

Chemical Name: Methyl N-Amyl Ketone

CASRN: 110-43-0

Submitter: Eastman Chemical

The following CASRN's are also included:

CHEMICAL NAME	CASRN
Methyl propyl ketone	107-87-9
Methyl isopropyl Ketone	563-80-4
Methyl isoamyl ketone	110-12-3

As the Agency received data from High Production Challenge Program participants, it posted notice of and links to those data here for public review and comment. Companies and consortia were requested to defer any proposed new testing on their chemicals for a period of 120 days from when their Test Plans and Robust Summaries were posted to the Internet, in order to allow for technical public comment regarding the possible provision of additional existing data or other technical information which might address or eliminate the need for some new testing.

Some sponsors of chemicals submitted revised test plans and robust summaries to the Agency and referred to them as "final" submissions. EPA previously referred to the most recent submission as "revised" and has made no distinction or judgment whether a submission is final. Lastly, technical public comments on test plans and robust summaries were also provided for several chemicals/categories.

TABLE OF CONTENTS

The pdf contains the following documents:

- Cover Letter for Test Plan & Robust Summaries – October 4, 2001 Page 2
- Test Plan for CASRN 110-43-0 – October 4, 2001 Page 3
- Robust Summaries for CASRN 110-43-0 – October, 2001 Page 10
- Environmental Defense Comments for CASRN 110-43-0 – March 29, 2002 Page 32
- EPA Comments for CASRN 110-43-0 - April 18, 2002 Page 33
- Response to Comments/Cover Letter for Revised Summaries – May 21, 2002 Page 36
- Revised Test Plan for CASRN 110-43-0 – May 21, 2002 Page 39
- Revised Robust Summaries for CASRN 110-43-0 – May, 2002 Page 46
- Test Plan for CASRN 110-12-3 – July 1, 2002 Page 68
- Robust Summaries for CASRN 110-12-6 – July 11, 2002 Page 76
- PETA Comments for CASRN 563-80-4 – July 29, 2002 Page 100
- EPA Comments for CASRN 563-80-4 - August 13, 2002 Page 102

EASTMAN

AR20-13219

Eastman Chemical Company
P. O. Box 431
Kingsport, Tennessee 37662

October 4, 2001

Ms. Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the test plan and robust summaries for 2-heptanone (CAS No.: 110-43-0). Please note that in our March 12, 1999 commitment letter we called this chemical methyl amyl ketone. My company had agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003. However, due to the substantial amount of data that had been previously generated to understand the potential hazards of this chemical, we were able to complete our summarization ahead of schedule.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely,

James A. Deyo D.V.M., Ph.D., D.A.B.T.
Technical AssociateRECEIVED
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MR 52533

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL N-AMYL KETONE
(CAS NO.: 110-43-0)

PREPARED BY:
EASTMAN CHEMICAL COMPANY

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October 4, 2001

TABLE OF CONTENTS

OVERVIEW	3
TEST PLAN SUMMARY	3
TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT	4
SIDS DATA SUMMARY	6
EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY	7
REFERENCES	7
ROBUST SUMMARIES	
I. General Information	8
II. Physical-Chemical Data	
A. Melting Point	8
B. Boiling Point	9
C. Vapor Pressure	9
D. Partition Coefficient	10
E. Water Solubility	10
III. Environmental Fate Endpoints	
A. Photodegradation	11
B. Stability in Water	12
C. Biodegradation	13
D. Transport between Environmental Compartments (Fugacity)	15
IV. Ecotoxicity	
A. Acute Toxicity to Fish	16
B. Acute Toxicity to Aquatic Invertebrates	17
C. Toxicity to Aquatic Plants	18
V. Toxicological Data	
A. Acute Toxicity	19
B. Repeated Dose Toxicity	22
C. Genetic Toxicity – Mutation	26
D. Genetic Toxicity - Chromosomal Aberration	27
G. Developmental Toxicity	28
H. Reproductive Toxicity	29

OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl n-amyl ketone (MAK; CAS NO.: 110-43-0) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data in conjunction with EPA-acceptable predictive computer models, and values from reputable textbooks to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that these data are completely adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl n-amyl ketone is a colorless liquid capable of being manufactured to a high degree of purity. It has been in public use since the 1940's. It has been reported to be found in nature as part of clove oil and Ceylon cinnamon oil, and has been approved for use in food by the FDA (21CFR 172.515). Nevertheless, this solvent finds its primary function as a solvent in various coating applications and in the electronics industry. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 50 ppm (233 mg/m³) and by OSHA, which set a PEL level of 100 ppm (465 mg/m³).

TEST PLAN SUMMARY

CAS No. 110-43-0	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	Y	-	N	Y	N
Stability in Water	Y ¹	-	-	Y	N	Y	N
Biodegradation	Y	-	Y	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point -	A value for this endpoint was obtained from a reputable textbook referenced in Hazardous Substances Data Base (HSDB).
Boiling Point -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Vapor Pressure -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Partition Coefficient -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Water Solubility -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Conclusion: All end points haven been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation -	A value for this endpoint was obtained from a manuscript referenced in HSDB.
Stability in Water -	A technical discussion describing the stability of ketones in water was provided.
Biodegradation -	This endpoint was satisfied through the use multiple studies that were available. All studies were conducted following established guidelines and GLP assurances.
Fugacity -	A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1).

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Acute Toxicity to Aquatic Invertebrates -	This endpoint is filled by data from a study that followed OECD guideline #202 and was conducted under GLP assurances.
Toxicity to Aquatic Plants -	This endpoint is filled by data from a study that followed OECD guideline #201 and was conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from studies that were either conducted using established OECD guidelines and GLP assurances, or were published in reputable textbooks referenced within the HSDB. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity -	This endpoint is filled by data from studies assessing toxicity following both oral and inhalation exposures. Oral studies evaluated both rats and mice while the inhalation study only utilized rats. None of the studies followed established protocols and they were conducted prior to the establishment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions”.
Repeat Dose Toxicity -	This endpoint is filled by data from an oral gavage study of 13 weeks duration and an inhalation study of 10 months duration. Both studies were published in peer-reviewed journals. Neither study followed established protocols and were conducted prior to the establishment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions”.
Genetic Toxicity Mutation -	This endpoint is filled with a single “Ames-assay” study in <i>Salmonella typhimurium</i> strains TA 98, 100, 1535, 1537, and 1538. This study followed an established OECD guideline (#471) and was conducted under GLP assurances.
Aberration -	This endpoint is filled with data from an <i>in vitro</i> study using Chinese hamster ovary (CHO) cells that followed an established OECD guideline (#473) and was conducted under GLP assurances.
Developmental Toxicity -	This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.
Reproductive Toxicity -	This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. Some studies were conducted under GLP assurances while some were conducted prior to its enactment. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MAK were all obtained from textbooks referenced within the HSDB. These data indicate that MAK is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual studies, acceptable estimation modeling programs, and a technical discussion. As a result of its relatively high solubility in water and relatively low volatility, fugacity estimations predict that MAK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone will not undergo hydrolysis. The available biodegradation data indicate MAK is likely to be readily degraded in the environment. Nevertheless, due to its primary use in coatings applications, releases into the environment will primarily occur through evaporative emissions. Under such conditions, MAK is expected to rapidly degrade in the atmosphere.

The toxic potential of MAK to aquatic invertebrates and algae were determined through studies conducted under established OECD guidelines and GLP assurances. While that of fish was derived from a published reference within HSDB. The results of these studies demonstrate fish and *Daphnia* are not sensitive species NOEC's >90 mg/l. Whereas, the 72-hour E_0C_{50} and E_1C_{50} values for algal effects indicate that MAK would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in coatings applications. Furthermore, it is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low with an LD_{50} value noted in both rodent species of 1600 mg/kg and an LC_{50} value of between 2000-4000 ppm following a 6-hour exposure. Repeat exposure data following exposure durations of both 13-weeks (oral; rats) and 10 months (inhalation; rats and primates) indicate the material is well tolerated. The NOEL in the 13-week study was 20 mg/kg. No alterations were noted in appearance, behavior, or body weight gains. No statistically significant changes from control were noted in hematology, serum chemistries, or urinary parameters. The only significant finding was that of an increase in urine cellularity in males and changes in the relative organ weights in the liver of both sexes and in the kidneys of males. These organ weight changes were not accompanied by any histological alterations. The NOAEL from the 10-month exposure study was 1,025 ppm for both species. Neither of which developed overt signs of toxicity, alterations in weight gains or clinical chemistries, nor were any gross or microscopic changes exhibited in any organ or tissue examined. Results from mutagenicity and chromosomal aberration studies that utilized OECD guidelines and GLP assurances indicate these compounds do not induce genotoxicity. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MAK is not likely to induce either type of effect at dose levels up to 1000 ppm. Evidence of maternal effects were noted at 80 ppm and higher, and consisted primarily of decreases in activity level.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MAK that either followed established protocols under GLP assurances or were derived from data published in peer-reviewed journals. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (2) and the systematic approach described by Klimisch *et al.* (3). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 1.2, Syracuse Research Corporation, Syracuse, New York.
2. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.
3. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.
4. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

1. General Information

CAS Number: 110-43-0
Name: 2-Heptanone
 Methyl n-Amyl Ketone
 Methyl pentyl ketone
 Butyl acetone
 n-Pentyl methyl ketone
 M A K

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	M A K
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-35.5 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	
	Lide, D.R. (Ed.). CRC Handbook of Chemistry and Physics. 73 rd ed. Boca Raton, FL: CRC Press Inc., 1992- 1993.
Other	
	Last revision date: 19990921

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B. Boiling Point

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	151.5 °C
Pressure:	760 mmHg
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	
	Budavari, S. (Ed.). The Merck Index – Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc 1989, 737
Other	
	Last revision date: 19990921

C. Vapor Pressure

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Vapor pressure value:	1.6 – 3.86 mmHg
Temperature:	25 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	
	Sunshine, I. (Ed.). CRC Handbook of Analytical Toxicology. Cleveland: The Chemical Rubber Co., 1969, 633.
	Riddick, J.A., <i>et al.</i> ; Organic Solvents 4 th ed. NY: Wiley Interscience, (1986)
Other	
	Last revision date: 19990921

D. Partition Coefficient

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Log K _{ow} :	1.98
Temperature:	Unknown
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Hansch, C., Leo, A.J.; Medchem Project Issue No. 26 Claremont, CA: Pomona College 1985
Other	Last revision date: 19990921

E. Water Solubility

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	4300 mg/L
Temperature:	25° C
Description:	Slight (1-10 g/L)
Remarks:	The same solubility value was indicated in two different references within HSDB. Temperature was not given with reference (1), but was listed as 25° C in reference (2).
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	(1) Kirk-Othmer Encyclopedia of Chemical Technology. 3 rd Ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984 V13 p. 896 (1981) (2) Riddick, J.A., <i>et al.</i> ; Organic Solvents 4 th ed. NY: Wiley Interscience, (1986)
Other	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Remarks:</p> <p>Results Rate Constant: Temperature °C: Half-life: Remarks:</p> <p>Conclusions</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity was reported as >99%</p> <p>Flash Photolysis Resonance Fluorescence (FPRP) Hydroxyl radical reaction No Unknown (Study was published in 1987) Hydroxyl radicals were produced by the vacuum ultraviolet photolysis of water at -0.1 Torr. Following production, radicals were monitored as a function of time by the fluorescence excited by a microwave powered OH resonance lamp. Hydroxyl radical concentration was between 10^{10} and 10^{11} molecules /cm³. This level was deemed high enough to assure pseudo-first-order kinetics with respect to radical decay.</p> <p>8.67×10^{-11} cm³/molecule-second 23 °C 4.5 hours (based on an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm³)</p> <p>Material is expected to rapidly degrade in the atmosphere.</p> <p>Data obtained from Hazardous Substances Data Bank Number: 1122</p> <p>Wallington, T.J. and Kurylo, M.J. (1987). Flash Photolysis Resonance Fluorescence Investigation of the Gas-Phase Reaction of OH Radicals with a Series of Aliphatic Ketones over the Temperature Range 240-440 K. <i>J. Phys. Chem.</i> 91, 5050-5054.</p> <p>Last revision date: 19990921</p>
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B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.^{1,2}

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation³. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

- (1) Bell and Clunie, *Trans. Faraday Soc.*, **48**, 439, (1952).
- (2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
- (3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.7%
Method	
Method:	Method C.6., "Degradation, Chemical Oxygen Demand", Official Journal of the European Communities, No. L383A/227, 29 December 1992.
Test type:	Chemical Oxygen Demand (COD)
GLP:	Yes
Year:	1997
Remarks:	
Results	
Results:	2.42 grams COD/gram of test substance
Remarks:	The value is a mean of three replicates.
Conclusions	
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	
	Chemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00590. July 24, 1997.
Other	

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.7%
Method	
Method:	Method C.5., "Degradation, Biochemical Oxygen Demand", Official Journal of the European Communities, No. L251/212, 19.9.84. Method is similar to OECD: TG-301C: Modified MITI Test.
Test type:	Biochemical Oxygen Demand (BOD)
GLP:	Yes
Year:	1997
Remarks:	BOD was determined after 5 and 20 days. The 20-day value was performed in duplicate.
Results	
Results:	BOD5 was 1.77 grams BOD/gram of test substance BOD20 was 2.00 grams BOD/gram of test substance
Remarks:	The BOD 20 value was a mean of two replicates.
Conclusions	
	The test material is considered to be "Readily Biodegradable" based on a BOD5/COD ratio greater than 0.5 ($1.77/2.42 = 0.73$)
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	
	Biochemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00589. July 24, 1997.
Other	

D. Transport between Environmental Compartments (Fugacity)

<p>Test Substance Test substance: Remarks:</p> <p>Method Test type: Model used: Remarks:</p> <p>Results Model data and results: Estimated distribution and media concentration (levels II/III): Remarks:</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK</p> <p>Estimation Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation</p> <table style="margin-left: 40px;"> <thead> <tr> <th></th> <th style="text-align: right;">Concentration (%)</th> </tr> </thead> <tbody> <tr> <td>Air</td> <td style="text-align: right;">5.97</td> </tr> <tr> <td>Water</td> <td style="text-align: right;">39.4</td> </tr> <tr> <td>Soil</td> <td style="text-align: right;">54.6</td> </tr> <tr> <td>Sediment</td> <td style="text-align: right;">0.0724</td> </tr> </tbody> </table> <p>Physical chemical values utilized in this model were default values obtained from the EPIWIN program.</p> <p>Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 1.2, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay <i>et al.</i> 1996; <i>Environ. Toxicol. Chem.</i> 15(9), 1618-1626 and <i>Environ. Toxicol. Chem.</i> 15(9), 1627-1637.</p>		Concentration (%)	Air	5.97	Water	39.4	Soil	54.6	Sediment	0.0724
	Concentration (%)										
Air	5.97										
Water	39.4										
Soil	54.6										
Sediment	0.0724										

