

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### 2-Heptanone (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, EXTOXNET, 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 authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

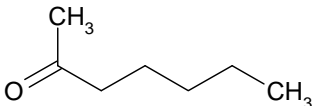
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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<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>.

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.

<b>Chemical Abstract Service Registry Number (CASRN)</b>	<b>110-43-0</b>
<b>Chemical Abstract Index Name</b>	<b>Methyl <i>n</i>-Amyl Ketone</b>
<b>Structural Formula</b>	

### Summary

CASRN 110-43-0 is a colorless 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 110-43-0 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute oral toxicity of CASRN 110-43-0 in rats and mice is low and the acute inhalation toxicity in rats is moderate. In a 90-day oral repeated-dose toxicity study in rats, increased urine cellularity and increased kidney weights were observed in males at 100 mg/kg/day; the NOAEL for systemic toxicity is 20 mg/kg/day. In a repeated-dose inhalation toxicity study in rats and monkeys exposed to CASRN 110-43-0 vapor for 10 months, no effects were observed on any measured parameters such as cardiopulmonary function, clinical chemistry, neurological function, or tissue histology; the NOAEC for systemic toxicity is 4.79 mg/L/day, the highest concentration tested. In an oral prenatal developmental toxicity study in rats exposed to CASRN 110-43-0, dams showed ataxic gait at 500 mg/kg-day; the NOAEL for maternal toxicity is 250 mg/kg/day. Signs of developmental toxicity consisted of decreases in fetal body weight and skeletal ossification in males only at 1000 mg/kg/day; the NOAEL for developmental toxicity is 500 mg/kg/day. In a combined inhalation reproductive/developmental toxicity study in rats, significant decreases in activity were observed at 1.9 mg/L; the NOAEC for maternal toxicity is 0.367 mg/L. There were no signs of reproductive or developmental effects; the NOAEC for both reproductive and developmental toxicity is 4.78 mg/L (highest concentration tested). CASRN 110-43-0 did not induce mutagenesis or chromosomal effects *in vitro*.

For CASRN 110-43-0, the 96-hour LC<sub>50</sub> for fish is 131 mg/L (measured). The 48-hour EC<sub>50</sub> for aquatic invertebrates is >90.1 mg/L (measured). The 72-hour EC<sub>50</sub> for aquatic plants is 98.2 mg/L (measured) for growth and 75.5 mg/L (measured) for biomass.

No data gaps were identified under the HPV Challenge Program.

The sponsor, the Eastman Chemical Company, submitted a Test Plan and Robust Summaries to EPA for 2-heptanone (CAS No. 110-43-0; 9th CI name: 2-heptanone) dated October 4, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 3, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/methamkt/c13219tc.htm>). EPA comments on the original submission were posted to the website on April 25, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 21, 2002, which were posted to the ChemRTK website on June 19, 2002.

## 1. Chemical Identity

### 1.1 Identification and Purity

CASRN 110-43-0 is a colorless liquid with high water solubility and high vapor pressure. The Robust Summary indicates that, when known, the purity of the tested substance is 97% or higher.

### 1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 110-43-0 are summarized in Table 1.

Property	Value
CASRN	110-43-0
Molecular Weight	114.19
Physical State	Colorless liquid
Melting Point	-35.5°C (measured)
Boiling Point	151.5°C (measured)
Vapor Pressure	1.6–3.86 mm Hg at 25°C (measured)
Water Solubility	4,300 mg/L at 25°C (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable
Henry's Law Constant	1.69×10 <sup>-4</sup> atm·m <sup>3</sup> /mole (measured) <sup>2</sup>
Log K <sub>ow</sub>	1.98 (measured)

<sup>1</sup> Eastman Chemical Company. May 30, 2002. Revised Test Plan and Robust Summary for 2-Heptanone. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/methamkt/c13219tc.htm> as of March 29, 2010.

<sup>2</sup> SRC. 2010. The Physical Properties Database (PHYSPROP). SRC: Syracuse, NY. Available online from <http://www.srcinc.com/what-we-do/free-demos.aspx> as of March 29, 2010.

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

According to the 2006 IUR submissions, CASRN 110-43-0 had an aggregated production and/or import volume in the United States between 50 and 100 million pounds.

