Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals

Cyclohexanone, Oxime (CASRN 100-64-1)

Contents:

BACKGROUND

Screening-level hazard, exposure and risk characterizations for high production volume chemicals (HPV) are important contributions to the chemicals cooperation work being done in North America[1] through the EPA Chemical Assessment and Management Program (ChAMP)[2]. These screening-level characterizations are developed by EPA for individual chemicals or chemical categories to support initial Risk-Based Prioritizations (RBPs) for HPV chemicals. These screening-level characterizations are technical documents intended primarily to inform the Agency's internal decision-making process. Accordingly, they are written for assessment professionals and assume a degree of technical understanding. Each of the support documents is described below.

The Risk-Based Prioritizations are found in an accompanying document and are written for a general audience. They present EPA's initial thinking regarding the potential risks presented by these chemicals and future possible actions that may be needed.

Hazard Characterizations for HPV Chemicals

EPA's screening-level hazard characterizations are based primarily on the review of the summaries of studies and other information submitted by the chemical sponsor(s) under the HPV Challenge Program[3]. These studies included in the scope of the HPV Challenge comprise the Screening Information Data Set (SIDS) of the Organization for Economic Cooperation and Development (OECD)[4], an internationally recognized battery of tests that provides the basic data necessary to make an initial evaluation of a chemical's hazards and fate. In preparing the initial hazard characterizations, EPA also consulted a variety of reliable sources[5] for additional relevant information and 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 an HPV submission, EPA also searched publicly available databases[6] for information entered from one year prior to the HPV submission through May 2008. The screening-level hazard characterization is performed according to established EPA guidance[7]. A more detailed description of the hazard characterization process is available on the EPA website[8].

With respect to chemicals for which internationally-accepted OECD SIDS Initial Assessment Profiles (SIAP) and Initial Assessment Reports (SIAR) were available, EPA did not generate its own screening-level hazard characterization, but did check for and incorporate updated information in the risk characterization.

Exposure Characterizations for HPV Chemicals

EPA recently received exposure-related data on chemicals submitted in accordance with the requirements of Inventory Update Reporting (IUR)[9]. The 2006 IUR submissions pertain to chemicals manufactured in

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[1] U.S. EPA – U.S. Commitments to North American Chemicals Cooperation: http://www.epa.gov/hpv/pubs/general/sppframework.htm.
[2] U.S. EPA – ChAMP information: http://www.epa.gov/champ/.
[3] U.S. EPA – HPV Challenge Program information: http://www.epa.gov/hpv.
[4] U.S. EPA – Technical Guidance Document, OECD SIDS Manual Sections 3.4 and 3.5: http://www.epa.gov/chemrtk/pubs/general/sidsappb.htm.
[5] U.S. EPA – Public Database Hazard Information: http://www.epa.gov/hpvis/hazardinfo.htm
[6] U.S. EPA – Public Database Update Information: http://www.epa.gov/chemrtk/hpvis/updateinfo.htm.
[7] U.S. EPA – Risk Assessment Guidelines: http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[8] U.S. EPA – About HPV Chemical Hazard Characterizations: http://www.epa.gov/hpvis/abouthc.htm.
[9] U.S. EPA – Basic IUR Information: http://www.epa.gov/opptintr/iur/pubs/guidance/basic-information.htm.

(including imported into) the U.S. during calendar year 2005 in quantities of 25,000 pounds or more at a single site. The reports include the identity, the quantity, and the physical form of the chemical manufactured or imported, and the number of workers reasonably likely to be exposed during manufacture of the chemical. For chemicals manufactured or imported in quantities of 300,000 pounds or more at a single site, additional reported information includes: the industrial processing and uses of the chemical; the number of industrial processing sites and workers reasonably likely to be exposed to the chemical at those sites; the consumer and commercial uses of the chemical; and an indication whether the chemical was used in products intended for use by children under 14 years of age.

EPA's screening-level exposure characterizations are based largely on the information submitted under the IUR reporting, although other exposure information submitted to the Agency (for example, in HPV submissions) or readily available through a limited set of publicly accessible databases[10] was also considered. The screening-level exposure characterizations identify a potential (high, medium, or low) that each of five populations – the environment, the general population, workers, consumers, and children – might be exposed to the chemical. In most cases, this potential doesn't address the quantity, frequency, or duration of exposure, but refers only to the likelihood that an exposure could occur.

