

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### SPONSORED CHEMICAL Methyl Isoamyl Ketone (CASRN 110-12-3)

### SUPPORTING CHEMICAL Methyl Amyl Ketone (CASRN 110-43-0)

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOWNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

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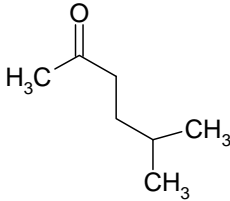
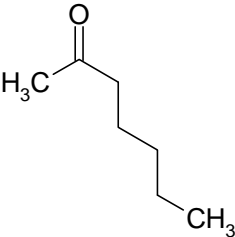
<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>	<p><b><u>Sponsored Chemical</u></b>          110-12-3  <b><u>Supporting Chemical</u></b>          110-43-0</p>
<p><b>Chemical Abstract Index Name</b></p>	<p><b><u>Sponsored Chemical</u></b>          2-Hexanone, 5-methyl-  <b><u>Supporting Chemical</u></b>          2-Heptanone, 6-methyl-</p>
<p><b>Structural Formula</b></p>	<p><b><u>Sponsored Chemical</u></b></p>  <p><b><u>Supporting Chemical</u></b></p> 
<p style="text-align: center;"><b>Summary</b></p> <p>CASRN 110-12-3 is a liquid with high water solubility and high vapor pressure at room temperature. It is expected to have high mobility in soil. Volatilization is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered moderate. CASRN 110-12-3 is expected to have low</p>	

persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of CASRN 110-12-3 is low in rats and mice treated via the oral route and moderate in rats via inhalation. Male rats gavaged at 2000 mg/kg/day (only dose tested) during a 90-day oral, repeated-dose toxicity study showed significant decreases in body weight and significant increases in clinical chemistry parameters (SGOT, SGPT, urea nitrogen) and (absolute/relative) adrenal and liver weights. Histological examination revealed treatment-related increases in gastric irritation, nephropathy (with hyaline droplet accumulation) and hepatic necrosis at this dose; a NOAEL for systemic toxicity was not established. A 13-week repeated-dose toxicity study in rats administered CASRN 110-12-3 via whole body inhalation showed signs of hepatic and renal toxicity at 4.84 mg/L; the NOAEC for systemic toxicity is 0.99 mg/L. A combined reproductive/developmental toxicity screening test showed no evidence of maternal, reproductive or developmental effects following inhalation exposure in rats; the NOAEC for maternal/reproductive/developmental toxicity is 4.72 mg/L (highest concentration tested). CASRN 110-12-3 did not induce gene mutations in bacterial cells or chromosomal aberrations in mammalian cells when tested *in vitro*.

The evaluation of available aquatic toxicity data (all on the supporting chemical, CASRN 110-43-0) indicates that for CASRN 110-12-3, the 96-hr LC<sub>50</sub> for fish is 131 mg/L, the 48-hr EC<sub>50</sub> for daphnia is greater than 90.10 mg/L, and the algal 72-hr EC<sub>50s</sub> are 75.5 mg/L (biomass) and 98.2 mg/L (growth rate).

No data gaps were identified under the HPV Challenge Program.

The sponsor, Eastman Chemical Company, submitted a Test Plan and Robust Summaries to EPA for methyl isoamyl ketone (CASRN 110-12-3; CA Index name: 2-hexanone, 5-methyl-) dated October 25, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 7, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/2hex5mth/c13288tc.htm>). EPA comments on the original submission were posted to the website on July 3, 2002. The sponsor submitted updated/revised documents on July 1, 2002, which were posted to the ChemRTK website (posting date not indicated).

### **Justification for Supporting Chemicals**

The sponsor included data for methyl amyl ketone (CASRN 110-43-0) as a supporting chemical and EPA accepts its use for the aquatic toxicity evaluation. The data for CASRN 110-43-0 can be found at <http://www.epa.gov/chemrtk/pubs/summaries/methamkt/c13219tc.htm>.

#### **1. Chemical Identity**

##### **1.1 Identification and Purity**

The revised 2002 Test Plan and Robust Summary indicates “unknown purity” for test materials used to assess the acute toxicity of CASRN 110-12-3 to fish, aquatic invertebrates and rodents; purities reported for other endpoints ranged between 98 – 99%.

##### **1.2 Physical-Chemical Properties**

The physical-chemical properties of CASRN 110-12-3 are summarized in Table 1. This chemical is a liquid with high water solubility and high vapor pressure at room temperature.

