronic SARs for fish to a 14-day LC50 for earthworms in artificial soil. The ECOSAR Class Program is a computerized version of the ECOSAR analysis procedures as currently practiced by the Office of Pollution Prevention and Toxics (OPPT). It has been developed within the regulatory constraints of the Toxic Substances Control Act (TSCA). It is a pragmatic approach to SAR as opposed to a theoretical approach.
Test substance : CAS No. 110-82-7; cyclohexane; purity is unknown
Result : Calculated 96-hr EC50 for a green alga = 2.2 mg/L
Calculated 96-hr ChV for a green alga = 0.5 mg/L
Test condition : Experimental water solubility = 55.0 mg/l @ 25°C (McAuliffe, 1966), log Kow = 3.44 @ 20°C (Hansch, et.al, 1995), and melting point = 6.6°C (Lide,

2003) were entered into the program.
Class: Neutral organics

Reliability : (2) valid with restrictions
The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.

Flag : Critical study for SIDS endpoint

02.07.2008 (3)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	>5000 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	
GLP	:	
Remark	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Conclusion	:	Cyclohexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (32)

Type	:	LD50
Value	:	=29,800 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	
GLP	:	
Remark	:	
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Conclusion	:	Cyclohexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (7)

Type	:	LD50
Value	:	8,000 - 39,000 mg/kg
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	1970
GLP	:	pre-GLP
Remark	:	The oral LD50 in a 14-day old rat, a young adult rat and an older rat was 8.0, 39.0 and 16.5 ml/kg, respectively (6,240, 30,420 and 12,870 mg/kg,

respectively). Symptoms included depressive effect on the central nervous system, salivation and soft faeces.

Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Conclusion	:	Cyclohexane has a low order of toxicity by the oral route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (25)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> 32.88 mg/l
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Remark	:	Single 4-hour exposure at one dose level of 9500 ppm (32.28 mg/l). No death occurred at level tested. Exposure-related symptoms noted during the exposure included tremors, hyperactivity, rapid respiration, and also hypoactivity.
Result	:	
Conclusion	:	Cyclohexane has a low order of toxicity by the inhalation route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (33)

Type	:	LC50
Value	:	
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Exposure time	:	1 hour(s)
Method	:	other
Year	:	
GLP	:	pre-GLP
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Remark	:	A 1 hour acute inhalation exposure of rabbits to cyclohexane vapor produced effects on the central nervous system, with exposure-related observations including convulsions, tremors, hyperactivity, rapid respiration, cyanosis and diarrhea; all the animals exposed to 89.6 mg/L died (26,000 ppm).
Result	:	
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk

Assessment of cyclohexane.

Flag : Critical study for SIDS endpoint

14.07.2008 (45)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Result	:	No deaths or systemic symptoms were observed, a slight erythema and oedema were noted in a few animals.
Conclusion	:	Cyclohexane has a low order of toxicity by the dermal route of exposure
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (34)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Duration of study	:	7 days
Doses	:	
Method	:	EEC Directive 83/467/EEC
Year	:	
GLP	:	yes
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Result	:	not irritating
Remark	:	Test substance applied under a semi-occlusive dressing. Single application. Resulted in a 24-hr and 72-hr PI score of zero. Cyclohexane had no corrosive properties
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (35)

Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	6

Duration of study	:	7 days
Doses	:	
Method	:	EEC Directive 83/467/EEC
Year	:	
GLP	:	yes
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Result	:	not irritating
Remark	:	Test substance applied under a semi-occlusive dressing. Single application. Resulted in a mean erythema score for 24-hr and 72-hr of 1.93. A review of this study did however note that the erythematous reaction reached maximum severity at 5 days post-application (mean score 2.56). During this time, there was a gradual increase in dermal reaction for a further 144 h observation time (2.83). Overall, the irritation reactions were important and still present at the end of the study.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (24)