In many instances EPA is not able to fully disclose to the public all the IUR exposure-related data reviewed or relied upon in the development of the screening-level documents because some of the material was claimed as confidential business information (CBI) when it was submitted to the Agency. These CBI claims do limit the Agency's ability to be completely transparent in presenting some underlying exposure and use data for chemicals in public documents. EPA does consider all data, including data considered to be CBI, in the screening-level exposure and risk characterization process, and endeavors whenever possible to broadly characterize supporting materials claimed as confidential in ways that do not disclose actual CBI.

Risk Characterizations for HPV Chemicals

EPA combines the information from the screening-level exposure characterization with the screening-level hazard characterization to develop a qualitative screening-level risk characterization, as described in the Agency's guidance on drafting risk characterizations[11]. These screening-level risk characterizations are technical documents intended to support subsequent priority-setting decisions and actions by OPPT. The purpose of the qualitative screening-level risk characterization is two-fold: to support initial risk-based decisions to prioritize chemicals, identify potential concerns, and inform risk management options; and to identify data needs for individual chemicals or chemical categories.

These initial characterization and prioritization documents do not constitute a final Agency determination as to risk, nor do they determine whether sufficient data are available to characterize risk. Recommended actions reflect EPA's relative judgment regarding this chemical or chemical category in comparison with others evaluated under this program, as well as the uncertainties presented by gaps that may exist in the available data.

[10] U.S. EPA – Summary of Public Databases Routinely Searched: http://www.epa.gov/chemrtk/hpvis/pubdtsum.htm.
[11] U.S. EPA – Risk Characterization Program: http://www.epa.gov/osa/spc/2riskchr.htm.

QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Cyclohexanone, Oxime (CAS No. 100-64-1)
[9th CI Name: Cyclohexanone, Oxime]

September 2008

Prepared by

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QUALITATIVE SCREENING-LEVEL RISK CHARACTERIZATION FOR Cyclohexanone, Oxime (CAS No. 100-64-1)

1. Physical-Chemical Properties and Environmental Fate

Cyclohexanone, oxime is a white, crystalline solid at room temperature. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil. Volatilization is considered moderate based on its Henry's Law constant. Cyclohexanone, oxime is stable to hydrolysis. In the atmosphere it is degraded by photochemically generated hydroxyl radicals at a rate that is considered moderate. No data were provided for the biodegradation of cyclohexanone, oxime. EPA estimates that the aerobic degradation half-life is on the order of weeks and also estimates a bioconcentration factor of 3. Thus, cyclohexanone, oxime is expected to have low persistence (P1) and low bioaccumulation potential (B1).

2. Hazard Characterization

Aquatic Organism Toxicity. The acute toxicity of cyclohexanone, oxime to fish is low. No data were submitted by the sponsor for the acute toxicity of cyclohexanone, oxime to either aquatic invertebrates or aquatic plants.

Human Health Toxicity. The acute oral toxicity of cyclohexanone, oxime to rats and the acute dermal toxicity to rabbits are low. Repeated-dose and reproductive data were not required for the HPV Challenge Program because cyclohexanone, oxime is a closed-system intermediate. However, an oral repeated-dose toxicity study of cyclohexanone, oxime in rats was submitted and showed high systemic toxicity. A repeated-dose toxicity study with mice exposed to cyclohexanone, oxime via drinking water showed low systemic toxicity. A prenatal developmental toxicity study of cyclohexanone (CAS No. 108-94-1), a major metabolite of cyclohexanone,oxime, showed low maternal and developmental toxicity in rats. Cyclohexanone, oxime induced gene mutations and gave an equivocal response for chromosomal aberrations *in vitro*. However, it did not induce chromosomal aberrations *in vivo.*

3. Exposure Characterization

Cyclohexanone, oxime (CAS No. 100-64-1) has an aggregated production and/or import volume in the United States of 100 million to 500 million pounds. IUR information for this chemical indicates that it is used as an industrial intermediate in the manufacturing of other basic organic compounds. No commercial use is reported in the IUR submissions or other data sources.