<b>Property</b>	<b>Value</b>
CASRN	110-12-3
Molecular Weight	114.19
Physical State	Liquid
Melting Point	-73.9°C (measured)
Boiling Point	144°C (measured)
Vapor Pressure	5.77 mm Hg at 25°C (measured)
Water Solubility	5,400 mg/L at 20°C (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable
Henry's Law Constant	1.6×10 <sup>-4</sup> atm·m <sup>3</sup> /mole (estimated) <sup>2</sup>
Log K <sub>ow</sub>	1.88 (measured)

<sup>1</sup> Eastman Chemical Company. July 1, 2002. Revised Robust Summary for Methyl Isoamyl Ketone. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/2hex5mth/c13288tc.htm> as of April 1, 2010.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitd1.htm> as of April 1, 2010.

## 2. General Information on Exposure

### 2.1 Production Volume and Exposure

According to the 2006 IUR submissions, CASRN 110-12-3 had an aggregated production and/or import volume in the United States between 10 and 50 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of this chemical include other basic organic chemical manufacturing as intermediates, solvents (which become part of product formulation or mixture), and “other”. Non-confidential commercial and consumer uses of this chemical include paints and coatings.

### 2.2 Environmental Exposure and Fate

The environmental fate properties are provided in Table 2. CASRN 110-12-3 is expected to have high mobility in soil. It was readily biodegradable using the closed bottle test (OECD 301D), achieving greater than 60% degradation within a 2-week incubation period. The rate of hydrolysis is expected to be negligible under environmental pH and temperature. The rate of volatilization is considered moderate based on its Henry’s Law constant. CASRN 110-12-3 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

<b>Property</b>	<b>Value</b>
Photodegradation Half-life	1.3 days (estimated) <sup>2</sup>
Hydrolysis Half-life	Not applicable
Biodegradation	>60% biodegradation in 14 days (readily biodegradable); 66% biodegradation in 28 days (readily biodegradable)
Bioaccumulation Factor	BAF = 7.1 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	1.4 (estimated) <sup>2</sup>
Fugacity (Level III Model) <sup>2</sup>	
Air (%)	5.4
Water (%)	35.9
Soil (%)	58.6
Sediment (%)	0.1
Persistence <sup>3</sup>	P1 (low)
Bioaccumulation <sup>3</sup>	B1 (low)

<sup>1</sup> Eastman Chemical Company. July 1, 2002. Revised Robust Summary for Methyl Isoamyl Ketone. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/2hex5mth/c13288tc.htm> as of April 1, 2010.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of April 1, 2010.

<sup>3</sup> Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

### 3. Human Health Hazard

The human health data are summarized in Table 3.

#### *Acute Oral Toxicity*

(1) Male rats (4/dose; strain not specified) were administered a single dose of CASRN 110-12-3 (purity unknown) via oral gavage at 1000, 2000, 4000 or 8000 mg/kg. All rats treated at 8000 mg/kg died; however, no other mortalities occurred during the 14-day observation period.

**LD<sub>50</sub> = 5657 mg/kg**

(2) Male rats (4/dose; strain not specified) were administered a single dose of CASRN 110-12-3 (purity unknown) via oral gavage at 200, 400, 800, 1600 or 3200 mg/kg. An additional two groups of four rats each were gavaged at 1600 or 3200 mg/kg. One of eight animals treated at 1600 mg/kg and two of eight animals treated at 3200 mg/kg died. No other mortalities occurred during the 14-day observation period.

**LD<sub>50</sub> > 3200 mg/kg**

(3) Male mice (4/dose; strain not specified) received a single dose of CASRN 110-12-3 (purity unknown) via oral gavage at 200, 400, 800, 1600 or 3200 mg/kg. No mortalities occurred during the 14-day observation period.

**LD<sub>50</sub> > 3200 mg/kg**

#### *Acute Inhalation Toxicity*

Male rats (4/group; strain not specified) were administered CASRN 110-12-3 (purity unknown) via whole body vapor inhalation at 802, 1603, 3207 and 5878 ppm (~3.75, 7.49, 15.0 or 27.5 mg/L) for 6 hrs. One animal exposed at 15 mg/L and all animals exposed at 27.5 mg/L died.

**LC<sub>50</sub> ~ 17.8 mg/L**

#### *Repeated-Dose Toxicity*

##### *Inhalation*

In a 13-week repeated-dose toxicity study, CRL:COBS CD (SD) rats (15/sex/group) were administered CASRN 110-12-3 (>99% purity) via whole-body inhalation at 0, 200, 1000 or 2000 ppm for 6 hours/day, 5 days/week. Actual (measured) exposure levels were 0, 212, 1025 or 2079 ppm (~ 0, 0.99, 4.84 or 9.81 mg/L). Eye and nose irritation were apparent following exposure at 4.84 mg/L; one animal from this group died following treatment. Increased (absolute/relative) liver (both sexes) and kidney weights (males) were observed at or above 4.84 mg/L. Males showed evidence of hepatic necrosis, thrombocytosis and tubular regeneration at this concentration. Decreased body weight and increased relative kidney weight (females), hyaline droplet degeneration in the proximal convoluted tubule (males) and hepatic necrosis and hypertrophy (both sexes) were observed at the highest concentration (9.81 mg/L). No significant treatment effects were noted at the lowest concentration (0.99 mg/L).