5.2.2 EYE IRRITATION

Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	none
Doses	:	Single undiluted
Method	:	Draize Test
Year	:	
GLP	:	yes
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Result	:	slightly irritating
Remark	:	After application of the test substance to one eye of the rabbit the eye was left unwashed. At one hour post instillation, corneal opacity, involving up to 25% of the cornea, was noted in one rabbit and iritis was noted in another rabbit. Conjunctival redness was noted in five rabbits with conjunctival chemosis in one rabbit. All ocular lesions had cleared within 24 hours and no conjunctival discharge was noted in any of the six animals.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (36)

Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	none
Doses	:	Single undiluted
Method	:	Draize Test
Year	:	

GLP	:	yes
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Result	:	slightly irritating
Remark	:	After application of the test substance to one eye of the rabbit the eye was rinsed / washed.
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (37)

5.3 SENSITIZATION

Type	:	Dermal sensitization
Species	:	Guinea pig
Strain	:	no data
Sex	:	male / female
Number of animals	:	9 male / 11 female
Vehicle	:	ethanol / acetone
Doses	:	
Method	:	EC Annex V Method B6 - modified Buehler method
Year	:	1996
GLP	:	yes
Test conditions	:	Twenty guinea pigs (9 males and 11 females) were induced dermally with 10% cyclohexane (purity 99.98%) in ethanol and challenged with 10% cyclohexane in acetone. Concurrent negative controls (no cyclohexane) and positive controls (DNCB-0.1% in 50% ethanol at induction and 0.07% in acetone at challenge) were tested. It should be noted that a maximisation test was not required because of the very poor tolerance to intra-dermal injection of solvents. During the induction phase, the response ranged from no redness (14/20 animals) to very faint redness on some tested animals (6/20 animals with a slight reaction). A very faint redness was observed 24 hours after the challenge application in 1/20 tested animals, no reactions were observed in other tested animals or negative controls. The incidence of sensitisation among cyclohexane induced and challenged animals was 0/20. The incidence of sensitisation among the DNCB induced and challenged animals was 8/10. A higher challenge concentration could have been chosen (15% in acetone did not produce any dermal irritation) and there were only a few animals with dermal reactions during the induction phase, these findings reduce the significance of this test.
Test substance	:	CAS No. 110-82-7; cyclohexane; (purity 99.98%)
Result	:	not a dermal sensitizer
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

14.07.2008 (8)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female

Number of animals	:	5/sex/group
Strain	:	other: Crl:CD.BR
Route of admin.	:	inhalation
Exposure period	:	9 days
Frequency of treatm.	:	6 hrs per day
Doses	:	3000, 6000, 9000 ppm
Control group	:	yes
NOAEL	:	= 3000 ppm
Method	:	EPA test method
Year	:	1995
GLP	:	yes
Test Methods	:	In a two-week inhalation range finding study, Crl CD.BR rats (5/sex/group) were exposed (whole body in an exposure chamber) to 0-3,000-6,000 and 9,000 ppm (0-10,500-21,000 and 31,500 mg/m3) of cyclohexane (purity 99.97%). Nine exposures, each lasting six hours, were performed in total. The animals were weighed before treatment, clinical signs were checked before, during and after exposure, and common biochemical parameters and histological examinations were conducted at the end of the study. For neurotoxicity assessment, the animals were checked for alerting behaviour in response to a standardised auditory stimulus at least three times during each exposure. They were also submitted to an abbreviated Functional Observational Battery (FOB) before and after exposure on two separate days (test days 4 and 11). This assessment was also performed prior to the initiation of exposures to establish baseline measurements. During the FOB, the following parameters were assessed: • in home cage: posture and palpebral closure, • in open field: righting reflex, convulsions, gait characteristics, vocalisations, labored breathing, coordination, arousal and palpebral closure, • during manipulations: approach and touch response, auditory response (clicker) and tail pinch. This study was performed according to EPA guidelines and following EPA and OECD GLPs.
Result	:	A slight but significant decrease in body weight gain was observed in males treated with 9,000 ppm. Except for a minimal increase in mitotic index figures detected in the hepatocytes of males at 6,000 ppm and higher and in females at 9,000 ppm, no other treatment related findings were observed for systemic toxicity. In particular, no modification in absolute and relative liver weights was noted in these studies. Based on these findings, a NO(A)EL of 3,000 ppm (10,320 mg/m3) can be assumed for systemic toxicity. For neurotoxic effects, diminished responses to stimulus were observed from day 2 at 9,000 ppm and from 7 exposures at 6,000 ppm. No effect was observed in FOB. A NOAEL of 3,000 ppm (10,320 mg/m3) can be assumed for neurotoxic effects in rats. This study served as a range-finding study for a 90-day inhalation toxicity study. It should be noted that this value is very conservative because the effects are very slight and may be of adaptive nature; this is taken into account in the risk characterisation.
Test substance	:	CAS No. 110-82-7; cyclohexane; (purity 99.97%)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