Potential for Exposures to Humans and the Environment: Based on the information considered, including IUR data and information from the HPV Challenge Program, and in combination with the Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, general population, consumers and children) and the environment. Persistence and bioaccumulation ratings for this chemical are P1 and B1, respectively. The P1/B1 rating suggests that the chemical is not persistent and is not bioaccumulative. The Agency has reviewed the information in the HPV submission and determined that the HPV chemical satisfies the guidance to

demonstrate that the chemical is a closed system intermediate. The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting the chemical in accordance with IUR requirements.

4. Risk Characterization

The statements and rationale provided below are intended solely for the purpose of this screening-level and qualitative risk characterization and will be used for prioritizing substances for future work in the Chemical Assessment and Management Program (ChAMP).

Risk Statement and Rationale

The Agency has reviewed the information in the HPV submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate. Cyclohexanone, oxime is manufactured and processed in closed systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting the chemical in accordance with IUR requirements. Therefore, there is low concern for potential risks to aquatic organisms and the general population from environmental releases, and also to workers, consumers, and children.

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

Cyclohexanone, Oxime (CAS No. 100-64-1)
[9th CI Name: Cyclohexanone, oxime]

September 2008

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SCREENING-LEVEL HAZARD CHARACTERIZATION
Cyclohexanone, Oxime (CAS No. 100-64-1)

Introduction

The sponsor, DSM Chemicals North America, Inc., submitted a Test Plan and Robust Summaries to EPA for cyclohexanone, oxime (CAS No. 100-64-1; 9th CI name: cyclohexanone, oxime) on March 10, 2006. EPA posted the submission on the ChemRTK HPV Challenge website on March 21, 2006 (http://www.epa.gov/chemrtk/pubs/summaries/cycloxim/c16215tc.htm). EPA comments on the original submission were posted to the website on November 14, 2007. Public comments were also received and posted to the website.

This screening level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. 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 2005 to May 2008: the NLM databases (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health effects is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

The sponsor proposed reduced health effects testing claiming that cyclohexanone oxime is a closed-system intermediate (CSI). EPA's evaluation of the original information indicated that the chemical meets the guidance to support the CSI claim for this chemical. Cyclohexanone oxime is produced at a single site, is consumed in the in-process reaction to make another substance and there are no offsite shipments. Therefore, EPA has determined that the chemical qualifies for reduced testing and waiving of repeated-dose and reproductive toxicity testing for the purposes of the HPV Challenge Program.

The sponsor did not submit data for the developmental toxicity endpoint but indicated in the test plan that a developmental toxicity study following the OECD guidelines would be conducted. However, based on the rapid metabolism of cyclohexanone, oxime in the mammalian system, EPA considered developmental toxicity data for cyclohexanone (CAS No. 108-94-1), a metabolite of cyclohexanone, oxime, adequate for addressing the developmental toxicity endpoint for the purposes of the HPV Challenge Program. These data are summarized in the ***Developmental Toxicity*** section. Cyclohexanone has been assessed in the OECD HPV program and the published data can be viewed at the following link: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html.

Hazard Characterization

Cyclohexanone, oxime is a white, crystalline solid at room temperature. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil. Volatilization is considered moderate based on its Henry's Law constant. Cyclohexanone, oxime is stable to hydrolysis. In the atmosphere it is degraded by photochemically generated hydroxyl radicals at a rate that is considered moderate. No data were provided for the biodegradation of cyclohexanone, oxime. EPA estimates that the aerobic degradation half-life is on the order of weeks and also estimates a bioconcentration factor of 3. Thus, cyclohexanone, oxime is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute toxicity of cyclohexanone, oxime to fish is low.

The acute oral toxicity of cyclohexanone, oxime to rats and the acute dermal toxicity to rabbits are low. Repeated-dose and reproductive data were not required for the HPV Challenge Program because cyclohexanone, oxime is a closed-system intermediate. However, an oral repeated-dose toxicity study of cyclohexanone, oxime in rats was submitted and showed high systemic toxicity. A repeated-dose toxicity study with mice exposed to cyclohexanone oxime via drinking water showed low systemic toxicity. A prenatal developmental toxicity study of cyclohexanone

(CAS No. 108-94-1), a major metabolite of cyclohexanone,oxime, showed low maternal and developmental toxicity in rats. Cyclohexanone, oxime induced gene mutations but gave an equivocal response for chromosomal aberrations *in vitro*. However, it did not induce chromosomal aberrations *in vivo*.