**LOAEC ~ 4.84 mg/L** (based on hepatic and renal effects)

## NOAEC ~ 0.99 mg/L

### *Oral*

In a 90-day repeated-dose toxicity study, Charles River CD rats (eight males) were administered CASRN 110-12-3 (>99% purity) via oral gavage at a concentration of 0 or 2000 mg/kg/day (only dose tested), for 5 days/week. There were no mortalities; however, significant decreases in body weight and food consumption were observed in treated versus control animals. Significant increases in (absolute/relative) liver and adrenal weights and clinical chemistry parameters (SGOT, SGPT and urea nitrogen) were also noted throughout this study. Histological examination revealed treatment-related increases in gastric irritation (epithelial hyperplasia, hyperkeratosis and edema), hepatic effects (hypertrophy, necrosis, hyperplasia) and renal toxicity (hyaline droplet formation, dilatation with casts and tubular regeneration).

**LOAEL/NOAEL = Not established** (only one dose tested)

### *Reproductive/Developmental Toxicity*

In a reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/group) were administered CASRN 110-12-3 (>99% purity) via whole body inhalation at 0, 0.96, 2.32 or 4.72 mg/L for 6 hours/day, 7 days/week, for 51 days (males) or 35 – 41 days (females; through gestation day 19). No treatment-related effects on reproductive organs or male gametogenesis (sperm count, motility) or developmental parameters (litter size, pup mortality) and anomalies (bruising, growth inhibition) were noted.

**NOAEC (maternal toxicity) = 4.72 mg/L** (highest concentration tested)

**NOAEC (reproductive/developmental toxicity) = 4.72 mg/L** (highest concentration tested)

### *Genetic Toxicity – Gene Mutation*

#### *In vitro*

*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA (pKM101) were exposed to CASRN 110-12-3 (>98% purity) at concentrations up to 5000 µg/plate in the presence or absence of metabolic activation. Responses to positive and negative controls were not indicated. Test material was evaluated in triplicate at each dose level. No evidence of cytotoxicity, precipitation or mutagenicity was observed under these conditions.

**CASRN 110-12-3 was not mutagenic in this assay.**

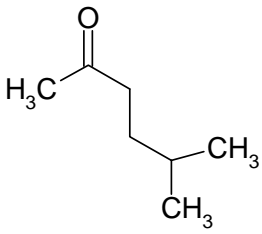
### *Genetic Toxicity -- Chromosomal Aberrations*

#### *In vitro*

Chinese hamster ovary cells were exposed to CASRN 110-12-3 (>98% purity) at concentrations up to 1200 µg/mL in the presence or absence of metabolic activation. Responses to positive and negative controls were not indicated. Endoreduplication was analyzed by evaluating at least 100 metaphases. Cytotoxicity (14% reduction in confluence) was evident at 1200 µg/mL. No precipitation or genotoxic effects were reported.

**CASRN 110-12-3 did not induce chromosomal aberrations in this assay.**

**Conclusion:** The acute toxicity of CASRN 110-12-3 is low in rats and mice treated via the oral route and moderate in rats via inhalation. Male rats gavaged at 2000 mg/kg/day (only dose tested) during a 90-day oral, repeated-dose toxicity study showed significant decreases in body weight and significant increases in clinical chemistry parameters (SGOT, SGPT, urea nitrogen) and (absolute/relative) adrenal and liver weights. Histological examination revealed treatment-related increases in gastric irritation, nephropathy (with hyaline droplet accumulation) and hepatic necrosis at this dose; a NOAEL for systemic toxicity was not established. A 13-week repeated-dose toxicity study in rats administered CASRN 110-12-3 via whole body inhalation showed signs of hepatic and renal toxicity at 4.84 mg/L; the NOAEC for systemic toxicity is 0.99 mg/L. A combined reproductive/developmental toxicity screening test showed no evidence of maternal, reproductive or developmental effects following inhalation exposure in rats; the NOAEC for maternal/reproductive/developmental toxicity is 4.72 mg/L (highest concentration tested). CASRN 110-12-3 did not induce gene mutations in bacterial cells or chromosomal aberrations in mammalian cells when tested *in vitro*.