17.07.2008 (17)

Type	:	
Species	:	rat
Sex	:	male/female

Number of animals	:	20/sex/group (controls & hi dose); 10/sex/group (intermediary doses)
Strain	:	other: Crl:CD.BR
Route of admin.	:	inhalation
Exposure period	:	13 weeks
Frequency of treatm.	:	6 hrs / day, 5 days / week (total 66 exposures)
Doses	:	500, 2000, 7000 ppm
Control group	:	yes
NOAEL	:	
Method	:	EPA test method
Year	:	1995
GLP	:	yes
Methods	:	In a 13-week repeated dose toxicity study conducted using CD BR rats (20/sex/group for controls and high concentration and 10/sex/group for intermediary concentration groups) were exposed by whole body inhalation to cyclohexane at target concentrations of 0, 500, 2,000, and 7,000 ppm for 6 hours/day, 5 day/week for 13 weeks (66 exposures). Ten rats per month were allowed a one-month recovery period for control group and 7,000 ppm groups. After 45 and 90 days of exposure, blood and urine were collected for evaluation of clinical pathology parameters. Gross pathology, organ weight, macroscopic and microscopic examinations were performed at the end of the study.
Result	:	No treatment-related effects were observed on body weight, body weight gain, food consumption, urine analysis and clinical examinations. A slight decrease (not significant) in succinate dehydrogense and lactate dehydrogenase was observed in males and females at 7,000 and 2,000 ppm at both sampling times. In males exposed to 7,000 ppm a slight increase in adrenals weight was observed at the end of the recovery period. This finding was not observed at the end of the 90 day exposure so the relevance and significance is questionable. In the 7,000 ppm group, a statistically significant increase in the relative liver weight with hepatic hypertrophy was observed in males (10/10), concurrent with an increase in the incidence of centrilobular hypertrophy in both sexes (9/10 males and 5/10 females). This finding was partially reversible in the one-month recovery period. For neurological effects, decreases in or absences of response to auditory stimulations were observed with a dose-response relationship from 500 ppm. In the 500 ppm group, there was a decrease in response on treatment days 61, 66, 67 and 68. In the 2,000 ppm group, there was decrease in the response during 16 exposures and no response during 50 exposures. In the 7,000 ppm group, a decreased response was observed in one exposure and no response was observed in the other 65 exposures. These effects were transient, and as no clinical observations of compromised neurological function were detected they were considered to be due to a reversible sedation caused by cyclohexane. The NOAEL for neurological effects was 500 ppm while the NOAEL for hepatic effects was 2,000 ppm. However, the partially reversible hepatic effects observed in males at 7,000 ppm were slight and may be considered of an adaptive nature.
Remark	:	Additional groups of rats (12/sex/group) were treated in parallel with those of the main study in order to assess neurotoxicity of cyclohexane in FOB, motor activity and neuropathology tests (Haskell Laboratory 1996c). Neurobehavioral evaluations were conducted prior to exposure and at week 4, 8, and 13. During each evaluation period FOB was performed prior to the motor activity test. At the end of the study, 6 rats/sex/group were selected for neuropathology, the controls and 7,000 ppm tissues selected were examined, and the intermediate dose tissues were saved. Neurological lesions were also assessed by examining sections of the brain, spinal cord, sciatic nerve, gasserian ganglia, cervical and dorsal root fibers and ganglia, cervical and lumbar ventral root fibers and gastrocnemius muscle. Similar to the main 90 day study, a sedative effect was observed at doses