Hydrolysis, ready biodegradation and acute toxicity for aquatic invertebrates and aquatic plants endpoints were identified as data gaps under the HPV Challenge Program.

1. Physical-Chemical Properties and Environmental Fate

The physical-chemical properties of cyclohexanone, oxime are summarized in Table 1a, while the environmental fate properties are given in Table 1b. Its structure is provided in the Appendix.

Physical-Chemical Properties Characterization

Cyclohexanone, oxime is a white, crystalline solid at room temperature. It has high water solubility and moderate vapor pressure.

Table 1a. Physical-Chemical Properties of Cyclohexanone, Oxime[1]

Property	Value
CAS No.	100-64-1
Molecular Weight	118.15
Physical State	White, crystalline solid
Melting Point	88–91°C (measured)
Boiling Point	208 °C (measured)
Vapor Pressure	0.029 mm Hg at 25°C (measured)[2]
Water Solubility	15,000 mg/L at 20°C (measured)[2]
Henry's Law Constant	8×10^{-5} atm-m^3/mole (estimated)[2]
Log K_{ow}	0.84 (measured)[2]

[1]DMS Chemicals North America Inc. 2006. Robust Summary and Test Plan for Cyclohexanone, oxime: http://www.epa.gov/chemrtk/pubs/summaries/cycloxim/c16215tc.htm
[2]US 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.

Environmental Fate Characterization

Cyclohexanone, oxime is expected to partition primarily to soil and water, according to the results of a Level III fugacity model that assumes equal emissions to air, water, and soil. In the atmosphere, cyclohexanone, oxime is not expected to undergo hydrolysis and degraded by photochemically generated hydroxyl radicals at a rate that is considered moderate. Volatilization of cyclohexanone, oxime is considered moderate based on its Henry's Law constant. It has moderate mobility in soil and its bioaccumulation potential is ranked low (B1) based on an estimated BCF of 3. No biodegradation data are available for cyclohexanone, oxime. EPA estimates that aerobic biodegradation half-life is several weeks (P1).

Table 1b. Environmental Fate Characteristics of Cyclohexanone, Oxime[1]	
Property	**Value**
Photodegradation Half-life	1.5 days[2]
Hydrolysis Half-life	Data Gap; Stable (estimated by EPA)[2]
Biodegradation	Data Gap; Half-life = weeks (estimated by EPA)[2]
Bioconcentration	BCF = 3 (estimated)[2]
Log K_{oc}	2.7 (estimated)[2]
Fugacity (Level III Model)[2]	Air = 2% Water = 41% Soil = 56.8% Sediment = 0.1%
Persistence[3]	P1 (low)
Bioaccumulation[3]	B1 (low)

[1]DMS Chemicals North America Inc. 2006. Robust Summary and Test Plan for Cyclohexanone, oxime: http://www.epa.gov/chemrtk/pubs/summaries/cycloxim/c16215tc.htm
[2]US 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.
[3]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: Cyclohexanone, oxime is a white, crystalline solid at room temperature. It has high water solubility and moderate vapor pressure. It has moderate mobility in soil. Volatilization is considered moderate based on its Henry's Law constant. Cyclohexanone, oxime is stable to hydrolysis. In the atmosphere it is degraded by photochemically generated hydroxyl radicals at a rate that is considered moderate. No data were provided for the biodegradation of cyclohexanone, oxime. EPA estimates that aerobic degradation half-life is on the order of weeks and also estimates a bioconcentration factor of 3. Cyclohexanone, oxime is expected to have low persistence low persistence (P1) and low bioaccumulation potential (B1).

2. Environmental Effects – Aquatic Toxicity

Acute Toxicity to Fish

The sponsor stated in the Revised Test Plan that study details were not available for the fathead minnow study provided in their robust summary and therefore proposed to conduct an acute toxicity study for fish. EPA has located the details of the fathead minnow study in EPA's ECOTOX database (www.epa.gov/ecotox) and in the reference cited by the sponsor, deemed the study adequate and used it in this hazard characterization.