<b>Table 3. Summary of Human Health Data</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL 5-Methyl-2-hexanone (CASRN 110-12-3)</b>
<b>Structure</b>	
<b>Acute Toxicity Oral LD<sub>50</sub> (mg/kg)</b>	<b>&gt;3200</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>~17.8 (6-h)</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg/day)</b>	<b>NOAEL = Not Established LOAEL = 2000</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L)</b>	<b>NOAEL ~ 0.99 LOAEL ~ 4.84</b>

<b>Table 3. Summary of Human Health Data</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL 5-Methyl-2-hexanone (CASRN 110-12-3)</b>
<b>Reproductive/ Developmental Toxicity NOAEL/LOAEL (Inhalation (mg/L))</b>	
<b>Maternal Reproductive/Developmental</b>	<b>NOAEL = 4.72 (hct) NOAEL = 4.72 (hct)</b>
<b>Genetic Toxicity - Gene Mutation <i>In vitro</i></b>	<b>Negative</b>
<b>Genetic Toxicity - Chromosome Aberrations <i>In vitro</i></b>	<b>Negative</b>

hct = highest concentration tested

#### **4. Hazard to the Environment**

The data for methyl amyl ketone (CASRN 110-43-0) as a supporting chemical can be found at the following website: <http://www.epa.gov/chemrtk/pubs/summaries/methamkt/c13219tc.htm>. The environmental hazard data are summarized in Table 4.

##### ***Acute Toxicity to Fish***

###### ***5-Methyl-2-hexanone (CASRN 110-12-3)***

Data submitted for this endpoint are inadequate because no effects were reported at the nominal test concentration of 100 µl/L and the loss of chemical during the test was not accounted for.

###### ***Methyl amyl ketone (CASRN 110-43-0, supporting chemical)***

Fathead minnow (*Pimephales promelas*) (20/group) were exposed to measured concentrations of 0, 40.9, 58.3, 96.0, 147 or 232 mg/L for 96 hours in a flow-through toxicity test.

**96-h LC<sub>50</sub> = 131 mg/L**

##### ***Acute Toxicity to Aquatic Invertebrates***

###### ***5-Methyl-2-hexanone (CASRN 110-12-3)***

Data submitted for this endpoint are inadequate because no effects were reported at the nominal test concentration of 100 µl/L and the loss of chemical during the test was not accounted for.

**Methyl amyl ketone (CASRN 110-43-0, supporting chemical)**

*Daphnia magna* were exposed to measured concentrations of 0, 6.46, 13.01, 24.52, 47.86 or 90.10 mg/L for 48 hours in a static toxicity test. No effects were seen at any test concentration.  
**48-h EC<sub>50</sub> > 90.10 mg/L**

**Toxicity to Aquatic Plants**

**Methyl amyl ketone (CASRN 110-43-0, supporting chemical)**

Green algae (*Pseudokirchneriella subcapitata*) were exposed to measured geometric mean concentrations of 0, 6.2, 11.9, 22.1, 42.7 or 86.3 mg/L for 72 hours in a static toxicity test. Information on growth and biomass effects at each concentration was not provided.

**72-h EC<sub>50</sub> (growth) = 98.2 mg/L**

**72-h EC<sub>50</sub> (biomass) = 75.5 mg/L**

**Conclusion:** The evaluation of available aquatic toxicity data (all on the supporting chemical, CASRN 110-43-0) indicates that for CASRN 110-12-3, the 96-hr LC<sub>50</sub> for fish is 131 mg/L, the 48-hr EC<sub>50</sub> for daphnia is greater than 90.10 mg/L, and the algal 72-hr EC<sub>50</sub>s are 75.5 mg/L (biomass) and 98.2 mg/L (growth rate).

**Table 4: Summary Table of the Screening Information Data Set  
as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data**

<b>Endpoints</b>	<b>SPONSORED CHEMICAL 5-Methyl-2-hexanone (CASRN 110-12-3)</b>	<b>SUPPORTING CHEMICAL Methyl amyl ketone (CASRN 110-43-0)</b>
<b>Fish 96-hour LC<sub>50</sub> (mg/L)</b>	No data (RA) 131	<b>131 (m)</b>
<b>Aquatic Invertebrates 48-hour EC<sub>50</sub> (mg/L)</b>	No data (RA) >90.10	<b>&gt;90.10 (m)</b>
<b>Aquatic plants Toxicity Algae 72-hour EC<sub>50</sub> (mg/L)</b>	No data (RA) 75.5 (biomass) 98.2 (growth rate)	<b>75.5 (m;biomass) 98.2(m; growth rate)</b>

**BOLD**=measured data