of 2,000 ppm and higher characterized by a decrease in the mean response to an alerting stimulus. This effect was transient since no effects were observed immediately after removal from the exposure chamber. No effects were observed during the FOB and motor activity assessment. Histologically, no treatment-related findings were observed, the only lesions observed being identical in character and severity to those observed in controls. These have already been described as occurring spontaneously in the rat. The NOAEL for neurotoxicity was 500 ppm based on the transient sedative effect observed at 2,000 ppm and higher.

Test substance : CAS No. 110-82-7; cyclohexane; (purity 99.98%)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
17.07.2008 (18)(20)

Type :
Species : mouse
Sex : male/female
Number of animals : 20/sex/group (controls & hi dose); 10/sex/group (intermediary doses)
Strain : other: Crl:CD1 (ICR) BR
Route of admin. : inhalation
Exposure period : 13 weeks
Frequency of treatm. : 6 hrs / day, 5 days / week (total 66 exposures)
Doses : 500, 2000, 7000 ppm
Control group : yes
NOAEL :
Method : EPA test method
Year : 1996
GLP : yes
Methods : A 13 week inhalation toxicity study in mice was also performed following a 2-week range finding study in mice. The study was comparable in experimental conditions to that performed on rats.

After a stimulus, the animals of the 500 ppm group reacted as controls. In the 2,000 ppm group, a decrease in or an absence of response was observed from the third exposure onwards, the effects appearing to get worst with time (more and more no-response with increasing numbers of exposures). In the 7,000 ppm group, there was an increase in the incidence of decreased response, absence of response and hyperactive state from test day 4 to test day 30. From test day 30 to the end of the study, the response to the stimulus was impossible to determine due to the hyperactive state of the animals. These symptoms were observed just after exposure but were reversible until the next exposure. The most frequently described symptoms were: abnormal gait or mobility, excessive grooming, hyperactivity, hyper reactivity, spasms, aggressivity, hypo-activity and ruffled fur.

In males, haematological abnormalities were observed from 500 ppm, these symptoms (increase in RBC - increase in Hb - increase in Ht and decrease in platelets) were not always statistically significant and not always dose-related. In females, increases in RBC, Hb and Ht were only observed at 7,000 ppm. Variation in the haematological parameters occured for all animals at the 7,000 ppm dose level, but could not be explained in relation to the lack of systemic symptoms of dehydration. They were considered to be of no toxicological importance.

An increase in absolute and relative liver weight was observed in males at 7,000 ppm (absolute: 1.504 g vs 1.275 g). Only the relative weight was increased in females. No concomitant histological findings were observed. These results were not in accordance with those found during the two-week range finding test (histological findings from 3,000 onwards in

females and at 9,000 in males) but did not interfere with the determination of a NOEL.

Result : For neurologic effects, a NOAEL of 500 ppm was determined based on signs of sedation observed in animals at 2,000 ppm. The NOAEL for systemic effects was 2,000 ppm based on effects observed in the liver at 7,000 ppm (increase in absolute and relative liver weights).