Fathead minnows (*Pimephales promelas*) were exposed to nominal concentrations of cyclohexanone, oxime of 72.8, 112, 172, 265 and 408 mg/L under flow-through conditions for 96 hours. Measured concentrations were 72.1, 102, 153, 236 and 374 mg/L.
96-h LC_{50} = 208 mg/L

Acute Toxicity to Aquatic Invertebrates

Data gap

Toxicity to Aquatic Plants

Data gap

Conclusion: The acute toxicity of cyclohexanone, oxime to fish is low. Acute toxicity to aquatic invertebrates and aquatic plants endpoints were identified as data gaps under the HPV Challenge Program.

3. Human Health Effects

Acute Oral Toxicity

Fischer 344 rats (10/sex/dose) were administered cyclohexanone, oxime via gavage to seven doses (males, ranging from 562 to 5000 mg/kg-bw) or five doses (females, ranging from 398 to 5000 mg/kg-bw). All animals were observed for 14 days. The control group received distilled water.
LD_{50} = 1765 mg/kg-bw (males) and 883 mg/kg-bw (females)

Acute Dermal Toxicity

New Zealand white rabbits (5/sex/dose) were administered cyclohexanone, oxime dermally at 0 (distilled water control), 800, 2000 or 5000 mg/kg-bw under occluded conditions for 24 hours and observed for 14 days. No mortalities, clinical signs, changes in body or organ weights, or gross pathology were observed. Hematological effects included elevated reticulocyte counts in males decreased hemoglobin values in high-dose females and increased methemoglobin levels in males and females.
LD_{50} > 5000 mg/kg-bw

Repeated-Dose Toxicity

Although cyclohexanone, oxime is a CSI, the sponsor submitted data for the repeated-dose toxicity endpoint that are summarized below and are used in this hazard characterization.

(1) Fischer 344 rats were administered cyclohexanone, oxime via gavage at 0, 0.25, 2.5 or 25 mg/kg-bw/day, 5 days/week for 30 days (10/sex/dose), 60 days (10/sex/dose) or 90 days (20/sex/dose). No compound-related mortality was noted. Clinical signs of toxicity occurred in males during the first 9 weeks and included red nasal discharge at the high dose, chromodacryorrhea and swollen conjunctiva at the mid- and high dose and corneal opacity at all dose levels. Clinical signs of toxicity occurred in females after 2 weeks and included chromodacryorrhea at the high dose and corneal opacity at the mid- and high dose. No exposure-related effects were noted for body weight, food consumption, urinalysis, neurobehavioral effects or clinical chemistry. A small but progressive decrease in erythrocytes, hematocrit and total hemoglobin with time was seen in both sexes at the high dose. A statistically significant increase in circulating reticulocytes at all doses demonstrated a dose response. Increases in the degree of anisocytosis, poikilocytosis and polychromasia were evident and leukocyte and platelet counts were also elevated at the high dose. Spleen weights were increased in males and females at the high dose. Histopathological examination at 90 days revealed a progressive increase in splenic hemosiderin deposition and hematopoiesis in the bone marrow and spleen at all doses. Liver and kidney weights were higher in the high-dose females.
LOAEL = 0.25 mg/kg-bw/day (based on blood effects in bone marrow and spleen)
NOAEL = Not established

(2) In a National Toxicology Program (NTP) study, B6C3F1 mice (10/sex/dose) were administered cyclohexanone, oxime in drinking water at 0, 635, 1200, 2500, 5000, or 10,000ppm (~127, 240, 500, 1000 or 2000 mg/kg-bw/day) for 90 days. Mortality was observed in the 10,000 ppm. Decreased body weight gain was noted at 5000 ppm in females and 10,000 ppm in males and females. Increased absolute and/or relative spleen weights at 5000 and 10,000 ppm and increased absolute and relative liver weight at 10,000 ppm were seen. Histopathological examination revealed hematopoietic cell proliferation in the spleen at 5000 and 10,000 ppm, hypertrophy of centrilobular hepatocytes at 2500, 5000 and 10,000 ppm in males and at 5000 and 10,000 in females and olfactory epithelial degeneration at all doses. No treatment-related effects were noted for clinical signs of toxicity, water consumption, sperm motility or vaginal cytology parameters.
LOAEL = 500 mg/kg-bw/day (based on histopathological effects on the liver)
NOAEL = 240 mg/kg-bw/day

Reproductive Toxicity

No data were submitted for this endpoint. The sponsor proposed reduced health effects testing claiming that cyclohexanone, oxime is a CSI. EPA's evaluation of the original information indicated that the chemical meets the guidance to support the CSI claim for this chemical. Therefore, testing for the reproductive toxicity endpoint is waived for the purposes of the HPV Challenge Program.