IV. Ecotoxicity

A. Acute Toxicity to Fish

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring:</p> <p>Exposure period: Remarks:</p> <p>Results Endpoint value: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Not Specified Flow-through Unknown Unknown Fathead minnow (<i>Pimephales promelas</i>) Dissolved oxygen 7.2 mg/L, hardness 46.4 mg/L, alkalinity 42.1 mg/L, pH 7.72, and temperature 24.2 °C. 96-hr</p> <p>LC₅₀ 131 mg/L (confidence limit 126–137 mg/l); EC₅₀ 128 mg/L</p> <p>The LC₅₀ value indicates that the test substance would not be classified according to the European Union’s labeling directive and would correspond to a “low concern level” according to the U.S. EPA’s assessment criteria.</p> <p>Reliable with restrictions Data obtained from Hazardous Substances Data Bank Number: 1122 and were noted to have been peer reviewed. However, no raw data were available for review.</p> <p>Geiger D.L., Poirier S.H., Brooke L.T., Call D.J., eds. Acute Toxicities of Organic Chemicals to Fathead Minnows (<i>Pimephales Promelas</i>). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior, 1986. 179</p> <p>Last revision date: 19990921</p>
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B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-202 and EEC/Annex V C.2
Test type:	Acute immobilization
GLP:	Yes
Year:	1998
Species/strain:	<i>Daphnia magna</i>
Analytical monitoring:	Aliquots of exposure solution were submitted for concentration determinations at 0, 24, and 48 hours. Temperature, dissolved oxygen, and pH were also determined at these same time periods.
Test details:	48-hour exposure period; semi-static
Remarks:	No protocol deviations were noted. Study was conducted in duplicate and results were averaged.
Results	
Nominal concentration:	6.25, 12.5, 25, 50, and 100 mg/L
Measured concentration:	6.46, 13.01, 24.52, 47.86, 90.10 mg/L
Endpoint value:	EC ₅₀ > 90.10 mg/L
Biological observations:	The behavior of all <i>Daphnia</i> was comparable to controls.
Statistical methods:	NA (no effects were seen at highest exposure concentration)
Remarks:	Water temp ranged from 19 to 21 °C, pH ranged from 8.2 to 8.7, and dissolved oxygen ranged from 8.6 to 9.3 mg/L.
Conclusions	
	The 48-hour EC ₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	
	An Acute Aquatic Effects Test with the Daphnid; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-431-902185-A; June 15, 1998
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	1998
Species/strain:	<i>Selenastrum capricornutum</i>
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	
Results	
Nominal concentration:	12.5, 25, 50, 100, and 200 mg/L
Measured concentration:	6.2, 11.9, 22.1, 42.7, 86.3 mg/L (geometric mean)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 75.5 mg/L; the E_rC_{50} (0-72 hr) was 98.2 mg/L
NOEC, LOEC, or NOEL, LOEL:	The 72 hr NOEC was estimated to be 42.7 mg/L
Biological observations:	No deformed cells were noted
Was control response satisfactory:	Yes (culture concentrations increased by a factor of 136-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software program AL_ACUTE (Ver. 2.2).
Remarks:	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.3 to 7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	
	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive and would be classified in a “moderate concern level” according to the U.S. EPA’s assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	
	A Growth Inhibition Test with the Alga, <i>Selenastrum capricornutum</i> ; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-902185-B; October 13, 1998
Other	

V. Toxicological Data

A. Acute Toxicity

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No (Pre-GLP) 1964 Rat/unknown Unknown 10 animals in total were used Material was administered undiluted Oral Rats were administered doses of MAK ranging from 200-3200 mg/kg. Animals were monitored for clinical observations and weight change for 14-days.</p> <p>LD₅₀ = 1600 mg/kg Report only indicated deaths occurring at 1600 mg/kg on day 1 after 5 hours Clinical signs of toxicity included slight to very weak, prostration, vasodilatation, labored breathing, and ataxia. Except for labored breathing, which was noted at doses of 800 mg/kg and above, clinical signs at specific dose levels were not indicated. Autopsy was negative.</p> <p>Material is considered slightly toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No (Pre-GLP) 1964 Mouse/unknown Unknown 6 animals in total Material was administered undiluted Oral A total of 6 mice were administered doses of MAK ranging from 400-1600 mg/kg. They were monitored for clinical observations and weight change for 14-days.</p> <p>LD₅₀ = 1600 mg/kg No deaths were noted at any dose Animal appearance was noted as normal to quite weak.</p> <p>Material is considered slightly toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LC₅₀ estimate No (Pre-GLP) 1964 Rat/unknown Unknown 3 animals/exposure level None Inhalation, whole -body Rats were exposed to MAK in whole-body chambers for 4 hours at 5,126 ppm, and 6 hours at 4,169, 832, 1,437, and 2,016 ppm. It was noted that the inhalation chambers were maintained at 24 °C. Animals were monitored for clinical observations and weight change for 14-days.</p> <p>LC₅₀ 2000-4000 ppm (6-hr) At 5,126 ppm all 3 animals died shortly after their 4-hour exposure. At 4,169 ppm, 1/3 died after 4 hours and the other 2 died shortly after their 6-hour exposure ended. No deaths were noted at 2,016 ppm or lower. Clinical signs in all studies included piloerection, vasodilatation, hypernea, lassitude, ataxia, and prostration. All animals gained weight, although higher-dosed animals gained less.</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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B. Repeated Dose Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity was 97%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (Pre-GLP)
Year:	Unknown (studies were published in 1978, 79, and 81)
Species/strain:	Rat/Sprague-Dawley and Primate/ <i>Macaca fascicularis</i>
Route of exposure:	Inhalation
Duration of test:	10-months
Exposure levels:	100 and 1000 ppm
Sex:	Males
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	<p>Groups of 50 rats and 8 monkeys were randomly assigned to each of the three exposure groups. Animals were exposed using whole-body chambers. At necropsy, lungs, liver, heart, spleen, kidney, adrenals, pancreas, testes, brain, and sciatic nerve were harvested for microscopic examinations. Clinical chemistries were conducted in primates after 1, 3, and 6 months of exposure and at study termination. Blood and urine was collected from both species at termination for metabolite identification. Liver microsomal enzyme induction was evaluated in rodents by assessing barbiturate-induced sleeping times. Rats also had tissue distribution analyses conducted following both ip (10 mg/kg) and inhalation exposure to [¹⁴C]MAK. Tissues, urine and feces were collected 2, 4, 8, 12, 24, 48, and 72 hours after administration of the radiolabeled MAK. Distribution and excretion was assessed in both naive and pre-exposed animals. At monthly intervals both species were evaluated for neurological function by assessing maximum motor-nerve conduction velocity (MCV) of the sciatic and ulnar nerves and amplitude of evoked muscle action potential (MAP). Primates also underwent electroencephalograms (EEG) and had visually evoked action potential recorded. Cardiopulmonary studies, including mechanical properties (compliance and resistance), lung volumes, flow-volume dynamics, distribution of ventilation, diffusion, and gas exchange were conducted on monkeys at the start of the study and after 6 months of exposures. Electrocardiographic (ECG) examinations were also conducted at the time of pulmonary function testing.</p>

<p>Results</p> <p>NOAEL (NOEL): Actual exposure levels: Toxic responses by dose:</p> <p>Statistical methods:</p> <p>Remarks:</p> <p>Conclusions</p> <p>Data Quality</p> <p>Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>1025 ppm (both species) 131 +/-30 ppm and 1025 +/- 136 ppm</p> <p>Both species tolerated the exposures without developing overt signs of toxicity or alterations in weight gains or clinical chemistries. There was no effect on barbiturate sleeping times. Neither species exhibited any gross or microscopic changes in any organ or tissue examined. Six months of exposure did not alter the overall cardiopulmonary function, EEG and ECG readings, or induce any evidence of neurotoxicity. MAK was detected in the serum and urine from both species at both exposure levels. While methyl n-amyl alcohol was detected only in the urine and serum from high dose primates. Although some significant post-MAK peaks were observed, they were not identified by GC/MS. They were present in 4/14 low dose animals and 10/12 receiving 1025 ppm exposures. Regardless of the route of administration, i.e., ip or inhalation, or whether animals were naive or had been pre-exposed, the liver contained the most radioactivity. The next highest levels were detected in the kidney, pancreas, and lungs. The brain contained some of the lowest amounts. Excretion of MAK into the urine and feces peaked at 12 hours and remained relatively constant through 48-hours. Fecal excretion through 72-hours only accounted for 2% of the administered dose.</p> <p>Multivariate analysis of covariance (MANOVA), Kruskal-Wallis test, and Student's t test.</p> <p>Animals appeared to tolerate exposure to MAK with minimal effects.</p> <p>Reliable with restriction</p> <p>This appears to be a very robust and well-conducted study; however, basic data are not available for review.</p> <ol style="list-style-type: none"> Lynch, D.W., Lewis, T.R., Moorman, W.J., Plotnick, H.B., Schuler, R.L., Smallwood, A.W., and Kommineni, C. Inhalation Toxicity of Methyl n-Amyl Ketone (2-Heptanone) in Rats and Monkeys. <i>Toxicology and Applied Pharmacology</i> 58, 341–352, 1981. Johnson, B.L., Setzer, J.V., Lewis, T.R., and Hornung, R.W. An Electrodiagnostic Study of the Neurotoxicity of Methyl N-Amyl Ketone. <i>American Industrial Hygiene Association</i> 39, 866–872, 1978. Johnson, B.L., Anger, W.K., Setzer, J.V., Lynch, D.W., and Lewis, T.R. Neurobehavioral Effects of Methyl N-Butyl Ketone and Methyl N-Amyl Ketone in Rats and Monkeys: A Summary of NIOSH Investigations. <i>Journal of Environmental Pathology and Toxicology</i> 2, 113–133, 1979. <p>This study was conducted by The National Institute for Occupational Safety and Health, Division of Biomedical and Behavioral Science in Cincinnati, OH.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Duration of test: Dose levels: Sex: Frequency of treatment: Control group and treatment: Post-exposure observation period: Remarks:</p> <p>Results NOAEL (NOEL): Toxic responses by dose:</p> <p>Statistical methods:</p> <p>Remarks:</p> <p>Conclusions</p>	<p>MAK Purity was 98% at minimum</p> <p>Other Repeated exposure No (Pre-GLP) Unknown (studies were published in 1972) Rat/CFE Oral gavage 13-weeks 0, 20, 100, and 500 mg/kg Male and Female; 15/dose level A single daily gavage Yes; Corn oil None An additional 5 animals/sex receiving 100 and 500 mg/kg were terminated after 2 and 6 weeks of dosing. All animals were assessed for body weight, food and water intakes, clinical chemistries, hematology, and urinalysis. At termination, animals underwent a gross examination with 12 different organs harvested to assess changes in weight and 23 different tissues were preserved for microscopic analysis.</p> <p>20 mg/kg (NOEL) No alterations were noted in appearance, behavior, or body weight gains. No statistically significant changes from control were noted in hematology, serum chemistries, or urinary parameters. However, an increase in urine cellularity was noted in males at the mid- and high-dose levels after 13 weeks and in the high-dose group after 6 weeks. Changes in relative organ weights were noted in the liver of both sexes at the high dose at Week-13 and in males only after 6 weeks (high dose) and at 2 weeks (high and mid). Significant alterations were also seen after 13 weeks in relative kidney weight in mid and high dose males. Other organs exhibiting weight changes were not significant when corrected for body weight. Despite the reported organ weight changes, no histological alterations were noted in any tissue. No serum biochemical changes were noted that might also be reflective of renal or hepatic toxicity.</p> <p>Data present in graphs and figures were noted to have been compared using Student's t test.</p> <p>The effect in the liver was likely an adaptive response from continual exposure to large doses of test material. The increased urine cellularity was only noted in males and as not accompanied by any alterations in the histological appearance of the kidney or urinary bladder.</p>
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<p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>Reliable with restriction Acceptable, well-documented publication that meets scientific principles. Study was conducted by the British Industrial Biological Research association</p> <p>Gaunt, I.F., Carpanini, F.M.B., Wright, M.G., Grasso, P., Gangolli, S.D. (1972) Short-term Toxicity of Methyl Amyl Ketone in Rats. <i>Food Cosmet. Toxicology</i> 10, 625–636.</p>
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C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99%
Method	
Method:	OECD: TG-471
Test type:	<i>In vitro</i> mutagenicity
GLP:	Yes
Year:	1994
Species/strain:	<i>Salmonella typhimurium</i> /TA98, 100, 1535, 1537, 1538
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, 9-aminoacridine) were run concurrently. Negative control was the test vehicle dimethylsulfoxide. Test material as evaluated in triplicate at each dose level.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate
Precipitation concentration:	No precipitate was observed at 5000 ug/plate
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Means and standard deviation were determined for each of the dosing regimens; Further statistical analyses were not needed due to the absence of an increase in the number of revertants colonies at any dose beyond the positive control.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD-like guideline study conducted under GLP assurances.
References	Ames mutagenicity study of methyl n-amyl ketone. Microbiological Associates Inc., Rockville, MD; Sponsor Project Number STP-195; Laboratory Study Number G94BJ71.501; December 15, 1994.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-473
Test type:	<i>In vitro</i> mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1998
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 1200 ug/ml (this level exceeds the 10 mM max. recommended level)
Metabolic Activation:	Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed on analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances
References	Covance Laboratories Inc., Vienna, VA; Study number: 19226-0-437OECD; June 18, 1998
Other	

E. Developmental Toxicity

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: GLP: Year: Species/strain: Sex: Route of exposure: Exposure levels: Actual exposure levels: Exposure period: Frequency of treatment: Control group and treatment: Duration of test: Remarks:</p> <p>Results Maternal toxicity NOEL: Repro./Develop. toxicity NOEL: Parental toxic responses:</p> <p>Fetal toxic responses dose:</p> <p>Statistical Methods:</p> <p>Remarks:</p> <p>Conclusions</p>	<p>MAK Purity was >99%</p> <p>OECD: TG-421 Yes 1996 Rats/Sprague-Dawley Male and Female (12/exposure level) Inhalation, whole -body 0, 80, 400, and 1000 ppm 0, 78.6, 405.8, and 1022.6 ppm 6 hrs/day 7 days/week</p> <p>Controls were exposed to filtered room air and housed similarly Males were exposed for 50 days while females were exposed for 34 to 47 days</p> <p>80 ppm NOEL</p> <p>1000 ppm NOEL</p> <p>There were no mortalities. A dose responsive reduction in activity was noted during the exposure period in the high- and mid-dose animals only. Animals appeared to become acclimated as this reduction went from moderate, to minor, to minimal by study conclusion. Males in the high dose group exhibited a decrease in food consumption during the days 0-7 only. There was no effect on body weight in either sex, although mid-dose females exhibited less of a weight change during days 0-7 of gestation. There were no effects noted in any of the litter parameters due to MAK exposure (reproductive performance, gestation length, number of live/dead pups, implant total, prenatal loss, % survival, ratio of male/female pups, or pup weight). There were no effects noted in either sex on any of the selected organs that were weighed, or examined grossly or histologically.</p> <p>There were no treatment-induced changes in pup clinical signs or abnormalities, or weight gains at any measured time -period.</p> <p>Homogeneity of data was evaluated using Bartlett's test (p ? 0.01), one-way analysis of variance (ANOVA) (p ? 0.05), and Dunnett's t-test (p ? 0.05) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test (p ? 0.01), the data were evaluated using a Kruskal-Wallis H-test (p ? 0.05) followed by Mann-Whitney U-test (p ? 0.05). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test (p ? 0.05). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model (p ? 0.05).</p> <p>Test material did not induce reproductive or developmental toxicity under the conditions of this assay.</p>
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<p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>Reliable without restriction This was a well-documented OECD guideline study conducted under GLP assurances.</p> <p>Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 95-0202; October 7, 1996.</p>
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F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.