Test substance : CAS No. 110-82-7; cyclohexane; (purity 99.98%)
Reliability : (1) valid without restrictions
Flag : Critical study for SIDS endpoint
17.07.2008 (19)(29)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Test species/strain: Salmonella typhimurium TA100, TA1535, TA98, TA1537
Test concentration : 0 to 10000 nl/ml
Cytotoxic concentr. : 7800 µg/ml (10000 nl/ml)
Metabolic activation : with and without
Result : negative
Method : not data
Year : 1986
GLP : no data
Test Method : *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) were incubated with and without metabolic activation in DMSO. Two metabolic activation systems were used, one with SD rats livers and the other with Syrian hamster livers. Doses of cyclohexane ranged from 0 to 10,000 µg/plate.

Result : Signs of toxicity were noted in the 3,333 µg/plate for TA1537 and TA98 and in the 10,000 µg/plate for TA100 and TA1535.

There was no evidence of reverse mutation for any dose tested with and without metabolic activation.

Genotoxic effects:
With metabolic activation: negative
Without metabolic activation: negative

Test substance : CAS No. 110-82-7; cyclohexane
Reliability : (2) valid with restrictions
Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag : Critical study for SIDS endpoint
18.07.2008 (31)

Type : Mouse Lymphoma Assay
System of testing : L5178Y mouse lymphoma cells (TK locus)
Test concentration : 313 to 10000 nl/ml (250 to 7800 µg/ml)
Cycotoxic concentr. : 7800 µg/ml (10000 nl/ml)
Metabolic activation : with and without
Result : negative
Method : Method equivalent to current guidelines
Year : 1986
GLP : no data
Remark : Cyclohexane, solubilised in desionised water, was tested at doses ranging from 313 nl/ml to 10,000 nl/ml (250 µg/ml to 7,800 µg/ml) (API, 1986). The method used was equivalent to the guidelines.

Result	:	Cytotoxicity was seen at 10,000 nl/ml (7,800 µg/ml) with and without metabolic activation. Without metabolic activation the percentage of relative growths ranged from 39 to 59 % without dose-effect relationship. There was no evidence of forward mutation at any dose. With metabolic activation, the percentage of relative growths ranged from 46 to 64% and was not dose related. There were very slight increases in mutant frequency in four treatments, but not dose related, and it was decided to confirm this result with another test. Doses ranging from 3,000 to 8,000 nl/ml (2,340 to 6,240 µg/ml) were tested in the second trial (cytotoxicity was found at 9,000 nl/ml (7,020 µg/ml)). The percentage of relative growths ranged from 23 to 69%. In this trial the results were clearly negative. Overall, this test can be considered as negative with and without metabolic activation.
Test substance	:	CAS No. 110-82-7; cyclohexane
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
18.07.2008		(2)(38)

Type	:	Sister Chromatid Exchange Test
System of testing	:	Chinese Hamster Ovary cells
Test concentration	:	0.25 to 25 µg/ml in DMSO
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	Method equivalent to current guidelines
Year	:	1982
GLP	:	no data
Remark	:	Cyclohexane, solubilised in DMSO, was tested at doses ranging from 0.25 to 25 µgl/ml. The method used was equivalent to the guidelines.
Result	:	The higher dose tested corresponding to a complete growth inhibition of the cell culture (25 µg/ml). No effect was seen within the range of the doses tested and the test is considered negative.
Test substance	:	CAS No. 110-82-7; cyclohexane
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint
18.07.2008		(39)

Type	:	Unscheduled DNA synthesis
System of testing	:	Human lymphocytes
Test concentration	:	0.1 to 10 mM cyclohexane
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	Method equivalent to current guidelines
Year	:	1983
GLP	:	no data
Remark	:	Human lymphocytes (+ or – S9 mix) were cultured for 4 hours in the presence or absence of cyclohexane. The effects on the DNA synthesis were measured through cellular [^{3}H]TdR uptake.
Result	:	Cyclohexane induced a marked inhibition of [^{3}H]TdR uptake in the S9 mix-lacking cultures while the corresponding cellular viabilities were unaffected. No effect was seen with metabolic activation. The effects seen without metabolic activation were not dose-dependent; solvent controls and negative controls were highly variable. Decrease of the uptake for the

highest dose was within the values of the controls. No conclusion was drawn from this study.