Developmental Toxicity

Cyclohexanone (CAS No. 108-94-1, Metabolite of Cyclohexanone, oxime)
Pregnant Sprague-Dawley rats (23-24/dose) were exposed to cyclohexanone vapor via inhalation (whole-body) at 0, 300, 650, and 1400 ppm (~1.2, 2.6 and 5.6 mg/L) for 6 hours/day during days 6 to 19 of gestation with a necropsy on day 20. Clinical signs included lacrimation at highest concentration with increased incidence and severity over the course of the study. Nasal discharge, lethargy and vaginal discharge were also seen at this concentration in several females. Observations of startle responses followed concentration and time related patterns. At 300 ppm there were a few instances of sluggish responses. At 650 ppm, the incidence was higher and at 1400 ppm, there was a high incidence of lethargy and many rats were essentially non-responsive for the duration of daily exposure. No females aborted or delivered prematurely. Maternal body weight was markedly decreased (approximately 33-44% less than the controls) at 1400 ppm. No significant differences were noted in the numbers of corpora lutea, implantation sites, pups and resorptions or the sex ratio. Reduction in mean body weights of pups of both sexes were noted at 1400 ppm. A slight distention of the renal pelvis was present at low incidence at 650 and 1400 ppm. There was an increase in the incidence of generalized retardation of ossification at 1400 ppm; these include: incomplete ossification of the cranial bones and/or ossification irregularities of the hyoid, incomplete or unossified sternebrae and unossified metatarsals and forelimb phalanges.
LOAEL (maternal toxicity) = 5.6 mg/L/day (based on reduction in body weight and severe lethargy)
NOAEL (maternal toxicity) = 2.6 mg/L/day
LOAEL (developmental toxicity) = 5.6 mg/L/day (based on reduction in fetal body weight and increased incidence of variation in and retardation of ossification)
NOAEL (developmental toxicity) = 2.6 mg/L/day

Genetic Toxicity – Gene Mutation

In vitro
In an NTP study, *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 were exposed to cyclohexanone, oxime up to 6666 µg/plate in the presence and absence of metabolic activation. Positive and negative controls produced appropriate responses. The cytotoxic concentration was > 3333 µg/plate in the presence of metabolic activation and > 6666 µg/plate in the absence of metabolic activation. Mutagenicity was observed in TA1535 in the presence of metabolic activation.
Cyclohexanone, oxime was mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro
In an NTP study, Chinese hamster ovary (CHO) cells were administered cyclohexanone, oxime at 500 – 5000 µg/mL in the presence and absence of metabolic activation. Solvent and positive controls produced appropriate responses. The cytotoxic concentration was > 5000 µg/mL. In each of two trials, significant increase in aberrations was observed at one of three doses in the absence of metabolic activation. No induction of aberrations was seen in the presence of metabolic activation. The results were equivocal.
Cyclohexanone, oxime produced an equivocal response in this assay.

In vivo
(1) In an NTP study, B6C3F1 mice (5/sex/dose) were administered cyclohexanone, oxime in drinking water at 0, 625, 1250, 2500, 5000 or 10,000 ppm (approximately 127, 240, 500, 1000 or 2000 mg/kg-bw/day) for 90 days. Peripheral blood normochromatic erythrocytes were scored for micronuclei. No information on the use or response of positive controls was provided.
Cyclohexanone, oxime did not induce formation of micronuclei in this assay.