Environmental Defense Comments on Methyl N-Amyl Ketone

(Submitted via Internet 3/29/02)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Methyl N-Amyl Ketone.

The test plan and robust summary submitted by Eastman Kodak conclude that existing data are adequate to fulfill the requirements of the HPV program. We agree with this conclusion with one exception as noted below. We also have a concern about occupational exposures to this chemical.

The repeat dose inhalation and oral studies were conducted at unknown times according to the test plan, no raw data were available for review, and the studies were conducted pre-GLP. The studies were published in 1972, 1979 and 1981. The adequacy of the repeat dose studies must be questioned because the publications were not geared to fulfill the HPV requirements as raw data were not available to the sponsor and the completeness of the study including the range of histological analyses cannot be judged. Without additional information, it does not appear that the repeat dose study meets the HPV criteria for inclusion.

The combined reproductive/developmental study does fulfill the requirements of the HPV program and it was used to establish a maternal NOEL of 80 ppm. We were disturbed to read that the OSHA PEL for methyl N-amyl ketone is 100 ppm and the TLV-TWA is 50 ppm. The overlap with the NOEL raises concern that workers may be exposed to potentially harmful levels of methyl N-amyl ketone. Is information available on the actual exposures encountered by workers under different exposure circumstances? Although this information is not mandated by the HPV program, it certainly should be addressed as an occupational health issue by the sponsor and OSHA.

Thank you for this opportunity to comment.

George Lucier, Ph.D.
Consulting Toxicologist, Environmental Defense

Karen Florini
Senior Attorney, Environmental Defense

April 18, 2002

James A. Deyo, D.V.M., Ph.D., D.A.B.T.
Technical Associate
Eastman Chemical Company
P. O. Box 431
Kingsport, Tennessee 37662

Dear Dr. Deyo:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2-heptanone, posted on the ChemRTK HPV Challenge Program Web site on December 3, 2001. I commend Eastman Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Eastman Chemical Company advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Heffer, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsc hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:
2 - Heptanone (Methyl N–Amyl Ketone)**

SUMMARY OF EPA COMMENTS

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for methyl n-amyl ketone (CAS# 110-43-0; 2-heptanone) dated October 4, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 3, 2001.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. All appropriate SIDS-level tests/estimations have been performed. However, the submitter needs to provide additional data in its biodegradation robust summary.
2. Health Effects. All appropriate SIDS-level tests have been performed. However, the submitter needs to address several deficiencies in the robust summaries.
3. Ecological Effects. The submitted ecotoxicity data are adequate and no further testing is required. Additional information needs to be provided in the acute fish toxicity robust summary.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE 2 - HEPTANONE (METHYL N-AMYL KETONE) CHALLENGE SUBMISSION

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The submitter's approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The submitter's approach to these endpoints is acceptable for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate test data are available for these endpoints although the submitter needs to address a few deficiencies in the robust summaries (see "Specific Comments on Robust Summaries").

Acute Toxicity. Acute oral and inhalation toxicity tests in rats are adequate. The acute oral toxicity test in mice appears inadequate. The submitter needs to address the deficiencies noted in the robust summaries. No additional acute toxicity tests are needed.

Repeated Dose Toxicity. Both 10-month inhalation toxicity study in rats and monkeys and a 13-week oral gavage study in rats are adequate.

Genetic Toxicity (in vitro). Studies on reverse mutation in *Salmonella typhimurium* and on chromosomal aberration in Chinese hamster ovary cells adequately address genetic toxicity endpoints.

Reproductive/Developmental Toxicity. A combined reproductive/developmental inhalation toxicity study in rats is adequate for these endpoints although certain information is missing in the robust summary.

Ecotoxicity (fish, invertebrate, and algae). Adequate test data are available for acute fish, daphnia, and algae toxicity. Additional details are needed in the robust summary for the acute fish toxicity test.

Specific Comments on the Robust Summaries

Environmental Fate.

Biodegradation. The submitter needs to provide information on the source/concentration of the microbial inoculum, initial concentration of the chemical, and time required for 10 % biodegradation to take place.

Fugacity. To estimate transport and distribution, the sponsor used the EPIWIN Level III model which provides estimated values as default inputs. EPA recommends using the EQC level III model from the Canadian Environmental Modeling Centre at Trent University, which allows full control of data inputs. This model can be found at the following Web address: <http://www.trentu.ca/academic/aminss/envmodel/>.

Health Effects.

Acute oral toxicity. For both studies, the submitter needs to add, if available, all dose levels, and the number of animals at each dose. The submitter needs to clarify the LD₅₀ for the acute oral toxicity test in mice because the result of the study stated no deaths noted at any dose.

Acute inhalation toxicity. The submitter needs to add the method by which the test atmosphere was generated (e.g., as aerosol, vapor, etc.).

Repeated-dose inhalation toxicity. The submitter needs to clarify the three exposure groups, to add the method by which the test atmosphere was generated (e.g., as aerosol, vapor, etc.), and to specify the hematological, clinical chemistry, and urinalysis parameters assessed.

Repeated-dose oral toxicity. The submitter needs to add the frequency of data collection (for clinical signs, body weight, and food and water intake), the specific hematology, clinical chemistry and urinalysis parameters that were examined, and the specific organs that were weighed or examined for gross and microscopic pathology.

Reproductive/Developmental Toxicity (inhalation). Although the study is considered adequate, information missing from the robust summary includes: the method for generating the test atmosphere, the timing of exposure days in both sexes in relation to mating and gestation, the timing of final sacrifices with respect to gestation and lactation, and the maternal and paternal endpoints that were analyzed (including the specific organs weighed and examined histologically).

Ecotoxicity. The following information is missing from the acute fish robust summary: the test substance purity, number of fish tested, and concentrations tested.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EASTMAN

May 21, 2002

Ms. Christine Todd Whitman, Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RECEIVED
EPCPT/NCIC
02 MAY 30 PM 12:31

RE: HPV Chemical Challenge Program, AR-201

Dear Ms. Whitman:

This letter is submitted by Eastman Chemical Company ("Eastman") in response to comments received from the Environmental Protection Agency ("EPA") dated April 18, 2002 following EPA's review of the test plan and robust summaries for 2-heptanone (CAS No.: 110-43-0). I would like to thank the EPA for its review and welcome the recognition of its completeness and fulfillment of Eastman's obligation to this chemical in the HPV program.

Below are the EPA's comments to various robust summaries and our responses:

Health Effects

1. "*Acute Toxicity*. Acute oral and inhalation toxicity tests in rats are adequate. The acute oral toxicity test in mice appears inadequate. The submitter needs to address the deficiencies noted in the robust summaries. No additional acute toxicity tests are needed."

The EPA has provided no rationale as to why the acute toxicity study in mice appears inadequate, and Eastman disagrees with this conclusion. The study in mice was conducted at the same time as that of the rat, and the data available and summarized was essentially identical. Therefore, Eastman believes that this study should be considered as adequate. The reliability of this study was deemed as "reliable with restrictions." This was the same reliability as the rat acute oral toxicity study that was deemed adequate.

2. "*Acute oral toxicity*. For both studies, the submitter needs to add, if available, all dose levels, and the number of animals at each dose. The submitter needs to clarify the LD₅₀ for the acute oral toxicity test in mice because the result of the study stated no deaths noted at any dose."

Unfortunately, due to the date at which this study was completed (1964), the requested details are no longer available. Due to these study detail deficiencies, we graded the reliability of both studies as "reliable with restrictions." In regard to the mouse study in which no deaths were

Ms. Christine Todd Whitman, Administrator
Page 2
May 21, 2002

noted at the highest dose (1,600 mg/kg), we have changed the robust summary to read "LD₅₀ = >1,600 mg/kg."

3. "*Acute inhalation toxicity*. The submitter needs to add the method by which the test atmosphere was generated (e.g., as aerosol, vapor, etc.)."

The robust summary for this study has been modified to address the concerns over the method for generating the test atmosphere by noting that the animals were exposed to the test material in the form of a vapor.

4. "*Repeated-dose inhalation toxicity*. The submitter needs to clarify the three exposure groups, to add the method by which the test atmosphere was generated (e.g., as aerosol, vapor, etc.), and to specify the hematological, clinical chemistry, and urinalysis parameters assessed."

The robust summary has been changed to clarify the three exposure groups as the two test exposure levels plus the controls. The summary has been modified to address the concerns over the method for generating the test atmosphere by noting that the animals were exposed to the test material in the form of a vapor. The clinical chemistry parameters analyzed have also been added to the summary. The manuscript did not indicate that any hematological or urinalyses were performed. Blood and urine were collected solely for the purpose of metabolite identification and was so noted in the robust summary.

5. "*Repeated-dose oral toxicity*. The submitter needs to add the frequency of data collection (for clinical signs, body weight, and food and water intake), the specific hematology, clinical chemistry and urinalysis parameters that were examined, and the specific organs that were weighed or examined for gross and microscopic pathology."

The robust summary for this study has been modified to address the EPA's concerns.

6. "*Reproductive/Developmental Toxicity (inhalation)*. Although the study is considered adequate, information missing from the robust summary includes: the method for generating the test atmosphere, the timing of exposure days in both sexes in relation to mating and gestation, the timing of final sacrifices with respect to gestation and lactation, and the maternal and paternal endpoints that were analyzed (including the specific organs weighed and examined histologically)."

The robust summary for this study has been modified to address the concerns over the method for generating the test atmosphere by noting that the animals were exposed to the test material in the form of a vapor. We have also provided more detail relative to the specific organs weighed and examined, and that exposure to females occurred through gestation.

Ms. Christine Todd Whitman, Administrator
Page 3
May 21, 2002

Ecotoxicity

7. "The following information is missing from the acute fish robust summary: the test substance purity, number of fish tested, and concentrations tested."

The robust summary for this study has been modified to address the EPA's concerns. The primary reference for this study was obtained and the detail provided within it has also allowed us to change the study reliability score from "reliable with restrictions" to "reliable without restrictions."

Environmental Fate

8. "*Biodegradation*. The submitter needs to provide information on the source/concentration of the microbial inoculum, initial concentration of the chemical, and time required for 10% biodegradation to take place."

Information in regard to the source/concentration of the microbial inoculum and initial concentration of the chemical has been added to the summary. However, the time required for 10% biodegradation to take place is not a calculated endpoint in this assay.

9. "*Fugacity*. To estimate transport and distribution, the sponsor used the EPIWIN Level III model which provides estimated values as default inputs. EPA recommends using the EQC level III model from the Canadian Environmental Modeling Centre at Trent University, which allows full control of data inputs. This model can be found at the following Web address: <http://www.trentu.ca/academic/aminss/envmodel/>."

While the Agency recommends use of the above-mentioned model, it is important to point out that the model in EPIWIN is a direct adaptation of the EQC level III model developed by Dr. Donald Mackay and co-workers (Mackay et al., 1996a, 1996b; Mackay 1991). It is noted in the EPIWIN suite users guide that this model uses the same equations as Mackay's EQC Level III Fugacity model; however, it was adapted specifically for use in EPIWIN. Based on the conclusion drawn by the Agency that "All appropriate SIDS-level tests/estimations have been performed," we have left the robust summary for this endpoint as is.

Enclosed with this letter is a computer diskette containing the test plan and modified robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical Company is

Sincerely,

James A. Deyo, D.V.M., Ph.D., D.A.B.T.
Technical Associate

Enclosure

AR201-13782A

RECEIVED
DPPT NCIC

02 MAY 30 PM 12:31

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL N-AMYL KETONE
(CAS NO.: 110-43-0)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

May 21, 2002

TABLE OF CONTENTS

OVERVIEW	3
TEST PLAN SUMMARY	3
TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT	4
SIDS DATA SUMMARY	6
EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY	7
REFERENCES	7
ROBUST SUMMARIES	
I. General Information	8
II. Physical-Chemical Data	
A. Melting Point	8
B. Boiling Point	9
C. Vapor Pressure	9
D. Partition Coefficient	10
E. Water Solubility	10
III. Environmental Fate Endpoints	
A. Photodegradation	11
B. Stability in Water	12
C. Biodegradation	13
D. Transport between Environmental Compartments (Fugacity)	15
IV. Ecotoxicity	
A. Acute Toxicity to Fish	16
B. Acute Toxicity to Aquatic Invertebrates	17
C. Toxicity to Aquatic Plants	18
V. Toxicological Data	
A. Acute Toxicity	19
B. Repeated Dose Toxicity	22
C. Genetic Toxicity – Mutation	26
D. Genetic Toxicity - Chromosomal Aberration	27
G. Developmental Toxicity	28
H. Reproductive Toxicity	29

OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl n-amyl ketone (MAK; CAS NO.: 110-43-0) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data in conjunction with EPA-acceptable predictive computer models, and values from reputable textbooks to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that these data are completely adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl n-amyl ketone is a colorless liquid capable of being manufactured to a high degree of purity. It has been in public use since the 1940's. It has been reported to be found in nature as part of clove oil and Ceylon cinnamon oil, and has been approved for use in food by the FDA (21CFR 172.515). Nevertheless, this solvent finds its primary function as a solvent in various coating applications and in the electronics industry. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 50 ppm (233 mg/m³) and by OSHA, which set a PEL level of 100 ppm (465 mg/m³).

