AR201-13288A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

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

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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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/m^3) and by OSHA which set a PEL of 100 ppm (475 mg/m^3).

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 ^{o}C	5.77 mmHg	1.88	5.4 g/L	1.45 x 10^{-4} atm-m^3/mole
MAK	151.5 ^{o}C	1.6 – 3.86 mmHg	1.98	4.3 g/L	1.56 x 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 haven 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 WP2*uvr*A). 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 under go 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 ul/L. The potential impact of MIAK on algal growth was estimated using the ECOSAR modeling program. The EC_{50} 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 EC_{50} values for reduction of growth and bio mass of 75.5 mg/L and 98.2 mg/L, respectively. The ECOSAR program estimated the EC_{50} 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 LD_{50} value noted in rats and mice was >3200 mg/kg, while data from a second rat study indicate the LD_{50} to be 5,657 mg/kg. An inhalation study in rats yielded an LC_{50} of 3,813 ppm (17, 806 mg/m^3) 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 induce neurotoxicity. The NOEL in the inhalation study was 200 ppm (934 mg/m^3). 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 with in 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

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2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

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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.