(2) In an NTP study, B6C3F1 mice (5/sex/dose) were administered cyclohexanone, oxime in corn oil via intraperitoneal injection at 0, 400, 600, 800 or 1000 mg/kg-bw for 24 hours intervals over 3 days. Twenty-four hours after the third injection, mice were sacrificed and smears of bone marrow cells were prepared to determine the frequency of micronucleated polychromatic erythrocytes. Solvent and positive controls responded appropriately. **Cyclohexanone, oxime did not induce formation of micronuclei in this assay.**

Additional Information

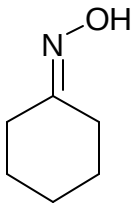
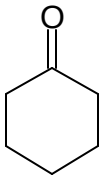
Metabolism

Cyclohexanone, oxime was found to be rapidly absorbed and cleared from the body within 24 hours after a single oral administration of 1, 10 and 30 mg/kg-bw of ^{14}C- cyclohexanone, oxime to the adult male F 344 rats. The majority of ^{14}C- cyclohexanone, oxime derived radioactivity (65-90% of the dose) was excreted in the urine. Elimination in the feces accounted for 5-10% of the dose and very low levels (2-3% of the dose) were retained in the tissues 24 hours after exposure. After intravenous administration of 1 mg/kg of ^{14}C- cyclohexanone, oxime, it was rapidly cleared from plasma with half-lives of 1.6 to 18.2 minutes. However when applied dermally at 30 mg/kg, only 4-5% of the dose was recovered in urine, feces and the tissues. The majority of the dose volatilized from the skin surface. However, the absorbed oxime was readily distributed and excreted and its metabolic fate was no different when observed after oral administration. HPLC analysis of urine showed that the majority of the radioactivity excreted was in the form of three metabolites, cyclohexaglucuronide and monoglucuronides of *cis* and *trans* cyclohexane-1,2-diol. In vitro studies showed that these metabolites arise primarily by hydrolysis of the oxime to cyclohexanone, which is then reduced to cyclohexanol and eliminated as the glucuronide conjugate. The cyclohexanol in turn could be metabolized to cis and trans-cyclohexane-1,2-diols, which are excreted as their monoglucuronides.
(Parmar, D and Burka, L, Metabolism of cyclohexanone, oxime in male F-344 rats, Cyclohexanone, oxime, NTP Toxicity Report Number 50).

Note: Although the main focus of the NTP study described above was metabolism of cyclohexanone, oxime and further transformation of cyclohexanone, hydroxylamine is also formed simultaneously as a major metabolite during the metabolism of cyclohexanone, oxime.

Conclusion: The acute oral toxicity of cyclohexanone, oxime to rats and the acute dermal toxicity to rabbits are low. Repeated-dose and reproductive data were not required for the HPV Challenge Program because cyclohexanone, oxime is a closed-system intermediate. An oral repeated-dose toxicity study of cyclohexanone, oxime in rats showed high systemic toxicity. However, a repeated-dose toxicity study of mice exposed to cyclohexanone oxime via drinking water showed low systemic toxicity. A prenatal developmental toxicity study of cyclohexanone (CAS No. 108-94-1), a major metabolite of cyclohexanone,oxime, showed low maternal and developmental toxicity in rats. Cyclohexanone, oxime induced gene mutations and gave an equivocal response for chromosomal aberrations *in vitro*. However, it did not induce chromosomal aberrations *in vivo*.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program		
Endpoints	**SPONSORED CHEMICAL Cyclohexanone oxime (100-64-1)**	**METABOLITE Cyclohexanone (108-94-1)**
Structure		
Summary of Environmental Effects –Aquatic Toxicity Data		
Fish 96-h LC_{50} (mg/L)	208	—*
Aquatic Invertebrates 48-h EC_{50} (mg/L)	Data gap	—*
Aquatic Plants 72-h EC_{50} (mg/L)	Data gap	—*
Summary of Human Health Data		
Acute Oral Toxicity LD_{50} (mg/kg-bw)	1765 (males) 833 (females)	—*
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 5000	—*
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = Not established LOAEL = 0.25	—*
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Parental Systemic and Reproductive Toxicity	Endpoint waived because the chemical is a closed system intermediate.	—*
Developmental Toxicity NOAEL/LOAEL Oral (mg/L) Maternal and Developmental Toxicity	No Data NOAEL = 2.6 LOAEL = 5.6 (RA)	NOAEL = 2.6 LOAEL = 5.6
Genetic Toxicity – Gene Mutation *In vitro*	Positive	—*
Genetic Toxicity – Chromosomal Aberrations *In vitro*	Negative	—*
Genetic Toxicity – Chromosomal Aberrations *In vivo*	Negative	—*

- indicates that endpoint was not addressed for this chemical; * indicates endpoint not necessary for supporting chemical.

Screening Level Exposure Characterization for HPV Challenge Chemical

Cyclohexanone, Oxime

CAS # 100-64-1

September 2008

Prepared by

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Screening Level Exposure Characterization
Cyclohexanone, oxime (CAS # 100-64-1)

Non-CBI Executive Summary

Cyclohexanone, oxime (CAS # 100-64-1) has an aggregated production and/or import volume in the United States of 100 million to 500 million pounds.[12] Non-confidential information in the Inventory Update Reporting (IUR) indicates that this chemical was manufactured and/or imported at the following companies and sites: DSM Chemicals/ Augusta, GA. Non-confidential IUR information for this chemical indicates that it is used as an industrial intermediate. No commercial use is reported in the IUR submissions or other data sources. Information submitted as part of the High Production Volume (HPV) Challenge Program indicates that 3- cyclohexanone, oxime is used in the chemical industry for synthesis of caprolactam, which is used to produce polycaprolactam fibers and resins.[13]

Potential for Exposures to Humans and the Environment:

Based on the information considered, including IUR data and information from the HPV Challenge Program information cited above, and in combination with Agency's professional judgment, EPA identifies, for the purposes of risk-based prioritization, a low relative ranking for each of the potentially exposed groups (including workers, general population, consumers and children) and the environment. Persistence and bioaccumulation ratings for this chemical are P1 and B1.[14] The P1/B1 rating suggests that the chemical is not persistent and is not bioaccumulative. The Agency has reviewed the information in the HPV submission or test plan and determined that the HPV chemical satisfies the guidance to demonstrate that the chemical is a closed system intermediate.[15] The chemical is manufactured and processed in systems that are expected to reduce the potential for worker exposure and environmental releases that could lead to other human and environmental exposure. The guidance for identifying this chemical substance as a closed-system intermediate was satisfied at all sites reporting the chemical in accordance with IUR requirements.

[12] USEPA, 2006. Partial Updating of TSCA Chemical Inventory.
[13] DSM, 2006. High Production Volume Test Plan for Cyclohexanone Oxime. Submitted by DSM Chemicals. Dated March 2006. http://www.epa.gov/chemrtk/pubs/summaries/cycloxim/c16215tc.htm Accessed May 22, 2008.
[14] USEPA, 2008. Screening Level Hazard Characterization for High Production Volume Chemicals, Cyclohexanone, Oxime.
[15] USEPA, 2007. EPA Comments on Chemical RTK HPV Challenge Submission. Letter dated November, 2007. http://www.epa.gov/chemrtk/pubs/summaries/cycloxim/c16215ct.pdf. Accessed June 20, 2008. Accessed June 20, 2008.

Non Confidential IUR Data Summary Cyclohexanone, oxime (CAS # 100-64-1)

Manufacturing/Import Information

Production and import volume:	100 million to 500 million pounds
List of non-CBI companies/sites:	DSM Chemicals /Augusta, GA*
Maximum number of exposed workers:	less than 100 (including those of manufacturing, industrial processing and use) **
Highest non-CBI maximum concentration:	greater than 90%*
Non-CBI physical forms:	liquid*

* There may be other companies/sites, concentrations and physical forms that are claimed confidential.
** There may be additional potentially exposed industrial workers that are not included in this estimate since not all submitters were required to report on industrial processing and use and/or there may be at least one use that contains a "Not Readily Obtainable" (NRO) response among the submissions.

Table 1
Industrial Processing and Use Information
Reported in 2006 IUR

Processing Activity	Industrial Sector	Functional Use
Processing as a reactant	Other Basic Organic Chemical Manufacturing	Intermediates

Table 2
Commercial/ Consumer Uses
Reported in 2006 IUR

Commercial/ Consumer Product Category Description	Highest maximum concentration range	Use in Children's Products
None reported		