TEST PLAN SUMMARY

CAS No. 110-43-0	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	Y	-	N	Y	N
Stability in Water	Y ¹	-	-	Y	N	Y	N
Biodegradation	Y	-	Y	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point -	A value for this endpoint was obtained from a reputable textbook referenced in Hazardous Substances Data Base (HSDB).
Boiling Point -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Vapor Pressure -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Partition Coefficient -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Water Solubility -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Conclusion: All end points haven been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB. No new testing is required.

B. Environmental Fate

Photodegradation -	A value for this endpoint was obtained from a manuscript referenced in HSDB.
Stability in Water -	A technical discussion describing the stability of ketones in water was provided.
Biodegradation -	This endpoint was satisfied through the use multiple studies that were available. All studies were conducted following established guidelines and GLP assurances.
Fugacity -	A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1).

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish -	A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
Acute Toxicity to Aquatic Invertebrates -	This endpoint is filled by data from a study that followed OECD guideline #202 and was conducted under GLP assurances.
Toxicity to Aquatic Plants -	This endpoint is filled by data from a study that followed OECD guideline #201 and was conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from studies that were either conducted using established OECD guidelines and GLP assurances, or were published in reputable textbooks referenced within the HSDB. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity -	This endpoint is filled by data from studies assessing toxicity following both oral and inhalation exposures. Oral studies evaluated both rats and mice while the inhalation study only utilized rats. None of the studies followed established protocols and they were conducted prior to the establishment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions”.
Repeat Dose Toxicity -	This endpoint is filled by data from an oral gavage study of 13 weeks duration and an inhalation study of 10 months duration. Both studies were published in peer-reviewed journals. Neither study followed established protocols and were conducted prior to the establishment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions”.
Genetic Toxicity Mutation -	This endpoint is filled with a single “Ames-assay” study in <i>Salmonella typhimurium</i> strains TA 98, 100, 1535, 1537, and 1538. This study followed an established OECD guideline (#471) and was conducted under GLP assurances.
Aberration -	This endpoint is filled with data from an <i>in vitro</i> study using Chinese hamster ovary (CHO) cells that followed an established OECD guideline (#473) and was conducted under GLP assurances.
Developmental Toxicity -	This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.
Reproductive Toxicity -	This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established OECD guidelines, or utilized methods that were very similar and scientifically appropriate. Some studies were conducted under GLP assurances while some were conducted prior to its enactment. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MAK were all obtained from textbooks referenced within the HSDB. These data indicate that MAK is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual studies, acceptable estimation modeling programs, and a technical discussion. As a result of its relatively high solubility in water and relatively low volatility, fugacity estimations predict that MAK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone will not undergo hydrolysis. The available biodegradation data indicate MAK is likely to be readily degraded in the environment. Nevertheless, due to its primary use in coatings applications, releases into the environment will primarily occur through evaporative emissions. Under such conditions, MAK is expected to rapidly degrade in the atmosphere.

The toxic potential of MAK to aquatic invertebrates and algae were determined through studies conducted under established OECD guidelines and GLP assurances. While that of fish was derived from a published reference within HSDB. The results of these studies demonstrate fish and *Daphnia* are not sensitive species NOEC's >90 mg/l. Whereas, the 72-hour E_6C_{50} and E_7C_{50} values for algal effects indicate that MAK would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in coatings applications. Furthermore, it is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low with an LD_{50} value noted in both rodent species of 1600 mg/kg and an LC_{50} value of between 2000-4000 ppm following a 6-hour exposure. Repeat exposure data following exposure durations of both 13-weeks (oral; rats) and 10 months (inhalation; rats and primates) indicate the material is well tolerated. The NOEL in the 13-week study was 20 mg/kg. No alterations were noted in appearance, behavior, or body weight gains. No statistically significant changes from control were noted in hematology, serum chemistries, or urinary parameters. The only significant finding was that of an increase in urine cellularity in males and changes in the relative organ weights in the liver of both sexes and in the kidneys of males. These organ weight changes were not accompanied by any histological alterations. The NOAEL from the 10-month exposure study was 1,025 ppm for both species. Neither of which developed overt signs of toxicity, alterations in weight gains or clinical chemistries, nor were any gross or microscopic changes exhibited in any organ or tissue examined. Results from mutagenicity and chromosomal aberration studies that utilized OECD guidelines and GLP assurances indicate these compounds do not induce genotoxicity. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MAK is not likely to induce either type of effect at dose levels up to 1000 ppm. Evidence of maternal effects were noted at 80 ppm and higher, and consisted primarily of decreases in activity level.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MAK that either followed established protocols under GLP assurances or were derived from data published in peer-reviewed journals. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (2) and the systematic approach described by Klimisch *et al.* (3). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (4). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.01, Syracuse Research Corporation, Syracuse, New York.
2. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.
3. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.
4. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

I. General Information

CAS Number: 110-43-0
Name: 2-Heptanone
 Methyl n-Amyl Ketone
 Methyl pentyl ketone
 Butyl acetone
 n-Pentyl methyl ketone
 MAK

II. Physical-Chemical Data**A. Melting Point**

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-35.5 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	
	Lide, D.R. (Ed.). CRC Handbook of Chemistry and Physics. 73 rd ed. Boca Raton, FL: CRC Press Inc., 1992-1993.
Other	
	Last revision date: 19990921

B. Boiling Point

Test Substance Test substance: Remarks:	MAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Boiling point value: Pressure: Remarks:	151.5 °C 760 mmHg
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Budavari, S. (Ed.). The Merck Index – Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc 1989, 737
Other	Last revision date: 19990921

C. Vapor Pressure

Test Substance Test substance: Remarks:	MAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Vapor pressure value: Temperature: Remarks:	1.6 – 3.86 mmHg 25 °C
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Sunshine, I. (Ed.). CRC Handbook of Analytical Toxicology. Cleveland: The Chemical Rubber Co., 1969, 633. Riddick, J.A., <i>et al.</i> ; Organic Solvents 4 th ed. NY: Wiley Interscience, (1986)
Other	Last revision date: 19990921

D. Partition Coefficient

Test Substance Test substance: Remarks:	MAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Log K _{OW} : Temperature: Remarks:	1.98 Unknown
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Hansch, C., Leo, A.J.; Medchem Project Issue No. 26 Claremont, CA: Pomona College 1985
Other	Last revision date: 19990921

E. Water Solubility

Test Substance Test substance: Remarks:	MAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Value: Temperature: Description: Remarks:	4300 mg/L 25° C Slight (1-10 g/L) The same solubility value was indicated in two different references within HSDB. Temperature was not given with reference (1), but was listed as 25° C in reference (2).
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	(1) Kirk-Othmer Encyclopedia of Chemical Technology. 3 rd Ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984 V13 p. 896 (1981) (2) Riddick, J.A., <i>et al.</i> ; Organic Solvents 4 th ed. NY: Wiley Interscience, (1986)
Other	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Remarks:</p> <p>Results Rate Constant: Temperature °C: Half-life: Remarks:</p> <p>Conclusions</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity was reported as >99%</p> <p>Flash Photolysis Resonance Fluorescence (FPRP) Hydroxyl radical reaction No Unknown (Study was published in 1987) Hydroxyl radicals were produced by the vacuum ultraviolet photolysis of water at -0.1 Torr. Following production, radicals were monitored as a function of time by the fluorescence excited by a microwave powered OH resonance lamp. Hydroxyl radical concentration was between 10^{10} and 10^{11} molecules /cm^3. This level was deemed high enough to assure pseudo-first-order kinetics with respect to radical decay.</p> <p>8.67×10^{-11} $\text{cm}^3/\text{molecule-second}$ 23 °C 4.5 hours (based on an average atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3)</p> <p>Material is expected to rapidly degrade in the atmosphere.</p> <p>Data obtained from Hazardous Substances Data Bank Number: 1122</p> <p>Wallington, T.J. and Kurylo, M.J. (1987). Flash Photolysis Resonance Fluorescence Investigation of the Gas-Phase Reaction of OH Radicals with a Series of Aliphatic Ketones over the Temperature Range 240-440 K. <i>J. Phys. Chem.</i> 91, 5050-5054.</p> <p>Last revision date: 19990921</p>
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B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.^{1,2}

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation³. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

- (1) Bell and Clunie, *Trans. Faraday Soc.*, **48**, 439, (1952).
- (2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
- (3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.7%
Method	
Method:	Method C.6., "Degradation, Chemical Oxygen Demand", Official Journal of the European Communities, No. L383A/227, 29 December 1992.
Test type:	Chemical Oxygen Demand (COD)
GLP:	Yes
Year:	1997
Remarks:	
Results	
Results:	2.42 grams COD/gram of test substance
Remarks:	The value is a mean of three replicates.
Conclusions	
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	
	Chemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00590. July 24, 1997.
Other	

<p>Test Substance Test substance: Remarks:</p>	<p>MAK Purity was 99.7%</p>
<p>Method Method: Test type: GLP: Year: Remarks:</p>	<p>Method C.5., "Degradation, Biochemical Oxygen Demand", Official Journal of the European Communities, No. L251/212, 19.9.84. Method is similar to OECD: TG-301C: Modified MITI Test. Biochemical Oxygen Demand (BOD) Yes 1997 BOD was determined after 5 and 20 days. The 20-day value was performed in duplicate. The microbial inoculum was prepared from a mixed liquor seed water sample obtained from Kings Landing water treatment facility. The concentration of the inoculum for the study was prepared at 100 mL of the seed water to 2 liters of distilled water. The initial concentration of the test substance was 1 mL of test substance to 1 liter of reagent water.</p>
<p>Results Results: Remarks:</p>	<p>BOD5 was 1.77 grams BOD/gram of test substance BOD20 was 2.00 grams BOD/gram of test substance The BOD 20 value was a mean of two replicates.</p>
<p>Conclusions</p>	<p>The test material is considered to be "Readily Biodegradable" based on a BOD5/COD ratio greater than 0.5 ($1.77/2.42 = 0.73$)</p>
<p>Data Quality Remarks:</p>	<p>This was a well-documented study that followed established guidelines and was conducted under GLP assurances.</p>
<p>References</p>	<p>Biochemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00589. July 24, 1997.</p>
<p>Other</p>	

D. Transport between Environmental Compartments (Fugacity)

<p>Test Substance Test substance: Remarks:</p> <p>Method Test type: Model used: Remarks:</p> <p>Results Model data and results: Estimated distribution and media concentration (levels II/III): Remarks:</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK</p> <p>Estimation Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation</p> <table style="margin-left: 40px;"> <thead> <tr> <th></th> <th style="text-align: right;">Concentration (%)</th> </tr> </thead> <tbody> <tr> <td>Air</td> <td style="text-align: right;">5.97</td> </tr> <tr> <td>Water</td> <td style="text-align: right;">39.4</td> </tr> <tr> <td>Soil</td> <td style="text-align: right;">54.6</td> </tr> <tr> <td>Sediment</td> <td style="text-align: right;">0.0724</td> </tr> </tbody> </table> <p>Physical chemical values utilized in this model were default values obtained from the EPIWIN program.</p> <p>Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.01, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay <i>et al.</i> 1996; <i>Environ. Toxicol. Chem.</i> 15(9), 1618-1626 and <i>Environ. Toxicol. Chem.</i> 15(9), 1627-1637.</p>		Concentration (%)	Air	5.97	Water	39.4	Soil	54.6	Sediment	0.0724
	Concentration (%)										
Air	5.97										
Water	39.4										
Soil	54.6										
Sediment	0.0724										

IV. Ecotoxicity

A. Acute Toxicity to Fish

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring:</p> <p>Exposure period: Remarks:</p> <p>Results Nominal concentration: Measured concentration: Endpoint value: Biological observations:</p> <p>Statistical Methods: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity was 98%</p> <p>Not Specified Flow-through Unknown 1985 Fathead minnow (<i>Pimephales promelas</i>) Dissolved oxygen 7.2 mg/L, hardness 46.4 mg/L, alkalinity 42.1 mg/L, pH 7.72, and temperature 24.2 °C. 96-hr Fish (20/concentration) were 32 days of age and had a mean length of 18.4 mm, a mean weight of 0.095 g, and were loaded at a rate of 0.950 g/L.</p> <p>0, 39.5, 60.8, 93.6, 144, 221 0, 40.9, 58.3, 96.0, 147, 232 LC₅₀ 131 mg/L (confidence limit 126 –137 mg/l); EC₅₀ 128 mg/L Affected fish lost schooling behavior and were hypoactive. Half of the affected fish were located at the surface and the other half on the aquarium bottom. They were under reactive to external stimuli, had increased respiration, were darkly colored and lost equilibrium prior to death. The estimated LC₅₀ and EC₅₀ values were calculated using the corrected average of the analyzed tank concentrations and the Trimmed Spearman-Kärber Method.</p> <p>The LC₅₀ value indicates that the test substance would not be classified according to the European Union’s labeling directive and would correspond to a “low concern level” according to the U.S. EPA’s assessment criteria.</p> <p>Reliable without restrictions This is a well-conducted and documented study.</p> <p>Geiger D.L., Poirier S.H., Brooke L.T., Call D.J., eds. Acute Toxicities of Organic Chemicals to Fathead Minnows (<i>Pimephales Promelas</i>). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior, 1986, 179.</p>
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B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-202 and EEC/Annex V C.2
Test type:	Acute immobilization
GLP:	Yes
Year:	1998
Species/strain:	<i>Daphnia magna</i>
Analytical monitoring:	Aliquots of exposure solution were submitted for concentration determinations at 0, 24, and 48 hours. Temperature, dissolved oxygen, and pH were also determined at these same time periods.
Test details:	48-hour exposure period; semi-static
Remarks:	No protocol deviations were noted. Study was conducted in duplicate and results were averaged.
Results	
Nominal concentration:	6.25, 12.5, 25, 50, and 100 mg/L
Measured concentration:	6.46, 13.01, 24.52, 47.86, 90.10 mg/L
Endpoint value:	EC ₅₀ > 90.10 mg/L
Biological observations:	The behavior of all <i>Daphnia</i> was comparable to controls.
Statistical methods:	NA (no effects were seen at highest exposure concentration)
Remarks:	Water temp ranged from 19 to 21 °C, pH ranged from 8.2 to 8.7, and dissolved oxygen ranged from 8.6 to 9.3 mg/L.
Conclusions	
	The 48-hour EC ₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	
	An Acute Aquatic Effects Test with the Daphnid; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-431-902185-A; June 15, 1998
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	1998
Species/strain:	<i>Selenastrum capricornutum</i>
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were
	assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after
Remarks:	72 hours.
Results	
Nominal concentration:	12.5, 25, 50, 100, and 200 mg/L
Measured concentration:	6.2, 11.9, 22.1, 42.7, 86.3 mg/L (geometric mean)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 75.5 mg/L; the E_rC_{50} (0-72 hr) was 98.2
NOEC, LOEC, or NOEL,	mg/L
LOEL:	The 72 hr NOEC was estimated to be 42.7 mg/L
Biological observations:	No deformed cells were noted
Was control response	
satisfactory:	Yes (culture concentrations increased by a factor of 136-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software
	program AL_ACUTE (Ver. 2.2).
Remarks:	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean
	temperature was 24°C and pH ranged from 7.3 to 7.7. Cultures were oscillated
	at 100 rpm. The significant loss (up to 82% over the course of the study) in test
	material was attributed to volatilization. No protocol deviations were noted.
Conclusions	
	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test
	substance would be classified as “harmful to aquatic organisms” according to
	the European Union’s labeling directive and would be classified in a “moderate
	concern level” according to the U.S. EPA’s assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP
	assurances.
References	
	A Growth Inhibition Test with the Alga, <i>Selenastrum capricornutum</i> ;
	Environmental Sciences Section, Health and Environment Laboratories,
	Eastman Kodak Company, Rochester, NY; Study No. EN-512-902185-B;
	October 13, 1998
Other	

