SCREENING-LEVEL HAZARD CHARACTERIZATION

3-Methyl-2-butanone (CASRN 563-80-4)

The High Production Volume (HPV) Challenge Program[1] 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[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

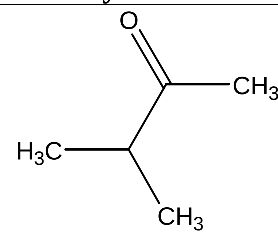
The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness 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[2,3] 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.

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] 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.

Chemical Abstract Service Registry Number (CASRN)	**563-80-3**
Chemical Abstract Index Name	**3-Methyl-2-butanone**
Structural Formula	

Summary

This chemical is a liquid with high water solubility and high vapor pressure. It is expected to have high mobility in soil. Volatilization of this chemical is considered moderate based on its Henry’s Law constant. The rate of hydrolysis is considered negligible under environmental conditions. The rate of atmospheric photooxidation is considered slow. The chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Acute oral and inhalation toxicity of the chemical to rats is low. Following repeated inhalation exposures of rats, systemic toxicity was observed at 5.24 mg/L/day based on decreased body weight and kidney effects; the NOAEL for systemic toxicity was 2.51 mg/L/day. A combined reproductive/developmental toxicity screening test in rats exposed by inhalation showed no reproductive toxicity; the NOAEL was 5.17 mg/L/day. In the same study, developmental toxicity, as evidenced by decreased pup survival, occurred at 2.51 mg/L/day by; the NOAEL was 1.05 mg/L/day. Dams showed decreased body weight gain at 1.05 mg/L/day; the NOAEL for maternal toxicity was not established. This chemical did not induce gene mutations or chromosome aberrations when tested *in vitro*.

The 96-hour LC_{50} of -methyl-2-butanone to fish is 864 mg/L, the 48-hour EC_{50} to aquatic invertebrates is >100 mg/L, and the 96-hour EC_{50} to aquatic plants is 34 mg/L (biomass).

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 3-methyl-2-butanone (methyl isopropyl ketone, MIPK) (CASRN 563-80-4; CA name: 2-butanone, 3-methyl-) on February 15, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on April 2, 2002 (http://www.epa.gov/chemrtk/pubs/summaries/2bt3meth/c13629tc.htm). EPA comments on the original submission were posted to the website on August 16, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on August 15, 2002, which were posted to the ChemRTK website on September 20, 2002.

1 Chemical Identity

1.1 Identification and Purity

The following description is taken from the August 14, 2002 final Test Plan:

[2-Methyl-2-butanone] is a water-white liquid that is manufactured to a high degree of purity. This ketone finds its primary uses in industrial applications where it is utilized as an intermediate in the synthesis of other chemicals and as an industrial solvent. It may also find some use as a solvent in coatings applications.

1.2 Physical-Chemical Properties

The physical-chemical properties of 3-methyl-2-butanone are summarized in Table 1a. 3-Methyl-2-butanone is a liquid with high water solubility and high vapor pressure.

Table 1a. Physical-Chemical Properties of 3-Methyl-2-Butanone[1]

Property	Value
CASRN	563-80-4
Molecular Weight	86.13
Physical State	Liquid
Melting Point	-79.46°C (estimated); -92°C (measured)[2]
Boiling Point	80.27°C (estimated); 94.3°C (measured)[2]
Vapor Pressure	95.5 mm Hg at 25°C (estimated); 52.2 mm Hg at 25°C (measured)[2]
Water Solubility	2,436 mg/L at 25°C (estimated); 60,800 mg/L at 25°C (measured)[2]
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	9.7×10^{-5} atm-m^3/mole (measured)[2]
Log K_{ow}	0.67 (estimated); 0.84 (measured)[2]

[1]The Eastman Chemical Company. September 9, 2002. Revised Robust Summary and Test Plan for 2-Butanone, 3-Methyl. http://www.epa.gov/chemrtk/pubs/summaries/2bt3meth/c13629tc.htm.
[2]SRC. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.syrres.com/esc/physprop.htm as of September 15, 2008.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical had an aggregated production volume in the United States of 1 million to 10 million pounds during calendar year 2005. Non-confidential information in the Inventory Update Reporting (IUR)[4] indicated that the industrial processing and use of this chemical included use as a solvent in other basic organic chemical manufacturing. The High Production Volume (HPV) submission for CASRN 563-80-4 stated that this chemical is used primarily as an intermediate in the synthesis of other chemicals and as an industrial solvent which may find some use in coating applications.[5]

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties are provided in Table 1b. 3-Methyl-2-butanone is expected to have high mobility in soil. This chemical was shown to be readily biodegradable in a closed bottle (OECD 301D) and Modified MITI (301C) test. The rate of volatilization from water and moist soil is considered moderate based on its Henry's Law constant. The rate of hydrolysis is considered negligible under environmental conditions. The chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).

[4] USEPA, 2006. Inventory Update Reporting Database.
[5] Eastman Chemical Company, 2002. Test Plan for Methyl Isopropyl Ketone. Accessed, 10/22/08. http://www.epa.gov/chemrtk/pubs/summaries/2bt3meth/c13629rt.pdf.

Table 1b. Environmental Fate Characteristics of 2-Butanone, 3-methyl-[1]	
Property	**Value**
Photodegradation Half-life	4.1 days (estimated)
Hydrolysis Half-life	Stable
Biodegradation	85% in 28 days (readily biodegradable); 99% in 14 days (readily biodegradable)[2]
Bioconcentration	BCF = 3.162 (estimated)[3]
Log K_{oc}	0.781 (estimated)[3]
Fugacity (Level III Model)	Air = 12.2% Water = 49.4% Soil = 38.3% Sediment = 0.0633%
Persistence[4]	P1 (low)
Bioaccumulation[4]	B1 (low)

[1]The Eastman Chemical Company. September 9, 2002. Revised Robust Summary and Test Plan for 2-Butanone, 3-Methyl. http://www.epa.gov/chemrtk/pubs/summaries/2bt3meth/c13629tc.htm.
[2]National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.
[3]U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. http://www.epa.gov/opptintr/exposure/pubs/episuite.htm.
[4]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

Acute Oral Toxicity

Crl:CD (SD) rats (5 sex/dose) were administered 3-methyl-2-butanone via gavage at 1250, 2500 or 5000 mg/kg-bw and monitored for 14 days. Mortality occurred at 2500 (2, 1/sex) and 5000 (10, 5/sex) mg/kg-bw. Clinical signs at the low and middle doses included slight to moderate weakness and ataxia. At the high dose, clinical signs included slight to severe weakness, ataxia and prostration. The exact cause of death was not determined in any animal at necropsy.
LD_{50} = 3078 mg/kg-bw

Acute Inhalation Toxicity

Crl:CD (SD) rats (5/sex/concentration) were exposed (whole-body) to 3-methyl-2-butanone vapor at nominal concentrations of 4000, 6000 or 9000 ppm for 6 hours and monitored for 14 days. Measured concentrations were 4026, 5708 and 8270 ppm (approximately 14.18, 20.11 and 29.13 mg/L, respectively). Mortality occurred at 5708 (3/10; 1M,2F)and 8270 ppm (9/10; 5M, 4F). On Day 0, one male and one female in the 5708 ppm level and all 5 males and 2 females in the 8270 ppm group died shortly after exposure. Two females in the 8270 ppm group died on Day 1. On Day 2, one female in the 5708 ppm group died. During exposure, all animals exhibited severe CNS depression, lacrimation and concentration-dependent hypoventilation.
LC_{50} ~ 22.46 mg/L, 6377 ppm

Repeated-Dose Toxicity

Crl:CD (SD) rats (5/sex/concentration) were exposed (whole-body) to 3-methyl-2-butanone via inhalation at nominal concentrations of 0, 750, 1500 or 3000 ppm for 6 hours/day, 5 days/week for 4 weeks. Measured exposure concentrations were 0, approximately 2.57, 5.24 and 10.42 mg/L, respectively. No mortalities were observed. Mean body weights were decreased in a concentration-dependent manner. Both sexes exhibited concentration-dependent lethargy at all doses and moderate to severe narcosis was observed at the high concentration during most exposures. High-concentration animals also exhibited gait disturbances. All clinical signs rapidly diminished post-exposure and were not observed in pre-exposure observations the following day. No changes in hematology or clinical chemistry parameters were observed. Increases in several organ weights were noted (specific organs were not identified in the robust summary), where reductions in body weight were also observed. Absolute organ weight increases were noted in the adrenal gland of males and the livers of females at the highest exposure concentration. Males at all exposure concentrations showed evidence of hyaline droplet formation in kidney with a marked increase in severity at the middle and high exposure levels. This observation suggests that the nephropathy in the males is occurring by an $alpha_{2u}$-globulin-mediated mechanism, and may not be relevant to humans. However, the key events and data necessary to demonstrate this rodent specific mode of action are not provided. Therefore, human relevance of the kidney effects cannot be ruled out. No histopathological changes were seen in females at any exposure concentration.
LOAEL = 5.24 mg/L/day (based on decreased body weight and kidney effects)
NOAEL = 2.57 mg/L/day

Reproductive/Developmental Toxicity

In a combined reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/concentration) were exposed (whole-body) to 3-methyl-2-butanone via inhalation (vapor) at nominal concentrations of 0, 1, 2.5 or 5 mg/L for 6 hours/day, 7 days/week for 35 – 48 days (females) or 51 days (males). Actual measured exposure concentrations were 0, 1.05, 2.51 and 5.17 mg/L, respectively. Exposures were initiated 2 weeks prior to mating and continued through day 19 of gestation in females and for 51 days in males. Reduction in general activity levels during the exposure was noted in exposed groups. Decreased body weight gain and feed utilization were noted in all treated exposure groups (significance not stated). Clinical signs noted at the middle and high exposure concentrations included unkempt haircoat, wet perioral hair and periocular porphyrin discharges. The only post-natal clinical sign was a single pup at the high concentration that had loose, fluid filled skin and hypothermia. In the 2.5 mg/L group there was an increase in the number of dead pups/litter at birth. Pup survival rate at 2.5 mg/L was 95.4% at Day 0 of lactation. The reduced survival was attributed to 2 of 12 dams having three dead pups at birth. The mean number of live pups per litter was reduced on lactation day 0 and 4 at the 5.17 mg/L dose (96.3% survival rate Day 4 vs. 100% in control group). The litter survival at 1.0 mg/L was comparable to control. Among the adult animals, there were no effects on fertility or other endpoints measuring reproductive performance in any treated group.
NOAEL (reproductive toxicity) = 5.17 mg/L/6-h/day (no effect at highest dose)
LOAEL (maternal toxicity) = 1.05 mg/L/6-h/day (decreased body weight gain)
NOAEL (maternal toxicity) = Not established

LOAEL (developmental toxicity) = 2.51 mg/L/6-h/day (based on decreased pup survival)
NOAEL (developmental toxicity) = 1.05 mg/L/6-h/day

Genetic Toxicity – Gene Mutation

In vitro
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2*uvrA* were exposed to 3-methyl-2-butanone at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. The test material was evaluated in triplicate at each dose level. Positive controls were tested concurrently and all criteria for a valid study were met.
3-Methyl-2-butanone was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
Chinese hamster ovary (CHO) cells were exposed to 3-methyl-2-butanone at concentrations up to 901 μg/mL in the presence and absence of metabolic activation. Negative and positive controls were tested concurrently, but control responses were not reported. The test substance did not induce any structural or numerical aberrations.
3-Methyl-2-butanone did not induce chromosomal aberrations in this assay.

Conclusion: Acute oral and inhalation toxicity of the chemical to rats is low. Following repeated inhalation exposures of rats, systemic toxicity was observed at 5.24 mg/L/day based on decreased body weight and kidney effects; the NOAEL for systemic toxicity was 2.51 mg/L/day. A combined reproductive/developmental toxicity screening test in rats exposed by inhalation, showed no reproductive toxicity; the NOAEL was 5.17 mg/L/day. In the same study, developmental toxicity, as evidenced by decreased pup survival, occurred at 2.51 mg/L/day by; the NOAEL was 1.05 mg/L/day. Dams showed decreased body weight gain at 1.05 mg/L/day; the NOAEL for maternal toxicity was not established. This chemical did not induce gene mutations or chromosome aberrations when tested *in vitro*.

4 Hazards to the Environment

A fish acute toxicity study was not submitted for this chemical. However, a 96-hour fish toxicity study that addresses this endpoint was located through a literature search and is provided below.

Acute Toxicity to Fish

Pimephales promelas (fathead minnow) were exposed to measured concentrations (not specified) of 3-methyl-2-butanone under flow-through conditions for 96 hours (Brooke *et al*, 1984).
96-h LC_{50} = 864 mg/L

Acute Toxicity to Aquatic Invertebrates

Daphnia magna (10/concentration) were exposed to nominal concentrations (not specified) of 3-methyl-2-butanone under static conditions for 48-hours. A 48-hour EC_{50} for *Daphnia* estimated with ECOSAR v1.00a was used to support the evaluation of the acute toxicity of this chemical.
48-h EC_{50} > 100 mg/L
48-h EC_{50} = 452 mg/L (estimated)

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to 3-methyl-2-butanone at nominal concentrations of 0, 7.8, 15.6, 31.3, 62.5 or 125.0 mg/L under static conditions for 72 hours. Measured concentrations, based on the geometric mean over all time points, were 0, 4.1, 7.5, 14.8, 29.5 or 61.8 mg/L, respectively. Control growth was satisfactory. No deformed cells were noted.
72-h EC_{50} (biomass) = 34.0 mg/L
72-h EC_{50} (growth) = 44.2 mg/L

Conclusion: The 96-hour LC_{50} of -methyl-2-butanone to fish is 864 mg/L, the 48-hour EC_{50} to aquatic invertebrates is >100 mg/L, and the 96-hour EC_{50} to aquatic plants is 34 mg/L (biomass).

<u>5 References</u>

Brooke, LT, Call, DJ, Geiger, DL and CE Northcott. 1984. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales promelas*), Vol. 1. Center for Lake Superior Env. Stud., Univ. of Wisconsin-Superior, Superior, WI: 414.

Table 2: Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL 3-Methyl-2-butanone (563-80-4)**
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**3078**
Acute Inhalation Toxicity LC_{50} (mg/L) LC_{50} (ppm)	**22.46** (6-h) **6377** (6-h)
Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)	**NOAEL = 2.57 (28-d) LOAEL= 5.24 (28-d)**
Reproductive/Developmental Toxicity NOAEL/LOAEL Inhalation (mg/L/day) Reproductive Toxicity Maternal Toxicity Developmental Toxicity	**NOAEL = 5.17 NOAEL = Not established LOAEL = 1.05 NOAEL = 1.05 LOAEL = 2.51**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vitro*	**Negative**
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC_{50} (mg/L)	**864**
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**>100**
Aquatic Plants 72-h EC_{50} (mg/L) (growth) (biomass)	**44.2 34.0**