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

## 2.2 Environmental Exposure and Fate

CASRN 110-43-0 is expected to have high mobility in soil. CASRN 110-43-0 was readily biodegradable using a method similar to the modified MITI test (OECD 301C), in which the test substance achieved roughly 71% of its theoretical biochemical oxygen demand (BOD) after 20 days and the five day BOD/COD ratio was greater than 0.5. CASRN 110-43-0 is also inherently biodegradable using a method similar to the Zahn-Wellens test (OECD 302B). The rate of volatilization is considered moderate based on the Henry's Law constant of this substance. The rate of hydrolysis is considered negligible. CASRN 110-43-0 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2 lists the environmental fate properties of CASRN 110-43-0.

<b>Table 2. Environmental Fate Characteristics of CASRN 110-43-0<sup>1</sup></b>	
<b>Property</b>	<b>Value</b>
Photodegradation Half-life	4.5 hours (estimated); 15.7 hours (estimated) <sup>2</sup>
Hydrolysis Half-life	Stable
Biodegradation	BOD/COD = 0.73 after 5 days and 71% after 20 days (readily biodegradable)
Bioaccumulation Factor	BAF = 8.8 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	1.4 (estimated) <sup>2</sup>
Fugacity (Level III Model) <sup>2</sup>	
Air (%)	4.8
Water (%)	34.8
Soil (%)	60.3
Sediment (%)	0.1
Persistence <sup>3</sup>	P1 (low)
Bioaccumulation <sup>3</sup>	B1 (low)

<sup>1</sup> Eastman Chemical Company. May 30, 2002. Revised Test Plan and Robust Summary for 2-Heptanone. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/methamkt/c13219tc.htm> as of March 29, 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/episuitedi.htm> as of March 22, 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) Rats (10 total, strain and sex not specified) were administered a single dose of CASRN 110-43-0 via oral gavage at doses ranging from 200 to 3200 mg/kg. Following a 14-day observation period, deaths were reported (number not specified) at 1600 mg/kg within 5 hours after dosing. **LD50 = 1600 mg/kg [no information on how this was determined]**

(2) Mice (6 total, strain and sex not specified) were administered CASRN 110-43-0 via oral gavage at doses ranging from 400 to 1600 mg/kg. Following a 14-day observation period, there were no deaths.

**LD50 > 1600 mg/kg**

#### *Acute Inhalation Toxicity*

Rats (3 rats/dose, strain and sex not specified) were exposed by inhalation to CASRN 110-43-0 vapor in whole-body chambers for 4 hours at 5126 ppm (approximately 23.9 mg/L), and for 6 hours at 832, 1437, 2016 or 4169 ppm (approximately 3.89, 6.71, 9.42 or 19.5 mg/L). All animals at 5126 ppm died shortly after exposure. At 4169 ppm, one animal died after 4 hours and the other two died shortly after their 6-hour exposure ended. There were no deaths at 2016 ppm or lower.

**LC50 ~ 9.34 – 18.7 mg/L**

#### *Repeated-Dose Toxicity*

##### *Oral*

CFE rats (15/sex/dose) were administered CASRN 110-43-0 in corn oil by oral gavage for 13 weeks at doses of 0, 20, 100 or 500 mg/kg/day. An additional 5 animals/sex receiving 100 and 500 mg/kg were terminated after 2 and 6 weeks of dosing. Body weight, food and water intake were measured weekly, and clinical chemistry, hematology, and urinalysis were assessed. A urine concentration study was also performed. At termination, gross examination, organ weight, and pathology were assessed. Statistically significant increased urine cellularity occurred in males at 100 and 500 mg/kg/day (according to publication of study summarized by the submitter – *Food Cosmet. Tox*, 1972, [10] pp 625-636). At 500 mg/kg/day, increased relative liver weight occurred in both sexes at week 13 and in males at week 6. Significantly increased relative kidney weight was noted in males at 100 and 500 mg/kg/day; the NOAEL was 20 mg/kg/day. No significant histopathological alterations were noted in any tissues. No statistically significant changes from control were noted in hematology, serum chemistries, or other urinary parameters.

**LOAEL = 100 mg/kg/day** (based on increased urine cellularity and increased relative kidney weight)

**NOAEL = 20 mg/kg/day**

### ***Inhalation***

Male Sprague-Dawley rats (50 animals total) and male Cynomolgus monkeys (*Macaca fascicularis*; 8 animals total) were exposed to 0, 100 or 1000 ppm CASRN 110-43-0 vapor (97% purity) by inhalation in whole-body vapor chambers. Actual exposure levels were reported to be approximately 131 and 1025 ppm (approximately 0.612 and 4.79 mg/L). Animals were exposed 6 hours/day, 5 days/week for 10 months and evaluated for effects on cardiopulmonary function, clinical chemistry, organ weights/histopathology and neurological function (the latter was assessed in both species on a monthly basis). There were no dose-dependent changes in cardiopulmonary, clinical chemistry or the measured neurological indices indicative of toxicity. No gross or microscopic changes in organs and tissues occurred in either rats or monkeys. **NOAEC ~ 4.79 mg/L** (highest dose tested)

### ***Reproductive/Developmental Toxicity***

(1) In a 1993 pilot prenatal developmental toxicity study not presented in the HPV submission, CASRN 110-43-0 (99.7% purity) was administered in corn oil by oral gavage to pregnant Crj:CD(SD) rats (12-13/dose) at doses of 0, 100, 250, 500, and 1000 mg/kg/day on days 6 to 15 of gestation. Dams were observed daily for mortality and clinical toxicity and body weight and food consumption was monitored periodically. Weight of gravid uterus, number of corpora lutea, implantations, fetal survival, sex, and fetal weight were examined. All fetuses were examined for external abnormalities, and half of fetuses from each litter were examined for skeletal and visceral abnormalities. CASRN 110-43-0 caused ataxia in dams at 500 and 1000 mg/kg/day and bradypnea, lacrimation, and prone position at 1000 mg/kg/day. Autopsy revealed cystic formation in esophagus and intracapsular hemorrhage in the thymus at 500 mg/kg/day only. Salivation at doses greater than 250 mg/kg/day were attributed to taste or irritation of the test substance. Maternal body weight gain was significantly decreased at 1000 mg/kg/day in the absence of changes in mean body weight and food consumption. Live fetal body weight and the number of ossified sacrococcygeal vertebral bodies in males were significantly decreased at 1000 mg/kg/day. Sex ratio (male/alive) was significantly increased at 500 mg/kg/day. CASRN 110-43-0 did not affect the number of corpora lutea, implantations and live fetuses, sex ratio, embryo, or fetal mortality or cause external, visceral, or skeletal anomalies or variations. (OTS0000892; <http://www.syrres.com/esc/tscats.htm>)

**LOAEL (maternal toxicity) = 500 mg/kg/day** (based on ataxic gait)

**NOAEL (maternal toxicity) = 250 mg/kg/day**

**LOAEL (developmental toxicity) = 1000 mg/kg/day** (based on effects on fetal body weight and skeletal ossification)

**NOAEL (developmental toxicity) = 500 mg/kg/day**

(2) In a combined reproductive/developmental toxicity study, Sprague-Dawley rats (12/sex/dose) were exposed to CASRN 110-43-0 vapor (>99% purity) via inhalation to 0, 78.6, 405.8 or 1022.6 ppm (approximately 0, 0.367, 1.90 or 4.78 mg/L) for 6 hours/day, 7 days/week, for 50 days (males) or 34 – 47 days (females; through gestation day 19). Survival, body weight, food consumption, reproductive performance, and litter parameters were assessed. Sex organs and accessory sex organs were examined histologically. A dose-related reduction in activity was noted at 1.90 or 4.78 mg/L (gender not specified) that declined over the course of exposure. Males at 4.78 mg/L exhibited decreased food consumption during days 0 – 7 only. There were

no effects in any of the selected organs that were weighed or examined grossly or histologically. There were no effects on litter parameters or reproductive performance. There were no treatment-induced changes in pup body weight, clinical signs or abnormalities.

**LOAEC (maternal/systemic toxicity) ~ 1.90 mg/L** (based on decreased activity)

**NOAEC (maternal toxicity) ~ 0.367 mg/L**

**NOAEC (reproductive/developmental toxicity) ~ 4.78 mg/L** (highest concentration tested)

### ***Genetic Toxicity – Gene Mutation***

#### ***In vitro***

*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed in triplicate to CASRN 110-43-0 (99% purity) at concentrations up to 5000 µg/plate in the presence and absence of metabolic activation (rat liver S9). Positive and negative controls were tested concurrently; their response was not reported. No evidence of cytotoxicity was observed. No increases in revertant colonies were induced in any of the strains.

**CASRN 110-43-0 was not mutagenic in this assay.**

### ***Genetic Toxicity – Chromosomal Aberrations***

#### ***In vitro***

Chinese hamster ovary (CHO) cells were exposed to CASRN 110-43-0 (99.8% purity) at concentrations up to 1200 µg/mL with and without metabolic activation (rat liver S9). Positive and negative controls were tested concurrently; their response was not reported. No evidence of cytotoxicity was observed. No significant increases in chromosomal aberrations, polyploidy, or endoreduplication were observed.

**CASRN 110-43-0 did not induce chromosomal aberrations in this assay.**

**Conclusions:** The acute oral toxicity of CASRN 110-43-0 in rats and mice is low and the acute inhalation toxicity in rats is moderate. In a 90-day oral repeated-dose toxicity study in rats, increased urine cellularity and increased kidney weights were observed in males at 100 mg/kg/day; the NOAEL for systemic toxicity is 20 mg/kg/day. In a repeated-dose inhalation toxicity study in rats and monkeys exposed to CASRN 110-43-0 vapor for 10 months, no effects were observed on any measured parameters such as cardiopulmonary function, clinical chemistry, neurological function, or tissue histology; the NOAEC for systemic toxicity is 4.79 mg/L/day, the highest concentration tested. In an oral prenatal developmental toxicity study in rats exposed to CASRN 110-43-0, dams showed ataxic gait at 500 mg/kg-day; the NOAEL for maternal toxicity is 250 mg/kg/day. Signs of developmental toxicity consisted of decreases in fetal body weight and skeletal ossification in males only at 1000 mg/kg/day; the NOAEL for developmental toxicity is 500 mg/kg/day. In a combined inhalation reproductive/developmental toxicity study in rats, significant decreases in activity were observed at 1.9 mg/L; the NOAEC for maternal toxicity is 0.367 mg/L. There were no signs of reproductive or developmental effects; the NOAEC for both reproductive and developmental toxicity is 4.78 mg/L (highest concentration tested). CASRN 110-43-0 did not induce mutagenesis or chromosomal effects *in vitro*.

<b>Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data</b>	
<b>Endpoints</b>	<b>2-Heptanone (CASRN 110-43-0)</b>
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg)</b>	<b>1600</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>~ 9.34 – 18.7</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg/day)</b>	<b>LOAEL = 100 NOAEL = 20</b>
<b>Repeated-Dose Toxicity NOAEC/LOAEC Inhalation (mg/L/day)</b>	<b>NOAEC ~ 4.79 mg/L (hct*)</b>
<b>Reproductive/Developmental Toxicity NOAEC/LOAEC Inhalation (mg/L/day)</b>  <b>Maternal Toxicity</b>  <b>Reproductive Toxicity</b>  <b>Developmental Toxicity</b>	<b>NOAEC ~ 1.90 LOAEC ~ 0.367</b>  <b>NOAEC ~ 4.78 (hct*)</b>  <b>NOAEC ~ 4.78 (hct*)</b>
<b>Developmental Toxicity NOAEL/LOAEL Oral (mg/kg/day)</b>  <b>Maternal Toxicity</b>  <b>Developmental Toxicity</b>	<b>LOAEL = 500 NOAEL = 250</b>  <b>LOAEL = 1000 NOAEL = 500</b>
<b>Genetic Toxicity – Gene Mutations <i>in vitro</i></b>	<b>Negative</b>
<b>Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i></b>	<b>Negative</b>

\* hct – highest concentration tested

#### 4. Hazard to the Environment

The environmental hazard data are summarized in Table 4.

##### *Acute Toxicity to Fish*

Fathead minnow (*Pimephales promelas*) (20/concentration) 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. The number of deaths per group was not indicated.

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

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

Water fleas (*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 semi-static toxicity test. No effects were seen at any test concentration.

**48-h EC<sub>50</sub> > 90.1 mg/L**

##### *Toxicity to Aquatic Plants*

Green algae (*Pseudokirchneriella subcapitata*) were exposed to measured concentrations of 0, 6.2, 11.9, 22.1, 42.7 or 86.3 mg/L for 72 hours in a static toxicity test.

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

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

**Conclusion:** For CASRN 110-43-0, the 96-hour LC<sub>50</sub> for fish is 131 mg/L (measured). The 48-hour EC<sub>50</sub> for aquatic invertebrates is >90.1 mg/L (measured). The 72-hour EC<sub>50</sub> for aquatic plants is 98.2 mg/L (measured) for growth and 75.5 mg/L (measured) for biomass.

<b>Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data</b>	
<b>Endpoints</b>	<b>2-Heptanone (CASRN 110-43-0)</b>
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>131</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>&gt;90.1</b>
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L) (growth/biomass)</b>	<b>98.2/75.5</b>

**Bold** = measured data