

AR201-13219A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

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

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RECEIVED  
07/17/01  
2001 OCT 16 AM 9:09

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/m<sup>3</sup>) and by OSHA, which set a PEL level of 100 ppm (465 mg/m<sup>3</sup>).

## 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
<b>PHYSICAL-CHEMICAL DATA</b>							
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
<b>ENVIRONMENTAL FATE ENDPOINTS</b>							
Photodegradation	Y	-	Y	-	N	Y	N
Stability in Water	Y <sup>1</sup>	-	-	Y	N	Y	N
Biodegradation	Y	-	Y	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
<b>ECOTOXICITY</b>							
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
<b>TOXICOLOGICAL DATA</b>							
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 *Salmonella typhimurium* 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 *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 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  $E_3C_{50}$  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.