V. Toxicological Data

A. Acute Toxicity

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No (Pre-GLP) 1964 Rat/unknown Unknown 10 animals in total were used Material was administered undiluted Oral Rats were administered doses of MAK ranging from 200-3200 mg/kg. Animals were monitored for clinical observations and weight change for 14-days.</p> <p>LD₅₀ = 1600 mg/kg Report only indicated deaths occurring at 1600 mg/kg on day 1 after 5 hours Clinical signs of toxicity included slight to very weak, prostration, vasodilatation, labored breathing, and ataxia. Except for labored breathing, which was noted at doses of 800 mg/kg and above, clinical signs at specific dose levels were not indicated. Autopsy was negative.</p> <p>Material is considered slightly toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No (Pre-GLP) 1964 Mouse/unknown Unknown 6 animals in total Material was administered undiluted Oral A total of 6 mice were administered doses of MAK ranging from 400-1600 mg/kg. They were monitored for clinical observations and weight change for 14-days.</p> <p>LD₅₀ = >1600 mg/kg No deaths were noted at any dose Animal appearance was noted as normal to quite weak.</p> <p>Material is considered slightly toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MAK Purity unknown</p> <p>Acute lethality; Other LC₅₀ estimate No (Pre-GLP) 1964 Rat/unknown Unknown 3 animals/exposure level None Inhalation, whole-body Rats were exposed to MAK as a vapor in whole-body chambers for 4 hours at 5,126 ppm, and 6 hours at 4,169, 832, 1,437, and 2,016 ppm. It was noted that the inhalation chambers were maintained at 24 °C. Animals were monitored for clinical observations and weight change for 14-days.</p> <p>LC₅₀ 2000-4000 ppm (6-hr) At 5,126 ppm all 3 animals died shortly after their 4-hour exposure. At 4,169 ppm, 1/3 died after 4 hours and the other 2 died shortly after their 6-hour exposure ended. No deaths were noted at 2,016 ppm or lower. Clinical signs in all studies included piloerection, vasodilatation, hypernea, lassitude, ataxia, and prostration. All animals gained weight, although higher-dosed animals gained less.</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.</p>
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B. Repeated Dose Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity was 97%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (Pre-GLP)
Year:	Unknown (studies were published in 1978, 79, and 81)
Species/strain:	Rat/Sprague-Dawley and Primate/ <i>Macaca fascicularis</i>
Route of exposure:	Inhalation
Duration of test:	10-months
Exposure levels:	100 and 1000 ppm
Sex:	Males
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	Groups of 50 rats and 8 monkeys were randomly assigned to each of the three exposure groups (0, 100 and 1000 ppm). Animals were exposed to MAK vapors using whole-body chambers. At necropsy, lungs, liver, heart, spleen, kidney, adrenals, pancreas, testes, brain, and sciatic nerve were harvested for microscopic examinations. Clinical chemistries (SGOT, LDH, ALP, total bilirubin, total protein, albumin, cholesterol, uric acid, BUN, glucose, inorganic phosphate, calcium, CPK, RBC cholinesterase, TG's, lactic acid, and blood glutathione) were conducted in primates after 1, 3, and 6 months of exposure and at study termination. Blood and urine was collected from both species at termination for metabolite identification. Liver microsomal enzyme induction was evaluated in rodents by assessing barbiturate-induced sleeping times. Rats also had tissue distribution analyses conducted following both ip (10 mg/kg) and inhalation exposure to [¹⁴ C]MAK. Tissues, urine and feces were collected 2, 4, 8, 12, 24, 48, and 72 hours after administration of the radiolabeled MAK. Distribution and excretion was assessed in both naive and pre-exposed animals. At monthly intervals both species were evaluated for neurological function by assessing maximum motor-nerve conduction velocity (MCV) of the sciatic and ulnar nerves and amplitude of evoked muscle action potential (MAP). Primates also underwent electroencephalograms (EEG) and had visually evoked action potential recorded. Cardiopulmonary studies, including mechanical properties (compliance and resistance), lung volumes, flow-volume dynamics, distribution of ventilation, diffusion, and gas exchange were conducted on monkeys at the start of the study and after 6 months of exposures. Electrocardiographic (ECG) examinations were also conducted at the time of pulmonary function testing.

<p>Results NOAEL (NOEL): Actual exposure levels: Toxic responses by dose:</p> <p>Statistical methods: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>1025 ppm (both species) 131 +/-30 ppm and 1025 +/- 136 ppm</p> <p>Both species tolerated the exposures without developing overt signs of toxicity or alterations in weight gains or clinical chemistries. There was no effect on barbiturate sleeping times. Neither species exhibited any gross or microscopic changes in any organ or tissue examined. Six months of exposure did not alter the overall cardiopulmonary function, EEG and ECG readings, or induce any evidence of neurotoxicity. MAK was detected in the serum and urine from both species at both exposure levels. While methyl n-amyl alcohol was detected only in the urine and serum from high dose primates. Although some significant post-MAK peaks were observed, they were not identified by GC/MS. They were present in 4/14 low dose animals and 10/12 receiving 1025 ppm exposures. Regardless of the route of administration, i.e., ip or inhalation, or whether animals were naive or had been pre-exposed, the liver contained the most radioactivity. The next highest levels were detected in the kidney, pancreas, and lungs. The brain contained some of the lowest amounts. Excretion of MAK into the urine and feces peaked at 12 hours and remained relatively constant through 48-hours. Fecal excretion through 72-hours only accounted for 2% of the administered dose.</p> <p>Multivariate analysis of covariance (MANOVA), Kruskal-Wallis test, and Student's t test.</p> <p>Animals appeared to tolerate exposure to MAK with minimal effects.</p> <p>Reliable with restriction This appears to be a very robust and well-conducted study; however, basic data are not available for review.</p> <ol style="list-style-type: none"> Lynch, D.W., Lewis, T.R., Moorman, W.J., Plotnick, H.B., Schuler, R.L., Smallwood, A.W., and Kommineni, C. Inhalation Toxicity of Methyl n-Amyl Ketone (2-Heptanone) in Rats and Monkeys. <i>Toxicology and Applied Pharmacology</i> 58, 341–352, 1981. Johnson, B.L., Setzer, J.V., Lewis, T.R., and Hornung, R.W. An Electrodiagnostic Study of the Neurotoxicity of Methyl N-Amyl Ketone. <i>American Industrial Hygiene Association</i> 39, 866–872, 1978. Johnson, B.L., Anger, W.K., Setzer, J.V., Lynch, D.W., and Lewis, T.R. Neurobehavioral Effects of Methyl N-Butyl Ketone and Methyl N-Amyl Ketone in Rats and Monkeys: A Summary of NIOSH Investigations. <i>Journal of Environmental Pathology and Toxicology</i> 2, 113–133, 1979. <p>This study was conducted by The National Institute for Occupational Safety and Health, Division of Biomedical and Behavioral Science in Cincinnati, OH.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Duration of test: Dose levels: Sex: Frequency of treatment: Control group and treatment: Post-exposure observation period: Remarks:</p> <p>Results NOAEL (NOEL): Toxic responses by dose:</p> <p>Statistical methods: Remarks:</p>	<p>MAK Purity was 98% at minimum</p> <p>Other Repeated exposure No (Pre-GLP) Unknown (studies were published in 1972) Rat/CFE Oral gavage 13-weeks 0, 20, 100, and 500 mg/kg Male and Female; 15/dose level A single daily gavage Yes; Corn oil None An additional 5 animals/sex receiving 100 and 500 mg/kg were terminated after 2 and 6 weeks of dosing. All animals were assessed for body weight, food and water intakes on a weekly basis, clinical chemistries (SGPT, SGOT, LDH, BUN, glucose, total protein, and albumin), hematology (Hb content, PCV, total counts of erythrocytes, reticulocytes, and RBC's with Heinz bodies, and total WBC and WBC differential), and urinalysis (appearance, microscopic constituents, and content of glucose, ketones, bile salts, and blood). A urine concentration study was also performed. At termination, animals underwent a gross examination with the following organs weighed: brain, pituitary, thyroid, heart, liver, spleen, kidneys, adrenals, gonads, stomach, sm. Intestine, and cecum. These aforementioned organs along with the salivary gland, trachea, aorta, thymus, lymph nodes, urinary bladder, colon, rectum, pancreas, uterus, and skeletal muscle were preserved for microscopic analysis.</p> <p>20 mg/kg (NOEL) No alterations were noted in appearance, behavior (frequency of appearance and behavior data collection was not noted), or body weight gains. No statistically significant changes from control were noted in hematology, serum chemistries, or urinary parameters. However, an increase in urine cellularity was noted in males at the mid- and high-dose levels after 13 weeks and in the high-dose group after 6 weeks. Changes in relative organ weights were noted in the liver of both sexes at the high dose at Week-13 and in males only after 6 weeks (high dose) and at 2 weeks (high and mid). Significant alterations were also seen after 13 weeks in relative kidney weight in mid and high dose males. Other organs exhibiting weight changes were not significant when corrected for body weight. Despite the reported organ weight changes, no histological alterations were noted in any tissue. No serum biochemical changes were noted that might also be reflective of renal or hepatic toxicity.</p> <p>Data present in graphs and figures were noted to have been compared using Student's t test.</p>
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<p>Conclusions</p>	<p>The effect in the liver was likely an adaptive response from continual exposure to large doses of test material. The increased urine cellularity was only noted in males and as not accompanied by any alterations in the histological appearance of the kidney or urinary bladder.</p>
<p>Data Quality Reliability: Remarks:</p>	<p>Reliable with restriction Acceptable, well-documented publication that meets scientific principles. Study was conducted by the British Industrial Biological Research association.</p>
<p>References</p>	<p>Gaunt, I.F., Carpanini, F.M.B., Wright, M.G., Grasso, P., Gangolli, S.D. (1972) Short-term Toxicity of Methyl Amyl Ketone in Rats. <i>Food Cosmet. Toxicology</i> 10, 625–636.</p>
<p>Other</p>	

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99%
Method	
Method:	OECD: TG-471
Test type:	<i>In vitro</i> mutagenicity
GLP:	Yes
Year:	1994
Species/strain:	<i>Salmonella typhimurium</i> /TA98, 100, 1535, 1537, 1538
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, 9-aminoacridine) were run concurrently. Negative control was the test vehicle dimethylsulfoxide. Test material as evaluated in triplicate at each dose level.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate
Precipitation concentration:	No precipitate was observed at 5000 ug/plate
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Means and standard deviation were determined for each of the dosing regimens; Further statistical analyses were not needed due to the absence of an increase in the number of revertants colonies at any dose beyond the positive control.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD-like guideline study conducted under GLP assurances.
References	Ames mutagenicity study of methyl n-amyl ketone. Microbiological Associates Inc., Rockville, MD; Sponsor Project Number STP-195; Laboratory Study Number G94BJ71.501; December 15, 1994.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-473
Test type:	<i>In vitro</i> mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1998
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 1200 ug/ml (this level exceeds the 10 mM max. recommended level)
Metabolic Activation:	Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed on analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 19226-0-437OECD; June 18, 1998
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity was >99%
Method	
Method:	OECD: TG-421
GLP:	Yes
Year:	1996
Species/strain:	Rats/Sprague-Dawley
Sex:	Male and Female (12/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 80, 400, and 1000 ppm
Actual exposure levels:	0, 78.6, 405.8, and 1022.6 ppm
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air and housed similarly
Duration of test:	Males were exposed for 50 days while females were exposed for 34 to 47 days (through Day 19 of gestation).
Remarks:	The following organs were histologically examined: ovaries, vagina, uterus, Fallopian tubes, and testes, epididymis, and male accessory sex organs. The testes and epididymis were also weighed. Animals were exposed to MAK as a vapor only.
Results	
Maternal toxicity NOEL:	80 ppm NOEL
Repro./Develop. toxicity NOEL:	1000 ppm NOEL
Parental toxic responses:	There were no mortalities. A dose responsive reduction in activity was noted during the exposure period in the high- and mid-dose animals only. Animals appeared to become acclimated as this reduction went from moderate, to minor, to minimal by study conclusion. Males in the high dose group exhibited a decrease in food consumption during the days 0-7 only. There was no effect on body weight in either sex, although mid-dose females exhibited less of a weight change during days 0-7 of gestation. There were no effects noted in any of the litter parameters due to MAK exposure (reproductive performance, gestation length, number of live/dead pups, implant total, prenatal loss, % survival, ratio of male/female pups, or pup weight). There were no effects noted in any of the selected organs that were weighed, or examined grossly or histologically.
Fetal toxic responses dose:	There were no treatment-induced changes in pup clinical signs or abnormalities, or weight gains at any measured time-period.
Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p \leq 0.05$) followed by Mann-Whitney U-test ($p \leq 0.05$). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p \leq 0.05$). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model ($p \leq 0.05$).
Remarks:	

Conclusions	Test material did not induce reproductive or developmental toxicity under the conditions of this assay.
Data Quality Reliability: Remarks:	Reliable without restriction This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 95-0202; October 7, 1996.
Other	

F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.

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HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
METHYL ISOAMYL KETONE
(CAS NO.: 110-12-3)

PREPARED BY:
EASTMAN CHEMICAL COMPANY

July 1, 2002

TABLE OF CONTENTS

OVERVIEW	3
TEST PLAN SUMMARY	3
JUSTIFICATION FOR USE OF SURROGATE DATA	4
TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT	4
SIDS DATA SUMMARY	6
EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY	8
REFERENCES	8
ROBUST SUMMARIES	
I. General Information	9
II. Physical-Chemical Data	
A. Melting Point	9
B. Boiling Point	10
C. Vapor Pressure	11
D. Partition Coefficient	11
E. Water Solubility	12
III. Environmental Fate Endpoints	
A. Photodegradation	13
B. Stability in Water	14
C. Biodegradation	15
D. Transport between Environmental Compartments (Fugacity)	16
IV. Ecotoxicity	
A. Acute Toxicity to Fish	17
B. Acute Toxicity to Aquatic Invertebrates	18
C. Toxicity to Aquatic Plants	19
V. Toxicological Data	
A. Acute Toxicity	21
B. Repeated Dose Toxicity	25
C. Genetic Toxicity – Mutation	29
D. Genetic Toxicity - Chromosomal Aberration	30
G. Developmental Toxicity	31
H. Reproductive Toxicity	32

OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for methyl isoamyl ketone (MIAK; CAS NO.: 110-12-3) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on MIAK or its structural isomer methyl amyl ketone (MAK) in conjunction with EPA-acceptable predictive computer models, and values from reputable textbooks to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

Methyl isoamyl ketone is a colorless liquid capable of being manufactured to a high degree of purity. It has been detected as a volatile component of roasted filbert nuts, fried bacon, and cooked beef and pork. The primary use for this ketone is as a solvent in various coating applications that involve a high-solids component such as various lacquers, vinyl primers, polyurethane coatings, epoxy maintenance enamels, general metal coatings, and thermosets. It may also find use as an industrial process solvent in the manufacture of other chemicals. Industrial work place exposure levels for this chemical have been established by the ACGIH, which set a TLV-TWA of 50 ppm (234 mg/m³) and by OSHA which set a PEL of 100 ppm (475 mg/m³).

TEST PLAN SUMMARY

CAS No. 110-12-3	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y ¹	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	-	-	Y ²	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	-	Y	-	N	Y	N
Genetic Toxicity – Mutation	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.
2. Surrogate data are also used in conjunction with a value obtained from the ECOSAR estimation program.

JUSTIFICATION FOR USE OF SURROGATE DATA

The SIDS endpoint evaluating the potential for MIAK to adversely affect the growth of algae was completed through the use of an estimation-modeling program (ECOSAR), as well as from data derived from a study conducted on its structural isomer, methyl amyl ketone (MAK). The use of modeling and surrogate data are believed to be suitable due to the fact that these two chemicals are structural isomers of each other and that their physical chemical properties are very similar. The potential accuracy of the value obtained on MIAK from the modeling program is strengthened by how well this model estimated the acute algal toxicity for MAK relative to the actual value derived through experimentation.

Accordingly, we believe the value derived from the ECOSAR estimation program can be utilized to complete this single endpoint for MIAK for which actual test data does not exist.

	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility	Henry's Law Constant
MIAK	144 °C	5.77 mmHg	1.88	5.4 g/L	1.45×10^{-4} atm-m ³ /mole
MAK	151.5 °C	1.6 – 3.86 mmHg	1.98	4.3 g/L	1.56×10^{-4} atm-m ³ /mole

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

- Melting point - A value for this endpoint was obtained from a reputable textbook referenced in Hazardous Substances Data Base (HSDB).
- Boiling Point - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
- Vapor Pressure - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
- Partition Coefficient - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.
- Water Solubility - A value for this endpoint was obtained from product literature referenced in HSDB.

Conclusion: All end points have been satisfied by the utilization of data obtained from various textbooks or corporate fact sheets referenced within the HSDB. No new testing is required.

B. Environmental Fate

- Photodegradation - A value for this endpoint was obtained using a computer estimation model.
- Stability in Water - A technical discussion describing the stability of ketones in water was provided.
- Biodegradation - This endpoint was satisfied through data derived from a study that followed an established OECD test guideline (301-D) and one was conducted under GLP assurances.
- Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model (1).

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Acute Toxicity to
Aquatic Invertebrates -

This endpoint is filled by data from a well-conducted study completed prior to the enactment of GLP.

Toxicity to Aquatic
Plants -

This endpoint is filled by values derived by a computer model estimation program (ECOSAR) and test data from MAK, a structural surrogate (2). The study conducted on MAK followed an established OECD guideline (#201) and was conducted under GLP assurances.

Conclusion:

All endpoints have been satisfied with data from either well-conducted studies, or through the use of an acceptable estimation program in conjunction with actual study data from a surrogate chemical. While the data from the fish and Daphnia studies were derived prior to the enactment of GLP, these data, as well as the values estimated for the algal toxicity, in total are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity -

This endpoint is filled by data from studies assessing toxicity following both oral and inhalation exposures. Oral studies evaluated both rats and mice while the inhalation study only utilized rats. None of the studies followed established protocols and they were not conducted under GLP assurances (some were conducted prior to its enactment). Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions”.

Repeat Dose Toxicity -

This endpoint is filled by data from an inhalation and oral gavage study of 13 weeks duration. Neither study followed established protocols and both were conducted prior to the enactment of GLP assurances. Nonetheless, sufficient information was available to ascertain the quality of these studies and to deem them “reliable with restrictions” to fulfill the requirements of this endpoint.

Genetic Toxicity
Mutation -

This endpoint is filled with a single study in *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2uvrA). This study followed an established guideline (EEC Annex V Guideline number B.14 and B.13) and was conducted under GLP assurances.

Aberration -

This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed an established OECD guideline (#473) and was conducted under GLP assurances.

Developmental
Toxicity -

This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Reproductive
Toxicity -

This endpoint is filled by data from an oral exposure study in rats that followed an established OECD guideline (#421) and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential.

Conclusion: All endpoints have been satisfied with data from studies whose methods followed established guidelines, or utilized methods that were very similar and or scientifically appropriate. Some studies were conducted under GLP assurances while some were conducted prior to its enactment. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for MIAK were all obtained from references within the HSDB. These data indicate that MIAK is a liquid at room temperature with a relatively low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is quite soluble in water despite being classified as “slight”.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of actual studies, acceptable estimation modeling programs, and a technical discussion. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that MIAK will distribute primarily to soil and water. A technical discussion has been provided that indicates this ketone will not undergo hydrolysis. The available biodegradation data indicate MIAK is likely to be readily degraded in the environment. Nevertheless, due to its primary use in coatings applications, releases into the environment will primarily occur through evaporative emissions. Under such conditions, MAK is expected to degrade in the atmosphere at a moderate rate.

The potential toxicity of MIAK to fish and Daphnia were determined through well-conducted studies. The results of these studies demonstrate fish and Daphnia are not sensitive species with both having a NOEC >100 µg/L. The potential impact of MIAK on algal growth was estimated using the ECOSAR modeling program. The EC₅₀ value estimated from this program was 72.4 mg/L. This value is quite close to actual data from the structural isomer methyl amyl ketone (MAK) which had 72 hr EC₅₀ values for reduction of growth and biomass of 75.5 mg/L and 98.2 mg/L, respectively. The ECOSAR program estimated the EC₅₀ value for MAK be 59 mg/L. All these values are quite similar. Based on these data MIAK would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive but would be classified in a “moderate concern level” according to the U.S. EPA’s assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary uses in coatings applications leading to evaporative emissions. Furthermore, MIAK is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The LD₅₀ value noted in rats and mice was >3200 mg/kg, while data from a second rat study indicate the LD₅₀ to be 5,657 mg/kg. An inhalation study in rats yielded an LC₅₀ of 3,813 ppm (17,806 mg/m³) following a 6-hour exposure. Data from two repeat exposure studies in rats following inhalation and oral exposure durations of 13 weeks indicate the material is well-tolerated and not anticipated to induce neurotoxicity. The NOEL in the inhalation study was 200 ppm (934 mg/m³). In this study animals were exposed to 0, 200, 1000, 2000 ppm MIAK. Evidence of irritation was observed in the mid and high dose animals and was characterized by a porphyrin-like nasal and ocular discharge. These two exposure levels induced dose-dependent (slight to moderate) clinical signs of lethargy and decreased auditory responses in the first few weeks that later diminished (none to slight) for the remainder of the study. Absolute and relative liver weights were statistically increased in both sexes, and absolute and relative kidney weights were increased in males. No biologically significant effects were noted in the hematology or clinical chemistry profiles. Histopathological changes noted in the liver of both sexes occurred in a dose-dependent manner and consisted of minimal to minor hypertrophy. Males also exhibited minimal to moderate eosinophilic cytoplasmic changes and minimal to minor necrosis. In the kidneys, some animals of both sexes showed evidence of minor to moderate tubular regeneration. Males had a possible increase in the severity of hyaline droplet degeneration in their proximal convoluted tubules. In the other 13-week study, rats (males only) received a single daily dose by oral gavage of MIAK at rate of 2,000 mg/kg. While numerous parameters were assessed, this study was completed to evaluate the neurotoxicity potential of this ketone against that of methyl n-butyl ketone (a known neurotoxicant). Body weight and feed consumption were assessed twice weekly and a full complement of tissues was harvested for histopathology with special emphasis placed on the handling and collection of neural tissues. Several other tissues were also weighed along with a complete hematology and clinical chemistry assessment. No NOEL was established in this study. No evidence of neurotoxicity was seen based on an absence of alterations in behavior and lack of

histological changes in nervous tissue. Feed intake was, in general, slightly depressed throughout the study and body weights were significantly reduced at essentially all time points. There was no effect on the erythron. Effects noted in the clinical chemistry profile included slight, but statistically significant, increases in SGOT, SGPT and urea nitrogen. Urea nitrogen levels were still within levels seen in historical controls. Absolute and relative increases in liver and adrenal weights were seen. Histological evidence of gastric irritation was noted. Liver changes consisted of a diffuse hepatocyte hypertrophy, and microfoci of hyperplasia in some rats. The significance of this is questioned by the absence of this effect following inhalation exposures despite similar peak blood levels. A few animals also exhibited necrosis of individual hepatocytes, a few others had vacuolation of individual hepatocytes. Some animals also had bile duct epithelial hyperplasia. Renal changes included an increased incidence of regenerating tubular epithelium and dilatation with casts, and hyaline droplet formation in the PCT epithelium. Results from mutagenicity and chromosomal aberration studies indicate this compound is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening inhalation study in rats that followed OECD test guideline #421. Results from this study indicate MIAK is not likely to induce either type of effect at dose levels up to 5 mg/L. The NOAEL for maternal effects was also 5 mg/L.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on MIAK that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA and supporting surrogate data. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to both workers and the general population.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- (3) **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- (4) **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.1, Syracuse Research Corporation, Syracuse, New York.
2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.
3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.
4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.
5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

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I. General Information

CAS Number: 110-12-3
Name: 2-Hexanone, 5-methyl-
 5-Methylhexane-2-one
 5-Methyl-2-hexanone
 2-Methyl-5-hexanone
 3-Methylbutyl methyl ketone
 Isoamyl methyl ketone
 Isopentyl methyl ketone
 Methyl iso-amyl ketone
 Methyl isoamyl ketone
 Methyl isopentyl ketone
 MIAK

II. Physical-Chemical Data**A. Melting Point**

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-73.9 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	
	Lewis, R.J., Sr. (Ed.). Hawley's Condensed Chemical Dictionary. 12 th ed. New York, NY: Van Nostrand Rheinhold Co., 1993.
Other	
	Last revision date: 19990921

B. Boiling Point

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	144 °C
Pressure:	Unknown
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	
	Lide, D.R. (Ed.). CRC Handbook of Chemistry and Physics. 76 th ed. Boca Raton, FL: CRC Press Inc., 1995-1996.
Other	
	Last revision date: 19990921

C. Vapor Pressure

Test Substance Test substance: Remarks:	MIAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Vapor pressure value: Temperature: Remarks:	5.77 mmHg 25 °C
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	Alarie, Y. <i>et al.</i> , Toxicol. Appl. Pharmacol. 134: 92-99, 1995.
Other	Last revision date: 19990921

D. Partition Coefficient

Test Substance Test substance: Remarks:	MIAK Purity unknown
Method Method: GLP: Year: Remarks:	Not specified Unknown Unknown
Results Log K _{OW} : Temperature: Remarks:	1.88 Unknown
Data Quality Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Hansch, C., Leo, A.J., and Hoekman, D. Exploring QSAR – Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society, 1995.
Other	Last revision date: 19990921

E. Water Solubility

Test Substance	
Test substance:	MIAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	5,400 mg/L
Temperature:	20° C
Description:	Slight (1-10 g/L)
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 2885
References	
	Union Carbide Corporation; Ketones. Booklet No. F-41971 pp.21, 1968.
Other	
	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: Remarks:</p> <p>Results Temperature: Hydroxyl radicals reaction OH Rate constant: Half-life Ozone reaction: Remarks:</p> <p>Conclusions</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK</p> <p>Estimation Atmospheric oxidation</p> <p>25 °C 8.1648 x 10⁻¹² cm³/molecule-sec 1.31 Days (12-hr day; 1.5x10⁶ OH/cm³) No ozone reaction estimation</p> <p>Material is oxidized by atmospheric hydroxyl radicals at a moderate rate.</p> <p>AopWin v1.88; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210.</p>
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B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.^{1,2}

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation³. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

- (1) Bell and Clunie, *Trans. Faraday Soc.*, **48**, 439, (1952).
- (2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
- (3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MIAK
Remarks:	Purity was 99.3%
Method	
Method:	OECD TG-301D
Test type:	Ready Biodegradability by the Closed Bottle Method
GLP:	Yes
Year:	2001
Contact time:	28-Days
Inoculum:	Activated sludge collected from Wareham, MA wastewater treatment plant
Remarks:	Benzoic acid at 10 mg/ml was used as a reference control. MIAK was assessed at a nominal concentration of 2.5 mg/L. Test vessels of 300ml BOD bottles were prepared per treatment (reference, test substance and inoculum blank), two each for Day 0 and three per sampling interval (Days 7, 14, 21, and 28). After the bottles were filled they were closed and wrapped in tin foil.
Results	
Degradation % at test end:	67% (>60% by Day 14)
Classification:	Readily biodegradable
Remarks:	Benzoic acid reference was degraded 72%. The temperature of the environment ranged from 20-22 °C. Dissolved oxygen concentrations in the control blank ranged from 8.7 mg/L on Day 0 to 7.1 mg/L on Day 28. The protocol stated that oxygen depletion in the controls should not exceed a loss of 1.5 mg/L before Day 28; however, the loss was 1.6 mg/L. This protocol deviation was viewed as minor and does not affect the overall conclusion as it occurred well after Day 14 when the material had already met the ready biodegradable pass level of >60%.
Conclusions	Material is considered readily biodegradable under the conditions of this test.
Data Quality	
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Methyl Isoamyl Ketone (MIAK) - Ready Biodegradability by the Closed Bottle Method; Springborn Laboratories, Inc Wareham, MA Study No. 1852.6173.
Other	

D. Transport between Environmental Compartments (Fugacity)

<p>Test Substance Test substance: Remarks:</p> <p>Method Test type: Model used: Remarks:</p> <p>Results Model data and results: Estimated distribution and media concentration (levels II/III):</p> <p>Remarks:</p> <p>Data Quality Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK</p> <p>Estimation Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 80%;"></th> <th style="text-align: right;">Concentration (%)</th> </tr> </thead> <tbody> <tr> <td>Air</td> <td style="text-align: right;">5.68</td> </tr> <tr> <td>Water</td> <td style="text-align: right;">41.6</td> </tr> <tr> <td>Soil</td> <td style="text-align: right;">52.7</td> </tr> <tr> <td>Sediment</td> <td style="text-align: right;">0.112</td> </tr> </tbody> </table> <p>Physical chemical values utilized in this model were default values obtained from the EPIWIN program.</p> <p>Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay <i>et al.</i> 1996; <i>Environ. Toxicol. Chem.</i> 15(9), 1618-1626 and <i>Environ. Toxicol. Chem.</i> 15(9), 1627-1637.</p>		Concentration (%)	Air	5.68	Water	41.6	Soil	52.7	Sediment	0.112
	Concentration (%)										
Air	5.68										
Water	41.6										
Soil	52.7										
Sediment	0.112										

IV. Ecotoxicity

A. Acute Toxicity to Fish

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Analytical monitoring: Exposure period: Remarks:</p> <p>Results Nominal concentration: Endpoint value: Biological observations: Statistical methods: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK Unknown</p> <p>Other Static No 1978 Fathead minnow (<i>Pimephales promelas</i>) Yes; Exposure solutions, temperature, pH, dissolved oxygen 96-Hour Water was filter-treated lake water with residual chlorine chemically removed. 10 fish per concentration level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mortality were conducted at 0, 6, 24, 48, 72, and 96 hours.</p> <p>100 ul/L LC₅₀ >100 ul/L; NOEC > 100 ul/L No behavioral abnormalities were noted. NA; no effects were noted at this concentration Exposure temperature was 19 °C, pH ranged from 7.4 to 7.9, and dissolved oxygen ranged from 4.8 to 8.7 mg/L.</p> <p>The LC₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.</p> <p>Reliable with restrictions Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.</p> <p>An Acute Aquatic Effects Test with the Fathead Minnow (<i>Pimephales promelas</i>); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 78-0260.</p>
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B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MIAK
Remarks:	Purity was not available
Method	
Method:	Other
Test type:	Acute immobilization, Static
GLP:	No
Year:	1978
Species/strain:	Daphnid/ <i>Daphnia magna</i>
Analytical monitoring:	Yes; Exposure solutions, temperature, pH, dissolved oxygen
Exposure period:	96-Hour; static exposure
Remarks:	Water was filter-treated lake water with residual chlorine chemically removed. 10 Daphnids per dose level were used. Exposure solutions were submitted for temperature, dissolved oxygen, and pH concentration determinations at 0, 24, 48, 72, and 96 hrs. Observations for stress and mobility were conducted at 0, 6, 24, 48, 72, and 96 hours.
Results	
Nominal concentration:	100 ul/L
Endpoint value:	EC ₅₀ (96-hr) > 100 ul/L; NOEC > 100 ul/L
Biological observations:	The <i>Daphnia</i> exhibited behavior comparable to controls at all test concentrations.
Statistical methods:	NA; no effects were noted at this concentration
Remarks:	Exposure temperature remained at 19 °C through out the test, pH was 7.4–7.9, and dissolved oxygen was 4.8-8.7 mg/L.
Conclusions	
	The LC ₅₀ value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Study lacked some basic information as well as data indicating test material purity and analytical conformation of test concentrations.
References	
	An Acute Aquatic Effects Test with the Daphnid (<i>Daphnia magna</i>); Environmental Sciences Section, Health and Environment Laboratories, at Eastman Kodak Company, Rochester, NY; HAEL No. 78-0260, June 13, 2000
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MIAK
Remarks:	
Method	
Method:	Estimation
Test type:	96-hour Green Algae EC ₅₀
Remarks:	ECOSAR class: neutral organics
Results	
EC ₅₀ :	72.414 mg/L
Remarks:	The 72 hr EC ₅₀ for reduction of growth and biomass for a structural isomer, methyl amyl ketone (MAK), was 75.5 mg/L and 98.2 mg/L, respectively. The EC ₅₀ value for this isomer using ECOSAR modeling was 59 mg/L.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	The estimation values derived from the ECOSAR modeling program for both MIAK and MAK, and the actual data from MAK are all quite close.
References	
	ECOSAR; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.1, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

<p>Test Substance Test substance: Remarks:</p>	<p>MAK Purity was 99.8%</p>
<p>Method Method: Test type: GLP: Year: Species/strain: Endpoint basis: Exposure period: Analytical procedures: Remarks:</p>	<p>OECD: TG-201 Growth inhibition of algae Yes 1998 <i>Selenastrum capricornutum</i> Cell concentrations (biomass) and growth rate 72-hours Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.</p>
<p>Results Nominal concentration: Measured concentration: Endpoint value: NOEC: Biological observations: Was control response satisfactory: Statistical methods: Remarks:</p>	<p>12.5, 25, 50, 100, and 200 mg/L 6.2, 11.9, 22.1, 42.7, 86.3 mg/L (geometric mean) The estimated E_bC_{50} (0-72 hr) was 75.5 mg/L; the E_rC_{50} (0-72 hr) was 98.2 mg/L The 72 hr NOEC was estimated to be 42.7 mg/L No deformed cells were noted Yes (culture concentrations increased by a factor of 136-fold) EC_{50} and NOEC values were determined through use of SAS statistical software program AL_ACUTE (Ver. 2.2). A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.3 to 7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.</p>
<p>Conclusions</p>	<p>The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would be classified as “harmful to aquatic organisms” according to the European Union’s labeling directive and would be classified in a “moderate concern level” according to the U.S. EPA’s assessment criteria.</p>
<p>Data Quality Reliability: Remarks:</p>	<p>Reliable without restrictions This was a well-documented OECD guideline study conducted under GLP assurances.</p>
<p>References</p>	<p>A Growth Inhibition Test with the Alga, <i>Selenastrum capricornutum</i>; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-902185-B; October 13, 1998.</p>
<p>Other</p>	<p>The estimated EC_{50} value using ECOSAR modeling was 59 mg/L. This value is very close to the actual EC_{50} values.</p>

V. Toxicological Data

A. Acute Toxicity

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No 1982 Rat/unknown Male 4 Undiluted Oral Animals were administered doses of MIAK at a rate of 1000, 2000, 4000, or 8000 mg/kg. Animals were monitored for 14 days, after which they were terminated, dissected, and examined grossly. The LD₅₀ estimate was determined by the geometric mean of the top two does levels.</p> <p>LD₅₀ = 5,657 mg/kg 1,000 and 2,000 mg/kg: No abnormal effects were noted. 4,000 mg/kg: Clinical signs seen included weakness, ataxia, tremors, and prostration. All recovered and survived to the end of the study. 8,000 mg/kg: All died within one day of dosing with clinical signs consisting of weakness, ataxia, tremors, and prostration.</p> <p>Material is considered practically non-toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HAEL No. 78-260, 1982.</p>
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<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose: Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK Purity unknown</p> <p>Acute lethality; Other LD₅₀ estimate No (Pre-GLP) 1978 Rat/unknown Male 4 Undiluted Oral Initially, four animals each were administered doses of 200, 400, 800, 1,600, or 3,200 mg/kg. An additional two groups of four animals, were administered 1,600 or 3,200 mg/kg several weeks thereafter as it was noted that some of the deaths in the first study may have been a result of aspiration of the test substance. Animals were monitored for 14 days, after which they were terminated, dissected, and examined grossly.</p> <p>LD₅₀ >3,200 mg/kg. 800 mg/kg or less: No deaths. Animals appeared slightly to quite weak on the day of dosing, but normal thereafter. 1,600 mg/kg: One of four died. Animals were weak and transiently ataxic on the day of dosing but appeared normal thereafter. On the repeat study (see remarks above), all animals appeared weak and had roughened coats, but all survived. 3,200 mg/kg: Animals were described as quite weak, and two of four died. On the repeat study, all animals appeared weak and had roughened coats, but all survived.</p> <p>At most, material is considered slightly toxic</p> <p>Reliable with restrictions Basic data are given.</p> <p>Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.</p>
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Test Substance Test substance: Remarks:	MIAK Purity unknown
Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/dose: Vehicle: Route of exposure: Remarks:	Acute lethality; Other LD ₅₀ estimate No (Pre-GLP) 1978 Mouse/unknown Male 4 Undiluted Oral Initially, four animals each were administered doses of 200, 400, 800, 1,600, or 3,200 mg/kg. Animals were followed for 14 days, after which they were terminated, dissected, and examined grossly.
Results Value: Deaths at each dose: Remarks:	LD ₅₀ >3,200 mg/kg. There were no deaths at any dose. 800 mg/kg and less: Animals appeared slightly weak to normal on the day of dosing and normal thereafter. 1,600 mg/kg: Animals were noted to be excitable with vasodilatation, slight tremors, and weakness on the day of dosing only. 3,200 mg/kg: Animals showed signs of restlessness, vasodilatation, weakness, and prostration on the day of dosing and weakness on Day 3
Conclusions	At most, material is considered slightly toxic
Data Quality Reliability: Remarks:	Reliable with restrictions Basic data are given.
References	Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.
Other	

<p>Test Substance Test substance: Remarks:</p> <p>Method Method: Test type: GLP: Year: Species/strain: Sex: Animals/sex/dose: Vehicle: Route of exposure: Remarks:</p> <p>Results Value: Deaths at each dose:</p> <p>Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>MIAK Purity unknown</p> <p>Acute lethality; Other LC₅₀ estimate No (Pre-GLP) 1978 Rat/unknown Male 4 animals/exposure level None Inhalation, whole-body Rats (181-233 grams) were exposed to MIAK using whole-body chambers for 6 hours at nominal concentrations of 800, 1,600, 3,200, or 6,400 ppm. Actual measured levels were 802, 1,603, 3,207, and 5,878 ppm. After exposure, animals were monitored for clinical observations and weight change for 14-days.</p> <p>LC₅₀ (6-hr) = 3,813 ppm (17,806 mg/m³) 800 ppm group: Animals appeared alert during exposure, but appeared a bit sluggish immediately afterwards. Animals gained weight normally. 1,600 ppm: Clinical signs were restricted to sluggish responses after six hours of exposure. All animals gained weight normally throughout the study. 3,200 ppm: Animals displayed eye irritation, unresponsiveness, and impaired gait within two hours. By 4-5 hours of exposure, all rats were narcotized with depressed respiration. One of four animals from this group died just prior to the end of the six-hour exposure period. The remaining three recovered fully following exposure cessation. Weight gain in these animals between Days 0 and 3 was reduced to a total of 3-13 grams, but subsequent weight gain was in the normal range. 6,400 ppm: All animals experienced eye irritation and narcosis, and all animals died within 2.5 hours after initiation of exposure.</p> <p>Reliable with restrictions Basic data are given</p> <p>Basic Toxicity of Methyl Isoamyl Ketone, Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. HS&HFL No. 78-260, December 18, 1978.</p>
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B. Repeated Dose Toxicity

Test Substance	
Test substance:	MIAK
Remarks:	Purity was 99.1%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No
Year:	1981
Species/strain:	Rat/CRL:COBS [®] CD [®] (SD)
Route of exposure:	Inhalation
Duration of test:	69 exposures over 96-Days
Exposure levels:	0, 200, 1,000, 2,000 ppm
Sex:	Both
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	One hundred twenty rats (60/sex) weighing 217-259 g (M) and 139-199 (F) were randomly assigned to each of the exposure groups (15/sex/dose). Animals were exposed using whole-body chambers. Body weights were recorded once per week and observed for clinical signs before and after exposure each day. At necropsy, complete hematology and clinical chemistry parameters were assessed and a full assortment of tissues was harvested for histological assessment (nasal passages, trachea, lungs, thymus, salivary glands, heart, tongue, esophagus, stomach, sm. & lg. intestine, liver, kidneys, urinary bladder, adrenals, pancreas, thyroids, parathyroids, spleen, mesenteric lymph nodes, bone marrow, brain, pituitary, testes, epididymis, accessory sex organs in males, fallopian tubes, uterus, vagina and ovaries). The liver, kidney, brain, adrenals, testes, ovaries, heart, and spleen were weighed prior to fixation.
Results	
NOEL:	200 ppm (934 mg/m ³)
Actual exposure levels:	212, 1,025, 2,079 ppm

<p>Toxic responses by dose:</p>	<p>2,000 ppm: The body weights of high dose females only were consistently decreased, although never at a statistically significant level. Evidence of irritation was manifested as a porphyrin-like nasal and ocular discharge. During the first 17 days of exposure, moderate lethargy and decreased auditory responses were noted. These effects were described as slight for the remainder of the study. From Day 35 on, gel-like casts were noted beneath the cages. Absolute and relative liver weights were statistically increased in both sexes. Absolute and relative kidney weights were increased in males while relative weights only were elevated in females. This was likely due to the decreased body weights seen in females though. Males only showed a statistically significant increase in platelet count. This effect was deemed to not be of any biological significance though. No other effects were noted in hematology or clinical chemistry. Histopathological changes noted in the liver consisted of minimal to minor hypertrophy (both sexes), minimal to moderate eosinophilic cytoplasmic changes and minor necrosis (males only). In the kidneys, some animals of both sexes showed evidence of minor to moderate tubular regeneration. Males had a possible increase in the severity of hyaline droplet degeneration in the PCT.</p> <p>1,000 ppm: One male died of unknown causes. Slightly more than half the animals showed evidence of irritation based on a porphyrin-like nasal and ocular discharge. During the first 17 days of exposure, lethargy and decreased auditory responses were noted and described as slight. From Day 35 on, gel-like casts were noted beneath the cages. Absolute and relative liver weights were statistically increased in both sexes. Absolute and relative kidney weights were increased in males only. The same effect on platelets noted at 2000 ppm was observed at this exposure level too. Histological changes in the liver and kidneys of males mirrored what were seen in the 2000-ppm animals but with a decreased rate of incidence and severity (except no PCT degeneration was noted).</p> <p>200 ppm: No statistically significant effects were noted in any measured parameter.</p>
<p>Statistical methods: Remarks:</p>	<p>One-way ANOVA followed by Bartlett's Test and Duncan's multiple range test.</p>
<p>Conclusions</p>	<p>Material was well tolerated with primary target organ effects only occurring at exposure levels that also induced nasal and ocular irritation. The effect in the liver was likely an adaptive response from continual exposure to large doses of test material.</p>
<p>Data Quality Reliability: Remarks:</p>	<p>Reliable with restrictions While this study was not conducted under GLP assurances it nevertheless is a well-documented study that has been published in a peer-reviewed journal.</p>
<p>References</p>	<p>Katz, G.V., Renner Jr, E.R., and Terhaar, C.J. Subchronic Inhalation Toxicity of Methyl Isoamyl Ketone in Rats. <i>Fund. Appl. Toxicol.</i> 6, 498-505 (1986).</p>
<p>Other</p>	

<p>Test Substance Test substance: Remarks:</p>	<p>MIAK Purity was 99.2%</p>
<p>Method Method: Test type: GLP: Year: Species/strain: Route of exposure: Duration of test: Dose levels: Sex: Frequency of treatment: Control group treatment: Post-exposure observation period: Remarks:</p>	<p>Other Repeated exposure No (Pre-GLP) 1979 Rat/Charles River CD Oral intubation 90-days 0 and 2000 mg/kg 8 Males A single daily gavage 5 days/week Yes; Water None This study involved only a single maximum tolerated dose, and was designed to determine the neurotoxicity and subchronic effects of a series of different ketones against that of n-heptane. Body weight and feed consumption was assessed twice weekly. A full complement of tissues was harvested for histopathology with special emphasis placed on the handling and collection of neural tissues assessment (trachea, lung, thymus, heart, tongue, esophagus, stomach, sm. & lg. intestine, liver, kidney, urinary bladder, adrenal, pancreas, thyroid, parathyroid, testes, epididymis, spleen, mesenteric lymph nodes, bone marrow, brain, spinal cord, sciatic-tibial nerves, dorsal root ganglia, and the quadriceps, calf, and hind limb interosseous muscle). Several tissues were also weighed. Complete hematology and clinical chemistries were also conducted.</p>
<p>Results NOAEL (NOEL): Toxic responses by dose:</p>	<p>Not established (Only a single high dose was used) No evidence of neurotoxicity was seen based on an absence of alterations in appearance or behavior, and histological changes in nervous tissue. Feed intake was, in general, slightly depressed throughout the study and was significantly lower during the first week. Body weights were significantly reduced at essentially all time points. There was no effect on the erythron. Effects noted in the clinical chemistry profile included slight, but statistically significant, increases in SGOT, SGPT and urea nitrogen. Urea nitrogen levels were still within levels seen in historical controls. Absolute and relative increases in liver and adrenal weights were seen. Relative increases were seen in other tissues; however, their significance is negated by a significantly decreased bodyweight. Histological evidence of gastric irritation was manifested by hyperkeratosis, and hyperkeratosis with pseudoepitheliomatous hyperplasia and submucosal thickening and edema. Liver changes consisted of a diffuse hepatocyte hypertrophy, and microfoci of hyperplasia in some rats. The latter effect was characterized by an increase in cytoplasmic and, generally, nuclear size. Three types of nodules were present. The first type was identified on the basis of diffuse increase in cytoplasmic basophilia, the second type contained heavily vacuolated cells, and the third had very large vesicular nuclei with prominent nucleoli. These types of nodules are generally regarded as pre-neoplastic changes. A few animals also exhibited necrosis of individual hepatocytes, a few others had vacuolation of individual hepatocytes. Some animals also had bile duct epithelial hyperplasia. Renal changes included an increased incidence of regenerating tubular epithelium and dilatation with casts, and hyaline droplet formation in the PCT epithelium.</p>

<p>Statistical methods: Remarks:</p>	<p>One-way ANOVA followed by Bartlett's Test and Duncan's multiple range test. Other than the finding of a diffuse hepatocyte hypertrophy, the observation of microfoci of hyperplasia was not reproduced following inhalation exposure. Inhalation is the most relevant route by which humans are exposed. Peak blood levels at the highest exposure level in the inhalation study were similar to that following oral intubation.</p>
<p>Conclusions</p>	
<p>Data Quality</p>	
<p>Reliability: Remarks:</p>	<p>Reliable with restrictions Although this study was completed prior to GLP guidelines, it is still a well-documented study that meets scientific principles.</p>
<p>References</p>	<p>90-Day Repeated Oral Administration of Five Ketones and n-Heptane to Rats. Eastman Kodak Company. Rochester, NY. January 21, 1980.</p>
<p>Other</p>	

C. Genetic Toxicity – Mutation

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >98%
Method	
Method:	EEC Annex V Guideline number B.14 and B.13 (OECD: TG-471-like)
Test type:	<i>In vitro</i> mutagenicity
GLP:	Yes
Year:	1999
Species/strain:	<i>Salmonella typhimurium</i> /TA98, 100, 1535, 1537, and <i>Escherichia coli</i> /WP2uvrA(pKM101)
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, and 4-nitroquinoline-N-oxide) were run concurrently. DMSO was used as a vehicle and vehicle control. Test material was evaluated in triplicate at each dose level.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Mean number of revertants and standard deviations were calculated. Various criteria were established to constitute a valid assay and a positive response was indicated by a 2-3 fold increase in mean revertant number dependent on the bacterial tester strain.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented EEC Annex guideline study conducted under GLP assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 20215-0-409R; March 8, 1999
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >98%
Method	
Method:	OECD: TG-473
Test type:	<i>In vitro</i> mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1999
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 1200 ug/ml (this level meets the 10 mM max. recommended level)
Metabolic Activation:	Yes; Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide.
	Negative control was the test vehicle dimethylsulfoxide. Endoreduplication was
	analyzed by evaluating at least 100 metaphases.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or
	endoreduplication were observed in analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml induced a 14% reduction in confluence
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and
	Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP
	assurances.
References	Covance Laboratories Inc., Vienna, VA; Study number: 20215-0-437OECD;
	April 20, 1999
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MIAK
Remarks:	Purity was >99%
Method	
Method:	OECD: TG-421
GLP:	Yes
Year:	2001
Species/strain:	Rats/Sprague-Dawley
Sex:	Male and Female (12/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 1, 2.5, and 5 mg/L
Actual exposure levels:	0.965 ± 0.0724, 2.32 ± 0.137, and 4.72 ± 0.283 mg/L
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air and housed similarly
Duration of test:	Males were exposed for 51 days while females were exposed for 35 to 41 days (through Day 19 of gestation)
Remarks:	The study design also included an analysis of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal toxicity NOAEL:	5 mg/L
Repro./Develop. toxicity NOAEL:	5 mg/L
Parental toxic responses:	All adult animals survived to study termination and there were no test substance-related changes in mean terminal body weight. For the 5 mg/L male group, the mean body weight gain and mean food utilization were higher ($p \leq 0.05$) on Day 35 when compared with the control group. Otherwise, there were no other differences in mean body weight, body weight gain, food consumption, or food utilization among the groups throughout the study. Except for minimal reductions in activity level observed in the 5 mg/L group during each exposure, no other test substance-related clinical abnormalities were noted. Mean sperm motility and mean epididymal spermatozoan and testicular spermatid counts were comparable among the groups. No test substance-related gross pathology was observed for adult animals from any group. No exposure-related changes were observed during histological examination of the reproductive organs of any of the test substance-exposed animals.
Fetal toxic responses dose:	Although trend analyses indicated reductions in the total number of pups per litter and in the number of live pups per litter. The Kruskal-Wallis H-test indicated that the total number of pups per litter and the number of live pups per litter were comparable among the groups. Abnormalities were observed for occasional pups from the 5.0, 2.5, and 0.0 mg/L groups. These abnormalities included the pups appearing small, having no milk in their stomachs, and having bruises under the skin. Additionally, pups were occasionally missing (presumably cannibalized) or found dead. Since the clinical abnormalities were observed for comparable numbers of pups from the control and treated groups and since the number of dead pups was not statistically different among the groups, these findings were not considered to be test substance-related.

<p>Statistical Methods:</p> <p>Remarks:</p> <p>Conclusions</p> <p>Data Quality Reliability: Remarks:</p> <p>References</p> <p>Other</p>	<p>Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p \leq 0.05$) followed by Mann-Whitney U-test ($p \leq 0.05$). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p \leq 0.05$). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model ($p \leq 0.05$).</p> <p>Test material did not induce reproductive or developmental toxicity under the conditions of this assay at exposure levels up to 5 mg/L.</p> <p>Reliable without restriction This was a well-documented OECD guideline study conducted under GLP assurances.</p> <p>Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 2000-0208; Laboratory Project ID 2000208I1, March 12, 2001.</p>
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F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.

July 29, 2002

Christine Todd Whitman, Administrator
U. S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N. W.
Washington, DC 20460

Re: Comments on the Eastman Chemical Company's HPV Test Plan for
Methyl Isopropyl Ketone

Dear Administrator Whitman:

The following comments on the Eastman Chemical Company's test plan for the individual chemical methyl isopropyl ketone are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

We commend the Eastman Chemical Company's test plan and robust summaries for methyl isopropyl ketone, a compound used as an intermediate in the manufacture of other chemicals and as an industrial solvent. The robust summaries include data that satisfy each of the HPV SIDS endpoints, and Eastman Chemical Company appropriately does not call for additional testing. ACGIH and NIOSH have already evaluated the health effects of this chemical and have set acceptable exposure limits of 200 ppm. Respiratory irritation, headaches, and nausea have been observed in humans at low levels of methyl isopropyl ketone. Further testing on animals would not expand the public health understanding of this chemical or change the way it is handled.

Eastman Chemical Company's proposal is therefore fully consistent with the requirement stated in the October 1999 agreement and reiterated in the December 2000 *Federal Register* notice that "participants shall conduct a thoughtful, qualitative analysis...Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, that certain endpoints need not be tested." And that "before generating new information, participants should consider whether any additional information obtained would be useful or relevant."

Thank you for your attention to these comments. I can be reached at 757-622-7382, ext.1304, or via e-mail at jessicas@peta.org.



PETA

PEOPLE FOR THE ETHICAL
TREATMENT OF ANIMALS

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FAX 757-622-0457

AN INTERNATIONAL
ORGANIZATION DEDICATED
TO PROTECTING
THE RIGHTS OF ALL ANIMALS

Sincerely,

A handwritten signature in black ink that reads "J. Sandler". The signature is written in a cursive style with a large, looped initial "J" and a stylized "Sandler".

Jessica Sandler, M.H.S.
Federal Agency Liaison

August 13, 2002

James A. Deyo, D.V.M., Ph.D., D.A.B.T.
Technical Associate
Eastman Chemical Company
P. O. Box 431
Kingsport, Tennessee 37662

Dear Dr. Deyo:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for methyl isopropyl ketone (MIPK), posted on the ChemRTK HPV Challenge Program Web site on April 2, 2002. I commend Eastman Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Eastman Chemical Company advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,
Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer

M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:
Methyl Isopropyl Ketone (MIPK)**

SUMMARY OF EPA COMMENTS

The Sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for Methyl isopropyl Ketone (CAS No. 563-80-4; MIPK) dated February 15, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 2, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical and Environmental Fate Data. The submitter needs to provide measured values for a number of these endpoints instead of relying almost exclusively on estimated values.
2. Health Effects. All appropriate SIDS-level tests have been performed.
3. Ecological Effects. EPA considers the algal toxicity study adequate for the purposes of the HPV Challenge Program. The submitted ecotoxicity data for fish and daphnia are inadequate. Testing is needed for these two endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

**EPA COMMENTS ON THE METHYL ISOPROPYL KETONE (MIPK) CHALLENGE
SUBMISSION**

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The submitter provided estimated values for all endpoints. EPA disagrees with the submitter's approach to these endpoints. Critical endpoints such as water solubility and vapor pressure should be measured values. The use of estimated values increases the level of uncertainty in subsequent modeling such as the fugacity calculation.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The test plan for these endpoints is adequate for the purposes of the HPV Challenge Program. The submitter supplied a technical discussion that MIPK would not be subject to hydrolysis because it does not contain hydrolyzable functional groups. Therefore, a stability in water test is not needed. EPA agrees with the submitter that MIPK would not be subject to hydrolysis.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate test data are available for all health endpoints for the purposes of the HPV Challenge Program. However, the submitter needs to supply a robust summary for the reproductive toxicity endpoint. HPV Challenge Program guidance states that when a study addresses multiple endpoints, robust summaries are needed for each endpoint.

Ecotoxicity (fish, invertebrates, and algae). The acute algal toxicity study, with mean measured concentrations, is adequate. However, the fish and daphnia acute toxicity studies are inadequate. These studies were performed under static conditions with nominal concentrations, and as reported in the algal study (up to 78.2 % loss), there was most likely a significant loss of test material through volatilization. Because of this substance's volatility, EPA suggests that all testing be done with measured concentrations in a closed system with no head space. Testing should follow the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, June 2000-available on the OECD website at <http://www.oecd.org/ehs/test/monos.htm>).

Specific Comments on the Robust Summaries

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

Fugacity. The input values used in the fugacity calculation need to be added to the robust summary.

Health Effects.

Repeated-Dose Toxicity. Although it is stated as "a full assortment of tissues," the submitter needs to define the specific tissues that were examined histopathologically.

Genetic Toxicity (in vitro). In both summaries, the submitter needs to list concentrations that were tested. The submitter also needs to provide the number of replicate plates per concentration for the reverse mutation in bacteria study and the number of metaphases per concentration that were examined for the chromosomal aberration assay.

Ecotoxicity.

Algae. Water hardness is the only missing data element and needs to be submitted if available.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.