Test substance	:	CAS No. 110-82-7; cyclohexane; purity = 99.8%
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

18.07.2008 (40)

Type	:	DNA cell binding assay
System of testing	:	*E. coli*
Test concentration	:	10 and 100 µM cyclohexane
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	no data
Year	:	1981
GLP	:	no data
Remark	:	Cyclohexane was tested in a DNA cell binding assay at doses of 10 and 100 µM. Cyclohexane was tested alone, mixed with lysozyme, mixed with liver extract and mixed with lysozyme and liver extract. Positive control was MMS and negative control was the culture middle only. The results are expressed as a "binding percentage". If this percentage is > 1%, the substance was considered positive.
Result	:	Cyclohexane was found negative when tested alone in the groups treated with liver extract and –with lysozyme and liver extract. A positive finding (1.6% only) was found in the group treated with cyclohexane + lysozyme at the highest dose (100 µM). This result is considered doubtful because this is a very slight increase and also because this effects is not found in the group - cyclohexane + lysozyme + liver extract.

Test substance	:	CAS No. 110-82-7; cyclohexane; purity = 99.8%
Reliability	:	(2) valid with restrictions Original study not retrieved and reviewed. Study used for EU Risk Assessment of cyclohexane.
Flag	:	Critical study for SIDS endpoint

18.07.2008 (26)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic Assay
Species	:	rat
Strain	:	Sprague Dawley
Sex	:	male/female
Number of animals	:	10 per sex
Route of admin.	:	inhalation
Exposure period	:	6 hours/day for 5 days
Doses	:	0, 97, 307, 1042 ppm
Method	:	other: not specified
Year	:	
GLP	:	no data

Remark	:	Samples of bone marrow cells were taken for cytogenetic analysis 6 hours after completion of the final dose. A positive control, triethyleneamine, showed a significant increase in structural aberration frequency. For cyclohexane a small but statistically significant increase in numerical aberrations was recorded in low and medium dose females, and pooled data at the low dose groups of both sexes. There was no information on general toxicity; no decrease on mitotic index was seen at all the doses tested. However, the authors of the report concluded that the lack of a dose-related response indicated that these increases were not of biological importance. Moreover, the numerical aberrations parameter had often shown great variation in this laboratory, having no statistical significance even for positive controls (numerical data is not available). It can be considered that cyclohexane does not produce chromosomal aberrations under the conditions of this test.
Result	:	Negative result. Some increased aberrations at low and medium doses but no dose-related effect.
Test substance	:	CAS No. 110-82-7; cyclohexane; purity is unknown
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

14.07.2008 (1)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type	:	Two generation reproductive study
Species	:	rat
Sex	:	male/female
Number of animals	:	30/sex/group
Strain	:	other: CD BR
Route of admin.	:	inhalation
Exposure period	:	90 days
Frequency of treatm.	:	5 day/week and 6 h/day
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	
No. Of generation studies	:	2
Doses	:	0, 500, 2,000, or 7,000 ppm
Control group	:	yes
NOAEL parental	:	
NOAEL F1 offspring	:	
Method	:	other: US and OECD Test guideline
Year	:	1997
GLP	:	yes
Remark	:	In this study, weanling F0 rats (30/sex/group) inhaled cyclohexane vapor at 0, 500, 2,000, or 7,000 ppm 5 day/week and 6 h/day. Exposure duration was 10 weeks before mating until sacrifice of the P1 generation and 11 weeks before mating until sacrifice of the F1 generation. Gravid females were not exposed from day 21 of gestation until day 4 of lactation. From day 5 of lactation until weaning the neonates were potentially exposed by maternal milk; no other exposure was administered. At post partum day 25, thirty F1 animals/sex/dose were chosen to produce the next generation, treatment was continued 11 weeks before mating and during gestation. Fertility parameters were calculated. From 500 ppm, there was an increased incidence of diminished response to a stimulus during exposure,

