U.S. EPA HPV Program

Data Set

Existing Chemical	:	Ketones, C12-branched
CAS No.	:	68514-41-0
Producer related part		
Company	:	ExxonMobil Chemical Company
Creation date	:	4.12.2009
Memo	:	Prepared by: ExxonMobil Biomedical Sciences Inc. - HPV Program
Date of last update	:	4.12.2009

1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Ketones, C12-branched
CAS No.	:	68514-41-0
Smiles Code	:	O=C(CCC(C)C)CCCC(C)C
Molecular formula	:	C12H24O1 (average)
Molecular weight	:	184.32 (average)

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic

1.2 LAST LITERATURE SEARCH

Type of search	:	Internal and External
Remark	:	Search covered all Physical Chemical Properties, Environmental Fate, Aquatic and Mammalian Toxicity endpoints related to the CAS number.

05.11.2009

2.1 MELTING POINT

Value	:	= -6.7 °C
Sublimation	:	
Method	:	other: calculated
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Method	:	Calculated values using MPBPWIN version 1.41, a subroutine of the computer program EPIWIN version 3.12
Test condition	:	Melting Point estimations performed by MPBPWIN are based on the average result of the calculation methods of K. Joback and Gold and Ogle. Joback's Method is described in Joback, K.G. 1982. A Unified Approach to Physical Property Estimation Using Multivariate Statistical Techniques. In The Properties of Gases and Liquids. Fourth Edition. 1987. R.C. Reid, J.M. Prausnitz and B.E. Poling, Eds. The Gold and Ogle Method simply uses the formula Tm = 0.5839Tb, where Tm is the melting point in Kelvin and Tb is the boiling point in Kelvin.
Reliability	:	(2) valid with restrictions The result is a calculated value based on the chemical structure and represents a potential melting point for the substance with the CAS number listed under test substance.
Flag	:	Critical study for SIDS endpoint

20.11.2006 (5)

2.2 BOILING POINT

Value	:	= 220.2 °C at 1013 hPa
Decomposition	:	
Method	:	other: calculated
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Test condition	:	Boiling point calculated by MPBPWIN subroutine, which is based on the method of S. Stein and R. Brown in "Estimation of Normal Boiling Points from Group Contributions". 1994. J. Chem. Inf. Comput. Sci. 34: 581-587.
Reliability	:	(2) valid with restrictions The result is a calculated value based on the chemical structure and represents a potential boiling point for the substance with the CAS number listed under test substance.
Flag	:	Critical study for SIDS endpoint

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2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .261 hPa at 25 °C

Decomposition	:	
Method	:	other (calculated)
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Method	:	Vapor pressure calculation by MPBPWIN ver. 1.40 using calculation method of Grain.
Remark	:	EPIWIN is used and advocated by the US EPA for chemical property estimation.
Reliability	:	(2) valid with restrictions The result is a calculated value based on the chemical structure and represents a potential vapor pressure for the substance with the CAS number listed under test substance.
Flag	:	Critical study for SIDS endpoint

20.11.2006 (5)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 4.04 at 25 °C
pH value	:	
Method	:	other (calculated)
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Method	:	Calculated values using KOWWIN version 1.67, a subroutine of the computer program EPIWIN version 3.12
Test condition	:	Octanol / Water Partition Coefficient estimations performed by KOWWIN are 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.
Reliability	:	(2) valid with restrictions The result is a calculated value based on the chemical structure and represents a potential partition coefficient for the substance with the CAS number listed under test substance.
Flag	:	Critical study for SIDS endpoint

20.11.2006 (5)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 18.7 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: calculated
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Method	:	Calculated values using WSKOWWIN version 1.41, a subroutine of the computer program EPIWIN version 3.12
Test condition	:	Water Solubility estimations performed by WSKOWWIN are based on a Kow correlation method described by W. Meylan, P. Howard and R.

Boethling in "Improved method for estimating water solubility from octanol/water partition coefficient". Environ. Toxicol. Chem. 15:100-106. 1995.

Reliability : (2) valid with restrictions
The result is a calculated value based on the chemical structure and represents a potential water solubility for the substance with the CAS number listed under test substance.

Flag : Critical study for SIDS endpoint
20.11.2006 (5)

3.1.1 PHOTODEGRADATION

Type	:	water
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (calculated): Technical discussion
Year	:	2006
GLP	:	
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Result	:	Photolysis as a Function of Molecular Structure

The direct photolysis of an organic molecule occurs when it absorbs sufficient light energy to result in a structural transformation (Harris, 1982). The reaction process is initiated when light energy in a specific wavelength range elevates a molecule to an electronically excited state. However, the excited state is competitive with various deactivation processes that can result in the return of the molecule to a non excited state.

The absorption of light in the ultra violet (UV)-visible range, 110-750 nm, can result in the electronic excitation of an organic molecule. Light in this range contains energy of the same order of magnitude as covalent bond dissociation energies (Harris, 1982). Higher wavelengths (e.g. infrared) result only in vibrational and rotational transitions, which do not tend to produce structural changes to a molecule.

The stratospheric ozone layer prevents UV light of less than 290 nm from reaching the earth's surface. Therefore, only light at wavelengths between 290 and 750 nm can result in photochemical transformations in the environment (Harris, 1982). Although the absorption of UV light in the 290-750 nm range is necessary, it is not always sufficient for a chemical to undergo photochemical degradation. Energy may be re-emitted from an excited molecule by mechanisms other than chemical transformation, resulting in no change to the parent molecule.

A conservative approach to estimating a photochemical degradation rate is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by the molecule (Zepp and Cline, 1977).

Ketones do absorb light above 290 nm (Harris J, 1982a). Therefore, direct photolysis may be an important transformation process for the degradation of ketones, C12-branched in the environment.

References:

Harris, J. C. 1982. "Rate of Aqueous Photolysis," Chapter 8 in: W. J. Lyman, W. F. Reehl, and D. H. Rosenblatt, eds., Handbook of Chemical Property Estimation Methods, McGraw-Hill Book Company, New York, USA.

Zepp, R. G. and D. M. Cline. 1977. Rates of Direct Photolysis in the Aqueous Environment, Environ. Sci. Technol., 11:359-366.

Boethling, R.S., Mackay, D. 2000. Handbook of Property Estimation Methods for Chemicals, CRC Press, Boca Raton, FL, USA.

Flag : Critical study for SIDS endpoint

20.11.2006 (4)

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	:	= .000000000000175386 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): Calculated values using AOPWIN version 1.91, a subroutine of the computer program EPIWIN version 3.12
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Result	:	Atmospheric Oxidation Potential

In the environment, organic chemicals emitted into the troposphere are degraded by several important transformation processes. The dominant transformation process for most compounds is the daylight reaction with hydroxyl (OH-) radicals (Atkinson, 1988, 1989). The rate at which an organic compound reacts with OH- radicals is a direct measure of its atmospheric persistence (Meylan and Howard, 1993).

AOPWIN estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The rate constants estimated by the program are then used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radicals.

Since the reactions only take place in the presence of sunlight, the atmospheric half-lives are normalized for a 12-hour day.

Calculated* half-life (days)	OH- Rate Constant (cm3/molecule-sec)
0.61	17.5386 E-12

References:

Atkinson, R. 1988. Estimation of gas-phase hydroxyl radical rate constants for organic chemicals. Environ. Toxicol. Chem. 7:435-442.

Atkinson, R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. J. Phys. Chem. Ref. Data Monograph No. 1, Amer. Inst. Physics & Amer. Chem. Soc., NY.

Meylan, W.M. and P.H. Howard. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 12:2293-2299.

Test condition :

Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson.

Temperature: 25°C
Sensitizer: OH radical
Concentration of Sensitizer: 1.5 E6 OH radicals/cm3

Reliability : (2) valid with restrictions
The results include calculated data based on chemical structure as modeled by AOPWIN. The data represent a potential atmospheric half-life

range for the test substance.

Flag : Critical study for SIDS endpoint
20.11.2006 (5)

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 : 2006
GLP :
Test substance : CAS No. 68514-41-0; Ketones, C12-branched
Result : Hydrolysis as a Function of Molecular Structure

Hydrolysis of an organic molecule occurs when a molecule (R-X) reacts with water (H2O) to form a new carbon-oxygen bond after the carbon-X bond is cleaved (Gould, 1959; Harris, 1982). Mechanistically, this reaction is referred to as a nucleophilic substitution reaction, where X is the leaving group being replaced by the incoming nucleophilic oxygen from the water molecule.

Chemicals that are susceptible to hydrolysis contain functional groups that can be displaced by a nucleophilic substitution reaction. Substances 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.

Ketones, C12-branched is expected to be resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive (Harris, 1982b). Therefore, hydrolysis will not contribute to its removal from the environment.

References:

Gould, E.S. (1959), Mechanism and Structure in Organic Chemistry, Holt, Reinhart and Winston, New York, NY, USA.

Harris, J.C. (1982), "Rate of Hydrolysis," Chapter 7 in: W.J. Lyman, W.F. Reehl, and D.H. Rosenblatt, eds., Handbook of Chemical Property Estimation Methods, McGraw-Hill Book Company, New York, NY, USA.

Neely, W. B. 1985. Hydrolysis. In: W. B. Neely and G. E. Blau, eds. Environmental Exposure from Chemicals. Vol I., pp. 157-173. CRC Press, Boca Raton, FL, USA.

Flag : Critical study for SIDS endpoint
20.11.2006 (3)

3.1.3 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

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 : 2006
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 3.12 program. Measured input values were also used where available and obtained from the EPIWIN database or other reliable sources. 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 = 184.32 g/mol
Water solubility = 18.7 mg/L
Vapour pressure = 26.1 Pa
log Kow = 4.04
Melting point = -6.7 deg C

Degradation half-lives:

Air - 7.3 hrs
Water - 360 hrs
Soil - 7200 hrs
Sediment - 72000 hrs

This model was run assuming the default emissions.

Result :

Air - 0.3%
Water - 3.6%
Soil - 94.2%
Sediment - 1.9%

Test substance : CAS No. 68514-41-0; Ketones, C12-branched
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
20.11.2006 (8)

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 : 2006
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 3.12 program. Measured input values were also used where available and obtained from the EPIWIN database or other reliable sources. 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 = 184.32 g/mol
Water solubility = 18.7 mg/L
Vapour pressure = 26.1 Pa
log Kow = 4.04
Melting point = -6.7 deg C

Result :

Air - 82.6%
Water - 1.6%
Soil - 15.5%
Sediment - 0.3%
Suspended Sed - 0.01%
Biota - <0.01%

Test substance : CAS No. 68514-41-0; Ketones, C12-branched
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
20.11.2006 (8)

3.2 BIODEGRADATION

Type : aerobic
Inoculum :
Contact time :
Degradation : (±) % after
Result : other: not readily biodegradable
Deg. product :
Method : other: calculated using BIOWIN version 4.02
Year : 2006
GLP : no
Test substance : CAS No. 68514-41-0; Ketones, C12-branched
Remark : Calculation of biodegradation and the timeframe for Primary and Ultimate biodegradation using BIOWIN version 4.02, a subroutine of the computer program EPI Suite version 3.12 as described by Howard, et al, 1994.

BIOWIN contains six models (linear regression (BIOWIN 1), non-linear regression (BIOWIN 2), ultimate degradation to CO2 and H2O (BIOWIN 3), primary degradation (BIOWIN 4), linear regression estimate of the probability of passing the OECD 301C / MITI-1 ready biodegradation test (BIOWIN 5), and non-linear regression estimate of the probability of passing the OECD 301C / MITI-1 ready biodegradation test (BIOWIN 6).

BIOWIN 1 - "Biodegrades Fast"
BIOWIN 2 - "Does Not Biodegrade Fast"
BIOWIN 3 - "Weeks"
BIOWIN 4 - "Days-Weeks"
BIOWIN 5 - "Does Not Biodegrade Fast"
BIOWIN 6 - "Biodegrades Fast"

According to the USEPA, BIOWIN 6 is better predictor of whether a chemical will pass or fail the OECD 301C / MITI-1 ready biodegradation test than BIOWIN 5.

Reliability : (2) valid with restrictions
The value was calculated based on the chemical structure as modeled by EPI Suite. This robust summary has a reliability rating of 2 because the data are modeled.

Flag	:	Critical study for SIDS endpoint
20.11.2006		(5) (7)
Type	:	Aerobic
Inoculum	:	Sewage sludge, domestic
Contact time	:	28 days
Degradation	:	59.8%
Result	:	Not readily biodegradable
Method	:	Ready Biodegradability: Manometric Respirometry Test, OECD 301F
GLP	:	Yes
Test substance	:	Analog Substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Test conditions	:	Triplicate test systems were used to evaluate the biodegradability of C8 Ketone Fraction at a mean concentration of 51.2 mg/L. The positive control substance was evaluated at mean concentrations of 50 mg/L. Blank test systems, which did not contain the test or positive control substance, were run concurrently in triplicate. The total suspended solids (TSS) of the activated sludge was determined to be 4.21 g/L. The inoculum was added at a 1% loading volume of sludge supernatant to test medium. The microbial count of the inoculum was 105 CFU/mL. One liter of test medium, which was aerated for 24 hours with carbon dioxide free air, was added to each one liter respirometer flask. The test substance was weighed in an air tight syringe and injected into the test medium. The test system was sealed immediately after addition of the test substance. An aliquot of the positive control stock solution was added to the appropriate test flasks. An unacclimated activated sludge inoculum was used in this study. The inoculum was obtained from the Somerset-Raritan Valley Sewage Authority, Bridgewater, New Jersey, USA. The treatment plant receives predominantly domestic sewage. All test systems were placed on a Coordinated Environmental Services (CES) automated respirometer which automatically recorded the oxygen uptake in general agreement with the OECD guideline. The study was conducted at a temperature range of 20.6 – 24.0°C.
Result	:	Biodegradation was based on oxygen consumption and the theoretical oxygen demand of the test substance was calculated using results of an elemental analysis of the test substance. By Day 2, >60% biodegradation of positive control was observed, which meets the guideline requirement. No deviations from the protocol occurred that affected the integrity of the study data. The average percent biodegradation on Day 34 of triplicate test systems containing C8 Ketone Fraction was 61.9%. C8 Ketone Fraction reached 10% biodegradation on Day 4 and reached 59.8% biodegradation on Day 28.
Conclusion	:	C8 Ketone Fraction is not readily biodegradable, but can be considered inherently biodegradable.
Reliability	:	(1) valid without restriction Guideline study without deviations from the protocol that would invalidate the study.
05.11.2009		(11)

3.3 BIOACCUMULATION

BCF	:	= 256.6
Elimination	:	
Method	:	other: calculated
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Method	:	Calculated values using BCFWIN version 2.15, a subroutine of the

computer program EPIWIN version 3.12.

Test condition : BCFWIN estimates the bioconcentration factor (BCF) of an organic compound using the compound's log octanol-water partition coefficient (Kow).

The estimation methodology used by BCFWIN is described in "Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient", SRC TR-97-006 (2nd Update), July 22, 1997.

Log Kow used = 4.04

Estimated BCF = 256.6
Estimated Log BCF = 2.409

Reliability : (2) valid with restrictions
The result is a calculated value based on the chemical structure and represents a potential bioaccumulation factor for the substance with the CAS number listed under test substance.

20.11.2006 (5)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: calculated
Species	:	other: freshwater fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 1.7 calculated
Method	:	other: ECOSAR Computer Model
Year	:	2006
GLP	:	
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Test condition	:	Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPI Suite computer model (2). 1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92. 2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.
Conclusion	:	Based on the calculated Kow value of 4.04, ketones, C12-branched is expected to have an acute 96-hour LC50 of 1.7 mg/L and a Chronic Value of 0.3 mg/L
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

20.11.2006 (2)

Type	:	other: calculated
Species	:	other: freshwater fish
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 1.2 calculated
Method	:	other: ECOSAR Computer Model
Year	:	2006
GLP	:	no
Test substance	:	Analog substance: CAS No. 6175-49-1; 2-dodecanone
Test condition	:	Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2). 1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92. 2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.
Conclusion	:	Based on the calculated Kow value of 4.18, 2-dodecanone is expected to have an acute 96-hour LC50 of 1.2 mg/L and a Chronic Value of 0.2 mg/L.
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.

20.11.2006 (2)

Type	:	
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 1.2 measured/nominal
Limit test	:	no
Analytical monitoring	:	
Method	:	other: no data
Year	:	1986
GLP	:	no data
Test substance	:	Analog substance: CAS No. 6175-49-1; 2-dodecanone; purity unknown.
Method	:	Trimmed Spearman Karber Method
Result	:	96 hour LC50 = 1.18 mg/L (95% CI 1.02 to 1.37) based upon measured values

Analytical method used was Gas-Liquid Chromatography.

Measured Conc. (mg/L)	Fish Total Mortality (@96 hrs)*
Control	0
0.33	0
0.55	0
0.66	1
1.06	9
2.43	20

* 20 fish added at test initiation

Test condition	:	Treatment solutions were prepared by diluting a 11.8 mg/L stock solution.

Nominal 2-dodecanone treatment levels were 0.9, 1.38, 2.12, 3.26, 5.01 mg/L, which measured 0.33, 0.55, 0.66, 1.06, and 2.43 mg/L, respectively.

Control/dilution water was EPA Duluth laboratory water.
Twenty fish were tested per treatment. Treatment volume = 1.0L. Test parameters were as follows: temperature=24.8 Deg C; dissolved oxygen = 6.8 mg/L; pH = 7.6; fish age = 33 days old; fish mean wt = 0.088g; fish mean length = 18.3 mm; fish loading = 1.76g/L/day.

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

Reliability	:	(1) valid without restriction

20.11.2006 (6)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 2 calculated
Method	:	other: ECOSAR Computer Model
Year	:	2006
GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Test condition	:	Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2).

1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92.

2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Conclusion : Based on the calculated Kow value of 4.04, ketones, C12-branched is expected to have an acute 48-hour EC50 of 2.0 mg/L and a Chronic Value of 0.3 mg/L.

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

20.11.2006 (2)

Type :
Species : Daphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 1.5 calculated
Method : other: ECOSAR Computer Model
Year : 2006
GLP : no
Test substance : Analog substance: CAS No. 6175-49-1; 2-dodecanone
Test condition : Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPI Suite computer model (2).

1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92.

2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Conclusion : Based on the calculated Kow value of 4.18, 2-dodecanone is expected to have an acute 48-hour EC50 of 1.5 mg/L and a Chronic Value of 0.2 mg/L.

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.

20.11.2006 (2)

Species : Daphnia magna Strauss
Endpoint : Immobility
Exposure period : 2 day(s)
Unit : mg/l
EC50 : = 5.2
EL50 : = 6.0
Method : OECD Guideline 202
GLP : Yes
Test substance : Analog Substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Result : Acute toxicity results are expressed as the Effect Loading / Effect Concentration 50 (EL/EC50); that is, the actual loading rate or measured concentration of test substance in dilution medium which is calculated to result in 50% immobilization compared to the control for the specified time of exposure. The 48 hour EL50 was 6.0 mg/L with a 99% confidence interval of 3.9 – 9.1 mg/L. The 48 hour EC50 was 5.2 mg/L with a 99% confidence interval of 3.3 – 8.0 mg/L. The maximum actual loading rate causing no immobilization was 3.9 mg/L. The maximum measured

concentration causing no immobilization was 3.3 mg/L. The minimum actual loading rate causing 100% immobilization was 9.1 mg/L. The minimum measured concentration causing 100% immobilization was 8.0 mg/L. Control survival was 100%. The method of analysis was automated static headspace gas chromatography with flame ionization detection (HS GC-FID).

Summary of In-Life Observations (% Immobilization)

Loading Rate (mg/L)	24-hour	48-hour
Control	0	0
0.75	0	0
2.0	0	0
3.9	0	0
9.1	0	100
22	0	100

Test condition : Individual Water Accommodated Fractions (WAFs) were prepared. The test substance was added to 4 L of reconstituted water in glass aspirator bottles (capacity 4.5 L). The test solutions and a control were mixed for 23.5 hours using a 4% vortex (of the static liquid depth). The mixtures were removed through an outlet at the bottom of each mixing vessel into four replicates of approximately 140 mL in 125 mL Erlenmeyer flasks (no headspace). Five daphnids were added to each replicate and the replicates were closed. The test was performed under static conditions with no aeration.
Dissolved oxygen ranged from 8.2 to 8.4 mg/L and pH ranged from 7.6 to 7.8 during the study. Water hardness was 142 mg/L as CaCO3. The TOC of the dilution water was 0.54 ppm. The test water temperatures ranged from 20.7°C to 20.9°C. The range of acceptable test water temperatures was 20° ± 1°C.
The environmental condition daily average temperatures ranged from 19.6°C to 20.6°C. The range of acceptable daily average temperatures is 20° ± 1°C. Diurnal light: 16 hours light; 8 hours dark: Light intensity ranged from 444 to 456 Lux during full light hours.
The daphnids were cultured in-house. Age was <24 hours old from 16-day old parents.
Due to the relatively complex nature and limited water solubility of the test substance, the following exceptions to the guideline apply for this study: The concentration of the test substance in solution was not determined prior to use. It was deemed more appropriate to prepare an individual treatment solution by adding the test substance to dilution water and removing the WAF for testing, rather than preparing a dilution of the stock solution as outlined in the guideline.

Conclusion : After *Daphnia magna* were exposed to a water accommodated fraction (WAF) prepared from Baton Rouge MEK Heavy Ketone Heart Cut - C8 Ketone Fraction for 48 hours, the EC50 was 5.2 mg/L and the EL50 was 6.0 mg/L.

Reliability : (1) valid without restriction
Guideline study with no deviations from the protocol.

05.11.2009 (12)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : other algae: green alga
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 1.4 calculated
Method : other: ECOSAR Computer Model
Year : 2006

GLP	:	no
Test substance	:	CAS No. 68514-41-0; Ketones, C12-branched
Test condition	:	Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2). 1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92. 2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.
Conclusion	:	Based on the calculated Kow value of 4.04, ketones, C12-branched is expected to have an acute 96-hour EC50 of 1.4 mg/L and a Chronic Value of 0.5 mg/L.
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

20.11.2006 (2)

Species	:	other algae: green alga
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	= 1.1 calculated
Method	:	other: ECOSAR Computer Model
Year	:	2006
GLP	:	no
Test substance	:	Analog substance: CAS No. 6175-49-1; 2-dodecanone
Test condition	:	Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2). 1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92. 2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.
Conclusion	:	Based on the calculated Kow value of 4.18, 2-dodecanone is expected to have an acute 96-hour EC50 of 1.1 mg/L and a Chronic Value of 0.4 mg/L.
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.

20.11.2006 (2)

Species	:	*Pseudokirchneriella subcapitata*
Endpoint	:	Biomass, growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
Method	:	OECD Guideline 201
GLP	:	Yes
Test substance	:	Analog substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Statistical methods	:	The EbC50 / ErC50 and confidence intervals for inhibition of area under the growth curve and growth rate were determined by a probit regression calculation of the growth inhibition/growth rate slope vs the log of the

concentration and associated confidence intervals based on the methods of D. J. Finney (Finney, 1971). Calculations were based on the PROC PROBIT procedure of SAS (SAS, 2002). The NOEC for the EbC50 and ErC50 was based on Multiple Range tests (Duncan, 1975) and (Dunnett, 1964), determined from the GLM procedure of SAS (SAS, 2002). The Shapiro-Wilk (Shapiro-Wilk, 1965) test for normality was used to test if the assumption of normality of the residuals was met; since the residuals were normally distributed the NOEC was based on the estimated values.
Finney, D.J. 1971. Probit Analysis, 3rd Edition, London: Cambridge University Press.
SAS Version 9.1, SAS Institute, Inc., Cary, NC. 2002-2003.
Duncan, D.B. 1975, “t-Tests and Intervals for Comparisons Suggested by the Data”, Biometrics, 31, 339-359.
Shapiro, S.S. and Wilk, M.B. 1965,“An analysis of variance test for normality (complete samples)” Biometrika, 52, pg 591-611.

Results : Effects on growth rate (r) based upon measured concentrations:
72-hr ErC50 = 16.0 mg/L (14.7 - 17.6 mg/L)
72-hr NOEC = 3.28 mg/L
Effects on growth rate (r) based upon actual loading rates:
72-hr ErL50 = 24.7 mg/L (22.6 - 27.6)
72-hr NOELR = 4.1 mg/L
Effects on biomass (b) based upon measured concentrations:
72-hr EbC50 = 8.00 mg/L (5.23 - 13.6 mg/L)
72-hr NOEC = 0.715 mg/L
Effects on biomass (b) based upon actual loading rates:
72-hr EbL50 = 11.3 mg/L (5.97 – 27.3 mg/L)
72-hr NOELR = 0.8 mg/L
Values in parentheses are 95% confidence intervals.

The analytical method used was static headspace gas chromatography with flame ionization detection.

Summary of In-Life observations (% Inhibition)

Loading Rate (mg/L)	Control	0.8	1.6	4.1	8.8	19.9
Meas. Conc. (mg/L)	0	0.715	1.42	3.28	7.71	12.9
Based on Growth Rate						
72 hours	n/a	-1.1	3.5	3.3	15	33
Based on Biomass						
72 hours	n/a	3.5	20	30	50	75

Negative(-) value indicates a stimulatory effect.

Test condition : Individual Water Accommodated Fractions (WAFs) were prepared for each treatment. The test substance was added to 4.0 L of algal nutrient medium augmented with sodium bicarbonate in glass aspirator bottles (capacity 4.5 L). The solutions were mixed for 24 hours using an 9.5% vortex (of the static liquid depth). The test solutions were removed through the outlet at the bottom of each mixing vessel into nine replicates of approximately 140 mL in 125 mL Erlenmeyer flasks (no headspace) containing two 14-mm glass spheres to facilitate mixing. The test chambers were inoculated with algae (1.0 x 104 cells/mL) and were closed with ground glass stoppers. Three replicates were sacrificed daily for cell density determination. The test chambers were placed on shaker tables (101 rpm) to keep the algae in suspension. The test was performed under static conditions with no aeration. The algae was cultured in-house from 5 day old stock cultures in log phase growth.
Test temperature range: 23.6 to 23.9°C. Continuous light: intensity was 7700 to 8400 Lux. The pH was 7.6 in the test solutions at test initiation and ranged from 8.6 to 8.7 at test termination.
Due to the complex nature and limited water solubility of the test substance, the following exceptions to the guideline apply for this study: The concentration of the test substance in solution was not determined prior to use. Test substance analysis was performed on samples of the WAFs at the start of the test (day 0) and at termination (day 4). It was

appropriate to prepare individual treatment solutions by adding the test substance to dilution water and removing the WAF of each mixture for testing than to prepare dilutions of a stock solution.
None of the above exceptions are believed to have affected the outcome, integrity, or quality of the study.

Conclusion : The 72-hour ErC50 was 16.0 mg/L. The 72-hour EbC50 was 8.00 mg/L. The 72-hour NOEC for growth rate was 3.28 mg/L and for biomass (area under the curve) was 0.715 mg/L.
The 72-hour ErL50 was 24.7 mg/L. The 72-hour EbL50 was 11.3 mg/L. The 72-hour NOELR for growth rate was 4.1 mg/L and for biomass (area under the curve) was 0.8 mg/L.

Reliability : (1) valid without restriction
Guideline study without deviations from the protocol that would invalidate the study.

05.11.2009 (13)

4.4 CHRONIC TOXICITY TO FISH

Species : other: Freshwater Fish (calculated toxicity values are not species specific)
Endpoint : other: LC50
Exposure period : 30 day(s)
Unit : mg/l
ChV : = .3 calculated
Method : other: ECOSAR Computer Model
Year : 2006
GLP : no
Test substance : CAS No. 68514-41-0; Ketones, C12-branched
Test condition : Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2).

1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92.

2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Conclusion : Based on the calculated Kow value of 4.04, ketones, C12-branched is expected to have an acute 96-hour LC50 of 1.7 mg/L and a Chronic Value of 0.3 mg/L.

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

20.11.2006 (2)

Species : other: Freshwater Fish (calculated toxicity values are not species specific)
Endpoint : other: LC50
Exposure period : 30 day(s)
Unit : mg/l
ChV : = .2 calculated
Method : other: ECOSAR Computer Model
Year : 2006
GLP : no
Test substance : Analog substance: CAS No. 6175-49-1; 2-dodecanone
Test condition : Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR

model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2).

Conclusion : Based on the calculated Kow value of 4.18, 2-dodecanone is expected to have an acute 96-hour LC50 of 1.2 mg/L and a Chronic Value of 0.2 mg/L.

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.

20.11.2006 (2)

4.5 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia sp. (Crustacea)
Endpoint : mortality
Exposure period : 16 day(s)
Unit : mg/l
EC50 : = .3 calculated
Method : other: ECOSAR Computer model
Year : 2006
GLP : no
Test substance : CAS No. 68514-41-0; Ketones, C12-branched
Test condition : Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2).

1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92.

2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Conclusion : Based on the calculated Kow value of 4.04, sec-Butyl Ether is expected to have an acute 48-hour EC50 of 2.0 mg/L and a Chronic Value of 0.3 mg/L.

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
20.11.2006 (2)

Species : Daphnia sp. (Crustacea)
Endpoint : mortality
Exposure period : 16 day(s)
Unit : mg/l
EC50 : = .2 calculated
Method : other: ECOSAR Computer model
Year : 2006
GLP : no
Test substance : Analog substance: CAS No. 6175-49-1; 2-dodecanone
Test condition : Log Kow (octanol/water partition coefficient) values and a chemical structure are needed to calculate aquatic toxicity using the ECOSAR model. The Kow calculation is performed by KOWWIN based on an atom/fragment contribution method of Meylan and Howard (1), which is a subroutine in the EPISuite computer model (2).

1. Meylan, W. and P. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84:83-92.

2. EPI SuiteTM (2000). Estimation Program Interface Suite, version 3.12. Syracuse Research Corporation, Syracuse, NY, USA.

Conclusion : Based on the calculated Kow value of 4.18, 2-dodecanone is expected to have an acute 48-hour EC50 of 1.5 mg/L and a Chronic Value of 0.2 mg/L.

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.

20.11.2006 (2)

5.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 8470 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	40
Vehicle	:	other: Tergitol 7
Doses	:	6300, 7950, 10000, 12600 mg/kg/bw
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	Analog substance: Trimethyl 4-nonanone (CAS #123-18-2); purity unknown
Remark	:	10 male albino rats (per group) were administered via gavage a 20% dispersion of the test substance in 1% Tergitol 7. Test doses included 6300, 7950, 10000 or 12600 mg/kg bw. A 14 day observation period followed dosing. Body weights were taken on the day of dosing and on day 14.
Result	:	LD50 = 8470 mg/kg (95% confidence limits = 7180 to 9990 mg/kg bw) High doses resulted in prostration and narcosis, with lung hemorrhages, congested livers, pale kidneys and opacity of the intestine notable on autopsy. Death was delayed for 72 hours or more in most cases. All surviving animals gained weight 124 days following dosing. The number of deaths are reported in the following table:

Dose (mg/kg)	Number dead/number dosed
6300	3/10
7950	4/10
10000	6/10
12600	10/10

Conclusion	:	Trimethyl nonanone has a low order of toxicity by the oral route of exposure.
Reliability	:	(2) valid with restrictions

21.11.2006 (1)

Type	:	LD50
Value	:	>2000 mg/kg bw
Species	:	rat
Strain	:	Crl:CD SD rats
Sex	:	Female (healthy nulliparous and non-pregnant)
Number of animals	:	Five females per dose
Vehicle	:	Corn oil
Doses	:	2000 mg/kg/bw
Dose interval	:	Animals were dosed in sequential order, one at a time, at a minimum of 48 hour intervals.
Method	:	EPA Health Effects Test Guidelines OPPTS 870.1100 Acute Oral Toxicity. EPA 712-C-02-190
GLP	:	Yes
Test substance	:	Analog substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Test conditions	:	Test substance was formulated as a concentration of 200 mg/ml in vehicle and administered at a volume of 10 ml/kg bw. Animals were observed at approximately 30 and 60 minutes post-dosing, followed by approximately hourly intervals throughout Day 1. Subsequently, animals were observed twice daily for 15 days post-dosing.
Result	:	LD_{50} > 2000 mg/kg bodyweight Strong odored urine and piloerection were observed in all females; an

unsteady gait in four females; partially closed eyelids, underactivity and salivation in two females; and urine staining of the peri-genital area, hunched posture, deep breathing, brown staining on the muzzle and head and pale light brown faeces in individual females.
All animals exhibited a satisfactory bodyweight gain throughout the study.
Macroscopic examination at study termination revealed no abnormalities.

Conclusion : The acute oral LD_{50} for methyl heptenone is greater than 2000 mg/kg.
Reliability : (1) valid without restriction
This study is reliable without restriction, on the basis that the study is well-documented and equivalent or similar to EPA Health Effects Test Guidelines OPPTS 870.1100 (Acute Oral Toxicity; EPA 712-C-02-190).

21.11.2006 (14)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Saturated Vapor
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	6
Vehicle	:	
Doses	:	Substantially Saturated Vapor
Exposure time	:	8 hour(s)
Method	:	
Year	:	1948
GLP	:	no
Test substance	:	Analog substance: Trimethyl 4-nonanone (CAS # 123-18-2); purity unknown
Method	:	Six rats were exposed to the test substance as a saturated vapor generated at room temperature for 8 hours.
Result	:	Two of the six rats died in 8 hours. Marked congestion of the lungs suggested the cause of death was direct damage to the lung.
Conclusion	:	Trimethyl nonanone has a low order of toxicity by the dermal route of exposure.
Reliability	:	(2) valid with restrictions

21.11.2006 (1)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 9030 - mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	male
Number of animals	:	40
Vehicle	:	other: none
Doses	:	7950, 10000, 12600 and 15800 ml/kg
Method	:	other: see remark
Year	:	1948
GLP	:	no
Test substance	:	Analog substance: Trimethyl 4-nonanone (CAS #123-18-2); purity unknown
Remark	:	The undiluted test substance was applied as a single dose to 4 groups of 10 male albino rabbits each at the following dose levels: 7950, 10000, 12600, or 15800 ml/kg, which correlates to doses of 6500, 8180, 10300, or 12900 mg/kg, respectively (density = 0.818 g/cm3). The test material was applied, undiluted at the appropriate dose, under an

impervious sheeting. The animals remained exposed to the test substance for 24 hours. Rabbits were observed for 14 days and body weights were obtained on the day of application and on day 14.

Result : LD50 = 9030 mg/kg bw (95% confidence limits = 7710 to 10590 mg/kg)

Erythema and occasionally necrosis of the skin resulted from the dose. The animals were sensitive to handling for a period of one week after the application. All but 2 animals (one each in the 10300 and 6500 mg/kg dose groups) lost weight during the 14 day post-application period. The weight losses may have been attributed in part to persistent diarrhea. The number of deaths are indicated in the following table.

Dose (mg/kg)	Number dead/number dosed
7950	2/10
10000	4/10
12600	5/10
15800	9/10

Conclusion : Trimethyl nonanone has a low order of toxicity by the dermal route of exposure.

Reliability : (2) valid with restrictions

21.11.2006 (1)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : undiluted
Exposure :
Exposure time : 24 hour(s)
Number of animals : 5
Vehicle :
PDII :
Result : slightly irritating
Classification :
Method : other
Year : 1951
GLP : no
Test substance : Analog substance: Trimethyl 4-nonanone (CAS #123-18-2); purity unknown
Remark : Undiluted trimethyl 4-nonanone produced mild irritation when tested undiluted under the conditions of the study.
Result : Grade 3: Mild Irritation
Test condition : The primary skin irritation test was performed by applying the test substance to an area of the skin that had been clipped. Two exposure conditions were tested. Under the first condition, 10 mg of the test substance was applied to the skin of 5 rabbits for 24 hours under a cover. Under the second test condition, 500 mg/kg of the test substance was applied to the skin of 5 rabbits uncovered for 24 hours. Grades 1-6 were used to classify the irritation observed following application of undiluted material. Grade 1 indicated the least visible capillary injection from undiluted chemical. Grade 6 indicated necrosis.
Conclusion : A single 24-hour application of the test material to occluded skin was mildly irritating.
Reliability : (4) not assignable
This study report did not contain sufficient experimental details of the study to be able to assess its scientific quality.

27.11.2006 (9)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	none
Result	:	slightly irritating
Classification	:	
Method	:	other
Year	:	1954
GLP	:	
Test substance	:	Analog substance: Trimethyl 4-nonanone (CAS #123-18-2); purity unknown
Remark	:	Eye injury was recorded based on degree of corneal necrosis on a scale of grades 1-10 when applying undiluted test material. Grade 1 indicates a very small area necrosis when at least 0.5 mL of test material is applied. Grade 10 indicates a sever burn from 0.5 mL of a 1% solution in water or propylene glycol.
Result	:	Grade 1: mild irritant
Conclusion	:	Based on these findings, the test material was mildly irritating to the eyes of rabbits.
Reliability	:	(4) not assignable This study report did not contain sufficient experimental details of the study to be able to assess its scientific quality.

27.11.2006 (10)

5.3 COMBINED REPEATED DOSE TOXICITY w/ REPRODUCTION / DEVELOPMENTAL SCREEN

Type	:	Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test
Species	:	rat
Sex	:	Male and Female (healthy nulliparous and non-pregnant) (age: 10 - 11 weeks)
No. of animals per sex per dose and control		10
Strain	:	Crl:CD® (SD)
Route of admin.	:	Oral gavage (vehicle: corn oil)
Frequency of treatm.	:	Single dose daily (5 mL/kg Body Weight)
Doses	:	Doses of 0, 100, 300 or 500 mg/kg/day (reduced from 1000 mg/kg/day on Day 3)
NOAEL	:	100 mg/kg/day was the maternal no observed adverse effect level (NOAEL) 500 mg/kg/day was the NOAEL in terms of reproductive function and fertility (male and female) 500 mg/kg/day was the NOAEL in terms of offspring survival and development
Method	:	Toxic Substances Control Act (TSCA) 15 U.S.C. 2601. 40CFR 799.9365.

Statistical Methods : Statistical analyses were applied where there was indication of possible meaningful inter-group differences. All statistical analyses were carried out using the individual animal (or litter) as the basic experimental unit. Where applicable, the litter was taken as the treated unit and the basis for statistical analysis and biological significance was assessed with relevance to the incidence of the finding within the background control population.

If 75% of the data (across all groups) were the same value, for example c, then a frequency analysis was applied. Treatment groups were compared using pairwise Fisher's Exact tests (1973) for each dose group against the control both for i) values <c versus values >=c, and for ii) values <=c versus values >c, as applicable.

If Bartlett's test for variance homogeneity (1937) was not significant at the 1% level, then parametric analysis was applied. The F1 approximate test was applied. This test is designed to detect significant departure from monotonicity of means when the main test for the comparison of the means is a parametric monotonic trend test, such as Williams' test (1971, 1972). The test statistic compares the mean square, NMS, for the deviations of the observed means from the maximum likelihood means, calculated under a constraint of monotonicity with the usual error mean square, EMS. The null hypothesis is that the true means are monotonically ordered. The test statistic is
F1 = NMS/EMS which can be compared with standard tables of the F distribution with 1 and EDF degrees of freedom. If the F1 approximate test for monotonicity of dose-response was not significant at the 1% level, Williams' test for a monotonic trend was applied. If the F1 approximate test was significant, suggesting that the dose response was not monotone, Dunnett's test (1955, 1964) was performed instead.

If Bartlett's test was significant at the 1% level, then logarithmic and square-root transformations were tried. If Bartlett's test was still significant, then non-parametric tests were applied. The H1 approximate test, the non-parametric equivalent of the F1 test described above, was applied. This test is designed to be used when the main test for comparison of the means is a non-parametric monotonic trend test, such as Shirley's test. The test statistic compares the non-monotonicity sums of squares, NRSS, for the deviations of the observed mean ranks from the maximum likelihood mean ranks with the non-parametric equivalent of the error sums of squares, ERSS (=N*(N+1)/12). The test statistic is H1 = NRSS/ERSS which can be compared to standard tables of the $\chi 2$-distribution with 1 degree of freedom. If the H1 approximate test for monotonicity of dose-response was not significant at the 1% level, Shirley's test for a monotonic trend (1977) was applied. If the H1 approximate test was significant, suggesting that the dose-response was not monotone, Steel's test (1959) was performed instead.

Significant differences between Control and treated groups were expressed at the 5% ($p<0.05$) or 1% ($p<0.01$) level.

GLP : Yes

Test substance : Analog substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)

Observations : Observations

During the acclimatization period, the animals were checked twice daily for health and general condition. Throughout the treatment period, detailed observations were recorded at the following times in relation to dose administration:
Pre-dose observation
As each animal was returned to its home cage
At the end of dosing of each group
Between one and two hours after completion of dosing of all groups
As late as possible in the working day

Males: daily through Week 1, twice weekly in Week 2 and weekly thereafter
Females: daily through Week 1, twice weekly in Week 2 and weekly until mated in Week 3. During gestation this took place on Days 1, 6, 12, 18 and 20 and on Days 2 and 6 of lactation.

Functional Observations
Sensory reactivity and grip strength assessments were performed (before dosing) on all male animals during Week 5 of treatment and all surviving females on Day 6 of lactation. The following measurements, reflexes and responses were recorded on all male animals during Week 5 of treatment and all surviving females on Day 6 of lactation: Approach response, Sensory reactivity, Grip strength, Touch response, Auditory startle reflex, Tail pinch response, and Motor activity (counting infra-red beam breaks over ten 6-minute intervals) using a Rodent Activity Monitoring System.

Result : NOAELs

- 100 mg/kg/day was the maternal no observed adverse effect level (NOAEL)
- 500 mg/kg/day was the NOAEL in terms of reproductive function and fertility (male and female)
- 500 mg/kg/day was the NOAEL in terms of offspring survival and development

Mortality
One female at 300 mg/kg/day and one female at 500 mg/kg/day were sacrificed early because they failed to litter. One female at 500 mg/kg/day was sacrificed following litter death. One control female was killed because of dystocia, with evidence of parturition in excess of 24 hours. One female at 500 mg/kg/day was killed on Day 16 of gestation with terminal signs that included underactive behavior, irregular respiration and a discharge of blood from the vagina. One Control male was found dead in the cage three days before the terminal sacrifice.

Clinical Signs
Initially a high dose of 1000 mg/kg/day was administered and animals were immediately underactive, had partially closed eyelids, piloerection, hunched posture, reduced body tone and prostration for up to 4 hours. From Day 3 on, the high dose was reduced to 500 mg/kg/day and there was an immediate reduction in acute effects.
The predominant signs observed in association with dose administration from Day 3 of study were increased salivation with associated chin rubbing and is most likely related to the palatability of the formulations, rather than a direct action of the test substance. Detailed physical examinations and arena observations did not reveal any signs that could be related to treatment with Methyl Heptenone.

Body Weight
Both males and females at the highest dose showed mean weight loss for the first four days and remained lower than controls as their weight gain increased through the study. Overall bodyweight gain for females at 500 mg/kg/day was slightly low when compared with Controls. For females receiving 100 or 300 mg/kg/day, bodyweight gain was essentially similar to Controls. During lactation absolute bodyweights for females receiving 500 mg/kg/day were significantly low compared with the Controls. Bodyweight gain at 300 and 500 mg/kg/day was slightly but not significantly low when compared with the Controls. Bodyweight gain at 100 mg/kg/day was unaffected by treatment during the lactation phase.

Food Consumption
Males and females that initially received 1000 mg/kg/day on Days 1 and 2 of study and subsequently received 500 mg/kg/day, had significantly low

food consumption during Days 1 to 3 of treatment. From Day 4 to Day 15 of the pre-pairing period food consumption values for both males and females at 500 mg/kg/day showed recovery and were essentially similar to Controls. Food consumption at 100 or 300 mg/kg/day was unaffected by treatment during the pre-pairing period.
During gestation females receiving 500 mg/kg/day showed marginally low food consumption. At 100 or 300 mg/kg/day food consumption was similar to the Controls.
At 500 mg/kg/day food consumption was significantly low during lactation (Days 1-7) and at 300 mg/kg/day consumption was low during Days 1-3 of lactation ($p<0.05$). Food consumption at 100 mg/kg/day was unaffected by treatment.

Hematology and Blood Chemistry
Hematological and blood chemistry investigations for males after 5 weeks of treatment and for females on Day 7 of lactation did not reveal any differences that could be attributed to treatment with Methyl Heptenone.

Functional Observations
Males receiving 500 mg/kg/day showed a high incidence of weak tail pinch response during Week 5 of treatment.
Forelimb grip strength values for females receiving 500 mg/kg/day were low on Day 6 of lactation, but hind limb values were unaffected.
During Week 5 of treatment, low beam scores (cage floor activity) for males in all treated groups were low, compared with Controls, during the first 6 minutes of recording, with a dose relationship being evident. Motor activity scores for females on Day 6 of lactation showed considerable inter and intra-group variation but there was no evidence of an effect of treatment.

Reproduction and Development
At 500 mg/kg/day there was an increase in the number of females exhibiting 4/5 day cycles or irregular cycles. At 100 or 300 mg/kg/day the majority of animals exhibited regular 4-day cycles. This effect on oestrous cycles was therefore not considered to represent an adverse effect of treatment.
The pre-coital interval, mating performance and fertility were unaffected by treatment.
At 500 mg/kg/day there was a treatment-related shift in the distribution of gestation lengths showing longer gestation periods compared with Controls. The treatment-related shift may be related to a slight delay in fetal growth. The gestation index was unaffected by treatment.
Litter size, sex ratio, offspring development, survival and bodyweight performance were unaffected by treatment with Methyl Heptenone at dose levels up to 500 mg/kg/day.

Gross Pathology
Increased incidence and minimal to moderate severity of cortical tubular hyaline droplets deposition, tubular granular casts and cortical tubular basophilia were observed in the kidney in all treated male groups, compared with Controls. An increased incidence of minimal to slight interstitial inflammation was seen in all treated male groups, compared with Controls.
Increased incidence and minimal to moderate severity of cortical tubular hyaline droplets deposition, tubular granular casts and cortical tubular basophilia were observed in the kidney in all treated male groups, compared with Controls. An increased incidence of minimal to slight interstitial inflammation was seen in all treated male groups, compared with Controls.

After 5 weeks of treatment treated males showed significantly high adjusted kidney weights at all dose levels (a dose response was apparent)

and males that received 300 or 500 mg/kg/day also showed significantly high adjusted liver weights. On Day 7 of lactation, adjusted ovarian weights for females that received 500 mg/kg/day were high when compared with the Controls.
At 500 mg/kg/day macroscopic examination at necropsy revealed two out of 10 males with pale kidneys and three out 10 with macroscopically enlarged livers. Macroscopic examination of females on Day 7 of lactation did not reveal any findings that could be attributed to treatment.
An increased incidence of aggregations of alveolar macrophages (minimal grade) was observed in the lungs of all treated male groups and the high dose female group. Only one male given 500 mg/kg/day presented a higher severity (slight grade) than Controls. The increase in incidence was slight and a dose response was not apparent, this finding was therefore considered not to be of any toxicological significance.
Slight hepatocyte centrilobular hypertrophy was observed during histopathological examination in the liver in all treated male and female groups. These observations are common findings in the livers of rodents that have been administered xenobiotics and as such are considered to be an adaptive change and not a toxic effect of treatment.
Increased incidence and minimal to moderate severity of cortical tubular hyaline droplets deposition, tubular granular casts and cortical tubular basophilia were observed in the kidney in all treated male groups, compared with Controls. An increased incidence of minimal to slight interstitial inflammation was seen in all treated male groups, compared with Controls.
Thyroid follicular cell hypertrophy (minimal severity) was noted in all treated male groups and in females given 300 or 500 mg/kg/day. These changes are not, however, considered of any toxicological significance to man.
Macroscopic examination of F1 offspring that died prematurely or were killed at scheduled termination on Day 7 of age did not reveal any findings that could be attributed to treatment.

Test condition :

Test substance :

Conclusion : It was concluded in this study that in terms of general toxicity, 100 mg/kg/day was the no observed adverse effect level (NOAEL), based on bodyweight and food consumption decreases, as well as adaptive changes in the liver morphology and rat specific changes in thyroid and kidney pathology. However despite evidence of systemic effects in the rat at 500 mg/kg/day there was no consequential impairment of reproductive function and the high dose of 500 mg/kg/day was considered to be the NOAEL in terms of reproductive function and fertility. The NOAEL in terms of offspring survival and development was 500 mg/kg/day.

Reliability : (1) valid without restriction
This study is reliable without restriction, on the basis that the study is well-documented and equivalent or similar to EPA Toxic Substances Control Act (TSCA) 15 U.S.C. 2601. 40CFR 799.9365 guidelines.

11.11.2009 (17)

5.4 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse gene mutation assay

System of testing : Salmonella typhimurium, strains TA1535, TA1537, TA98, and TA100

Tryptophan-dependent mutant of Escherichia coli, strain WP2 uvr A (pKM101)

Test concentration : Seven concentrations were tested, ranging from 5 µg/plate to 5000 µg/plate, the recommended limit dose

Metabolic activation	:	With and without - Independent tests were done in the presence and absence of liver S9 mix from rats treated with phenobarbital and 5,6-benzoflavone.
Vehicle	:	Dimethyl sulphoxide (DMSO)
Result	:	Negative
Method	:	US EPA Health Effects Test Guidelines OPPTS 870.5100 Bacterial Reverse Mutation Test. EPA 712-C-98-247
GLP	:	Yes
Test substance	:	Analog substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Remark	:	A solubility test determined that methyl heptenone was insoluble in water but dissolved in DMSO at 50 mg/ml, the highest concentration tested. Without metabolic activation (absence of S9): TA100 and TA1535: Sodium azide, 2 µg/plate TA1537: 9-Aminoacridine, 50 µg/plate TA98: 2-Nitrofluorene, 2 µg/plate WP2 uvrA: 4-Nitroquinoline-1-oxide, 2 µg/plate With metabolic activation (presence of S9): TA100, TA1535: 2-Aminoanthracene, 5 µg/plate WP2 uvrA: 2-Aminoanthracene, 10 µg/plate TA98, TA1537: Benzo[a]pyrene, 5 µg/plate In the initial test, the plate incorporation method was used. Briefly, aliquots of the test substance solutions (0.1 ml) were placed in glass vessels, followed by either S9 mix or phosphate buffer (0.5 ml), bacterial cultures (0.1 ml), and agar (2 ml). The mixtures were mixed thoroughly and overlaid onto Petri dishes pre-coated with minimal agar. Plates were incubated at 37°C for 72 hours. In a second test, the test substance solutions were pre-incubated with bacteria and S9 mix (or buffer) for 30 minutes at 37°C prior to addition of agar. The remaining steps were identical to the initial test. Each experimental condition (strain/test concentration/activation state) was plated onto three Petri dishes. A test was considered valid if the mean of the vehicle control revertant colony numbers for each strain was within or close to the 99% confidence limits of the current historical control range. The historical range is maintained as a rolling record over a maximum of five years. Secondly, positive control compounds must induce an increase in mean revertant colony number of two times (TA98, TA100, WP2 uvrA) or three times (TA1535, TA1537) the concurrent vehicle controls to be considered valid. Thirdly, mean viable cell counts in the 10-hour bacterial cultures (to be mixed with test substances) must be at least 10^9/ml. A substance was considered to have mutagenic activity if a reproducible increase in revertant colony numbers of at least twice (or three times, in the case of TA1535 and TA1537) the concurrent vehicle controls and some evidence of a positive dose-response relationship was exhibited. A substance was considered to have no mutagenic activity if a reproducible increase in revertant colony numbers was not exhibited. If criteria for a 'positive' or 'negative' response were not clearly met, statistical methods, in particular Dunnett's test, were employed to determine statistical significance. It was considered acceptable to conclude that the response was equivocal if no clear results were obtained.
Result	:	No evidence of toxicity was obtained following exposure to the C8 ketone fraction. No substantial increases in revertant colony numbers over control counts were obtained in any of the tester strains following exposure to the test substance at any concentration up to 5000 µg/plate, with or without metabolic activation.

Conclusion : Under the conditions of this study, the test material was not mutagenic.
Reliability : (1) valid without restriction
This study is reliable without restriction, on the basis that the study is well-documented and equivalent or similar to EPA Health Effects Test Guidelines OPPTS 870.5100 (Bacterial Reverse Mutation Test; EPA 712-C-98-247).

05.11.2009 (15)

Type : Chromosome aberration
System of testing : In vitro – Human lymphocytes
Test concentration : In the absence of metabolic activation by S9 mix, test substance concentrations ranged from 25 to 200 µg/ml.
In the presence of metabolic activation by S9 mix, test substance concentrations ranged from 50 to 1000 µg/ml.
Lymphocyte source : Blood taken from healthy male non-smoking donors was pooled and diluted with RPMI 1640 tissue culture medium supplemented with 10% foetal calf serum. 0.2 IU/mL sodium heparin, 20 IU/mL penicillin / 20 µg/mL streptomycin and 2.0 mM glutamine.
Vehicle : Dimethyl sulphoxide (DMSO)
Result : Negative
Method : US TSCA (2003) Test Guidelines In Vitro Mammalian Chromosome Aberration Test 40 CFR 799.9537 and US EPA Health Effects Test Guidelines OPPTS 870.5375 In Vitro Mammalian Chromosome Aberration Test. EPA 712-C-98-223.
GLP : Yes
Test substance : Analog substance: CAS No. 409-02-9; C8 Ketone Fraction (methyl heptenone)
Test condition : All lymphocyte cultures were exposed to the control or test substances in suspension. Duplicate cultures were prepared for each experimental condition.
Independent tests were done in the presence and absence of liver S9 mix from rats treated with phenobarbital and 5,6-benzoflavone.
All lymphocyte cultures were stimulated with phytohaemagglutinin prior to exposure to control or test substances. Aliquots (0.4 mL blood : 4.5 mL medium : 0.1 mL phytohaemagglutinin) of the cell suspension were placed in sterile universal containers and incubated at 37ºC in a 5% CO_2 atmosphere for approximately 48 hours. Cultures were gently shaken to resuspend the cells.
Cultures were treated with Colcemid two hours prior to the end of the recovery period in order to arrest cell division.

First test:
3 hour treatment with control or test substances followed by a 17 hour recovery period (presence and absence of S9)
Second test:
20 hour continuous treatment (absence of S9)
3 hour treatment followed by a 17 hour recovery period (presence of S9)

Positive Controls:
Without metabolic activation (absence of S9):
Mitomycin C in sterile purified water
0.2 µg/ml (3 hour treatment)
0.1 µg/ml (20 hour continuous treatment)
With metabolic activation (presence of S9):
Cyclophosphamide in sterile purified water
5 µg/ml (3 hour treatment)

One hundred cells in metaphase were evaluated from each culture at 1000x magnification using an oil immersion objective and chromosome aberrations were scored.
Only cells with 44 – 48 chromosomes were analyzed. Polyploid and endoreduplicated cells were noted when seen. The vernier readings of all

aberrant metaphase figures were recorded.
The number of aberrant metaphase cells in each treatment group was compared with the solvent control value using the one-tailed Fisher exact test. An assay was considered acceptable if the negative and positive control values were within the historical control range.
A positive response was recorded if the following conditions were met:
Statistically significant increases ($p<0.01$) in the frequency of metaphases with aberrant chromosomes at one or more test concentrations;
The increases exceeded the negative control range of the testing laboratory (99% confidence limit);
The increases are reproducible between replicate cultures;
The increases are not associated with large changes in pH, osmolality of the treatment medium, or extreme toxicity;
And evidence of a dose-response relationship exists to support the conclusion.
A negative response was recorded if no statistically significant increases occurred in the number of aberrant cells above concurrent control frequencies, at any dose level. If a clear positive or negative response was not evident, further evaluation was done.

Result : First Test:
Absence of S9:
Methyl heptenone caused no significant increases in the proportion of chromosomal aberrations at any dose level when compared with the solvent control.
Presence of S9:
Methyl heptenone produced a statistically significant increase in the proportion of chromosomal aberrations at the 600 µg/ml dose only. Due to the absence of a dose-dependent response, this increase was not thought to be biologically significant.

Second Test:
Both in the absence and presence of S9, methyl heptenone caused no statistically significant increase in the proportion of chromosomal aberrations at any dose level when compared to the solvent control.

Summary:
No statistically significant increases in the proportion of polyploid cells were observed during metaphase analysis, in either the first or second test.
All positive control compounds caused statistically significant increases in the proportion of aberrant cells, indicating that the test system was responding appropriately.

Conclusion : The C8 ketone fraction showed no evidence of causing an increase in the frequency of structural chromosomal aberrations in this in vitro cytogenetic test system under the described conditions.

Reliability : (1) valid without restriction
This study is reliable without restriction, on the basis that the study is well-documented and equivalent or similar to EPA Health Effects Test Guidelines OPPTS 870.5375 (In Vitro Mammalian Chromosome Aberration Test; EPA 712-C-98-223).

05.11.2009 (16)

6.1 ANALYTICAL METHODS

7.1 FUNCTION

8.1 METHODS HANDLING AND STORING

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