this finding being significant at 2,000 ppm and higher. At 7,000 ppm, major effects were observed on body weight, body weight gain and food efficiency. A decrease in mean body weight was seen with F1 male rats, P1 and F1 females during pre-mating, P1 females throughout gestation, and F1 females during lactation. A decrease in mean body weight gain was observed with F1 male rats and P1 and F1 females during pre-mating; however no reductions were seen for P1 females during gestation, suggesting that the reduction in mean gestation body weight was probably due to pre-existing body weight deficits established during the pre-mating period. The same findings were also seen with the F1 generation. A decrease in mean food efficiency of P1 and F1 females during lactation and a decrease in food consumption of P1 females during lactation were also observed. Effects on reproduction were limited to a decrease in mean pup weight for both the F1 and F2 generations at the high dose which was significant between post partum day 7 and 25 during which time pups were fed only maternal milk indicating the effect is due to cyclohexane via lactation. There was a slight increase in the incidence of pro-static inflammation at 7,000 ppm in P1 and F1 adults, but this was considered incidental due to the lack of severity and the reported common occurrence in rats. There was a slight but significant decrease in the mean percentage of animals born alive in the F1 litters dosed with 7,000 ppm, but given that the value was still in the range of historical controls and that this effect was not dose-related, this was not considered biologically significant.

Result : The NOAEL for adult reproductive toxicity was 2,000 ppm based on decreases in pup body weight observed at 7,000 ppm. The systemic NOAEL for this study was 500 ppm based on sedative effects observed at 2,000 ppm and higher.

Test substance : CAS No. 110-82-7; cyclohexane
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.07.2008 (23)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Type : Developmental toxicity
Species : rat
Sex : female
Number of animals : 8/group
Strain : other: Crl:CD BR
Route of admin. : inhalation
Exposure period : 9 days
Frequency of treatm. :
Duration of test : 14 days
Doses : 0, 3000, 6,000, or 9,000 ppm
Control group : yes
Method : other: US and OECD Test guideline
Year : 1997
GLP : yes
Remark : As a pilot study, four groups of eight pregnant CDBR rats were exposed whole-body to concentrations of 0, 3,000, 6,000, or 9,000 ppm cyclohexane from gestational day 7 to 16. Dams were sacrificed on day 22 and examined for gross pathologies; implantations and resorptions were counted and their relative positions recorded; fetuses were weighed and examined externally for alterations.

Result : Maternal effects were limited to a reduction in overall maternal bodyweight gain, overall food consumption and diminished response of animals to a

sound stimulus during exposure to 6,000 ppm and higher. No effects were observed in the pups. The NOAEL was 3,000 ppm for the dams and 9,000 ppm for the pups.

Remark : This pilot study served as a range-finding study used to design a more complete study which was carried out during the 90 day inhalation study previously described (Haskell Laboratory, 1997b). Four groups of CD BR rats were exposed whole body to cyclohexane at concentrations of 0, 500, 2,000 or 7,000 ppm from gestational day 7 to 16. Animals were sacrificed on day 22 and examined. Findings were limited to the dams and included a diminished response of the animals to a sound stimulus while in the chamber during exposure and at 2,000 ppm or higher and reductions in overall body weight gain and food consumption throughout the treatment period. A slight but significant decrease in implantation number with the number of corpora lutea unchanged was seen when compared with controls. This finding was consistent with slight pre-implantation losses and can be considered as not treatment-related since there was no treatment during the pre-implantation period. The NOAEL was 500 ppm for maternal toxicity and 7,000 ppm for developmental toxicity considering the lack of toxic effects noted.

Test substance : CAS No. 110-82-7; cyclohexane
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.07.2008 (21)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT