

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

Cyclohexyl isocyanate
(CASRN 3173-53-3)

SUPPORTING CHEMICAL

Cyclohexanamine
(CASRN 108-91-8)

The High Production Volume (HPV) Challenge Program¹ 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.

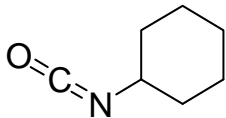

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

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.

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>Chemical Abstract Service Registry Number (CASRN)</p>	<p><u>Sponsored Chemical</u> 3173-53-3</p> <p><u>Supporting Chemical</u> 108-91-8</p>
<p>Chemical Abstract Index Name</p>	<p><u>Sponsored Chemical</u> Cyclohexane, isocyanato-</p> <p><u>Supporting Chemical</u> Cyclohexanamine</p>
<p>Structural Formula</p>	<p><u>Sponsored Chemical</u></p>  <p><u>Supporting Chemical</u></p> 
<p style="text-align: center;">Summary</p> <p>CASRN 3173-53-3 is a liquid possessing high vapor pressure. The water solubility cannot be determined because this substance undergoes rapid hydrolysis in water, which is the key determinant of its environmental fate. It is expected to possess moderate mobility in soil if it is not hydrolyzed. Volatilization is considered negligible since this compound hydrolyzes rapidly in water. The rate of atmospheric photooxidation is considered moderate. Due to its instability in water, CASRN 3173-53-3 is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 3173-53-3 to rats is moderate. Repeated-dose and reproductive toxicity data were required for the HPV Challenge Program because CASRN 3173-53-3 was not considered a closed-system intermediate. CASRN 3173-53-3 was not mutagenic in bacteria <i>in vitro</i>. Low molecular weight isocyanate chemicals are frequently reported to cause occupational asthma. In the absence of negative test data, the potential for CASRN 3173-53-3 to cause respiratory sensitization or asthma cannot be dismissed.</p> <p>The 96-h LC₅₀ of the supporting chemical (CASRN 108-91-8) for fish ranges from 33.4 to</p>	

470 mg/L. The measured 24-h EC_{50} of the supporting chemical (CASRN 108-91-8) for aquatic invertebrates is 36.3 mg/L. The 72-h EC_{50} and 96-h EC_{50} of the supporting chemical (CASRN 108-91-8) for aquatic plants is 14.3 mg/L (biomass) and 20 mg/L (biomass), respectively.

Repeated dose/reproductive/developmental and genetic toxicity (chromosomal aberrations) endpoints were identified as data gaps under the HPV Challenge Program.

The sponsor, Bayer Corporation, submitted a Test Plan and Robust Summaries to EPA for cyclohexyl isocyanate (CASRN 3173-53-3; CA Index name: cyclohexane, isocyanato-) on May 7, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on July 3, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/bayer/c13026tc.htm>). EPA comments on the original submission were posted to the website on July 3, 2001 and November 5, 2001. Public comments were also received and posted to the website.

The sponsor proposed reduced health testing, claiming that cyclohexyl isocyanate is a closed-system intermediate (CSI). EPA's preliminary review of the submission indicated that the submission does not provide adequate documentation to substantiate the CSI claim. EPA requested that the sponsor consider this issue and advise the Agency within 30 days of any modifications to its submission. To date, no revised submission has been posted to the website. Therefore, EPA has determined that the chemical does not qualify for reduced testing and data for repeated-dose and reproductive toxicity endpoints are needed for the purposes of the HPV Challenge Program.

Supporting Chemical Justification

Isocyanates hydrolyze to the associated amine (i.e. cyclohexanamine). Cyclohexyl isocyanate rapidly degrades to cyclohexanamine (CASRN 108-91-8) in water which is the product that is exposed to the aquatic environment. Therefore, EPA considers data for cyclohexanamine appropriate to address the ecotoxicity endpoints.

1. Chemical Identity

1.1 Identification and Purity

Cyclohexane, isocyanato- is a liquid possessing high vapor pressure. The water solubility cannot be determined because this substance undergoes rapid hydrolysis in water.

1.2 Physical-Chemical Properties

The physical-chemical properties of cyclohexane, isocyanato- are summarized in Table 1.

Property	Value
CASRN	3173-53-3
Molecular Weight	125.17
Physical State	Liquid
Melting Point	-80°C (measured)
Boiling Point	172°C (measured)
Vapor Pressure	1.6 mm Hg at 20°C (measured); 9.0 mm Hg at 50°C (measured)

Property	Value
Water Solubility	Not applicable (hydrolysis)
Dissociation Constant (pK _a)	Not applicable
Henry's Law Constant	Not applicable (hydrolysis)
Log K _{ow}	Not applicable (hydrolysis)

¹ Bayer Corporation. May 1, 2001. Test Plan and Robust Summary for Cyclohexyl Isocyanate. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/bayer/c13026tc.htm> as of August 28, 2010.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 3173-53-3 was not reported in the 2006 IUR.

2.2 Environmental Exposure and Fate

Cyclohexane, isocyanato- is expected to possess moderate mobility in soil. Cyclohexane, isocyanato- biodegraded 75% after 20 days using a closed bottle test (OECD 301D); however, these results likely pertain to the hydrolysis product rather than the parent compound. The rate of volatilization is considered negligible due to the rapid rate of hydrolysis. The sponsor did not present experimental rate data regarding the rate of hydrolysis of cyclohexane, isocyanato-; however, a structurally similar substance, 4,4'-methylenedicyclohexyl diisocyanate (CASRN 5124-30-1), had a hydrolysis half-life of approximately 2 hours at 23°C in a water/acetonitrile mixture. Due to the rapid rate of hydrolysis, cyclohexane, isocyanato- is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The environmental fate data are provided in Table 2.

Property	Value
Photodegradation Half-life	12.8 hours (estimated) ²
Hydrolysis Half-life	Hydrolyzes to cyclohexylamine; 2.0 hours at 23°C in 1/1 water/acetonitrile mixture (data for 4,4'-methylenedicyclohexyl diisocyanate CASRN 5124-30-1) ³
Biodegradation	75% after 20 days (readily biodegradable) ⁴
Bioaccumulation Factor	Not applicable (hydrolysis)
Log K _{oc}	2.9 (estimated) ²
Fugacity (Level III Model) ²	
Air (%)	Not applicable; model does not account for compartment losses due to rapid hydrolysis
Water (%)	
Soil (%)	
Sediment (%)	
Persistence ⁵	P1 (low)
Bioaccumulation ⁵	B1 (low)

¹ Bayer Corporation. May 1, 2001. Test Plan and Robust Summary for Cyclohexyl Isocyanate. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/bayer/c13026tc.htm> as of August 28, 2010.

² 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 June 28, 2010.

³ OECD SIDS Initial Assessment Report for 4,4'-Methylenedicyclohexyl Diisocyanate. SIAM 20. Paris, France April 19-22, 2005. Available online from: http://www.alipa.org/fileadmin/Alipa/OECD_DraftSIDS_5124301.pdf as of August 28, 2010.

⁴ Data likely corresponds to the hydrolysis product cyclohexylamine. Test was also performed with 1 g/L Emulgator W (CASRN 68130-72-3) used as an emulsifier.

⁵ Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Conclusion: Cyclohexane, isocyanato- is a liquid possessing high vapor pressure. The water solubility cannot be determined because this substance undergoes rapid hydrolysis in water, which is the key determinant of its environmental fate. It is expected to possess moderate mobility in soil if it is not hydrolyzed. Volatilization is considered negligible since this compound hydrolyzes rapidly in water. The rate of atmospheric photooxidation is considered moderate. Due to its instability in water, cyclohexane, isocyanato- is expected to have low persistence (P1) and low bioaccumulation potential (B1).

3. Human Health Hazard

A summary of the human health toxicity data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

(1) Sprague-Dawley albino rats (5/dose; mixed sexes) were administered cyclohexyl isocyanate via gavage at dose levels of 398, 501, 631 or 794 mg/kg-bw and observed for 14 days. Toxic signs included reduced appetite, decreased activity, increased weakness, collapse and death. One male; two males; two males and one female; and three males and one female died at 398, 501,

631 and 794 mg/kg-bw, respectively. Most deaths occurred within 1 day. Necropsy findings included lung and liver hyperemia and acute gastrointestinal inflammation.

LD₅₀ = 560 mg/kg-bw

(2) Sprague-Dawley rats (4/sex/dose) were administered cyclohexyl isocyanate via gavage at dose levels of 100, 200, 400 or 800 mg/kg-bw for male rats, and 400, 500, 625 or 781 mg/kg-bw for female rats and observed for 14 days. At 100, 200, 400 and 800 mg/kg-bw, 0, 1, 2 and 4 male rats died, respectively. At 400, 500, 625 and 781 mg/kg-bw, 0, 1, 1 and 4 female rats died, respectively. Rats exhibited lethargy and sedation.

LD₅₀ (males) = 335 mg/kg-bw

LD₅₀ (females) = 625 mg/kg-bw

Repeated-Dose Toxicity

No data were submitted for this endpoint.

Reproductive Toxicity

No data were submitted for this endpoint.

Developmental Toxicity

No data were submitted for this endpoint.

Genetic Toxicity – Gene Mutation

In vitro

In a study conducted by the National Toxicology Program (NTP), *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1538 were exposed to cyclohexyl isocyanate at concentrations ranging from 0 to 333 µg/plate in the presence and absence of metabolic activation. Positive controls were included. Cyclohexyl isocyanate was found to be equivocal for mutagenicity in this assay. However, in a repeat test using *Salmonella typhimurium* strains TA97, TA98, TA100, TA102, TA104 and TA1535 exposed to cyclohexyl isocyanate at concentrations ranging from 0 to 3 times the original highest exposure level (i.e., 1000 µg/plate) in the presence and absence of metabolic activation, Cyclohexyl isocyanate was found to be negative for mutagenicity.

Cyclohexyl isocyanate was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

No data were submitted for this endpoint.

Additional Information

Respiratory Sensitization

Except for contact irritation, isocyanates differ in their mode of action such that direct comparisons can not be made; however, based on available information, the potential for CASRN 3173-53-3 to elicit respiratory sensitization responses or asthma cannot be dismissed (AEGl, http://www.epa.gov/oppt/aegl/pubs/cyclohexyl_%20isocyanate_interim_%20nov_2007_v1.pdf; NIOSH, <http://www.cdc.gov/niosh/ipcsneng/neng0856.html>).

Conclusion: The acute oral toxicity of CASRN 3173-53-3 to rats is moderate. Repeated-dose and reproductive toxicity data were required for the HPV Challenge Program because CASRN 3173-53-3 was not considered a closed-system intermediate. CASRN 3173-53-3 was not mutagenic in bacteria *in vitro*. Low molecular weight isocyanate chemicals are frequently reported to cause occupational asthma. In the absence of negative test data, the potential for CASRN 3173-53-3 to cause respiratory sensitization or asthma cannot be dismissed.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Human Health Data	
Endpoints	SPONSORED CHEMICAL Cyclohexyl isocyanate (3173-53-3)
Acute Oral Toxicity LD₅₀ (mg/kg)	335 – 625
Repeated-Dose Toxicity NOAEL/LOAEL	No Data
Reproductive Toxicity NOAEL/LOAEL	No Data
Developmental Toxicity NOAEL/LOAEL	No Data
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i>	No Data

Bold = measured data (i.e., derived from testing).

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for the supporting chemical are used to read-across (RA) to the sponsored chemical.

Acute Toxicity to Fish

Cyclohexanamine (CASRN 108-91-8, supporting chemical)

(1) Rainbow Trout (*Oncorhynchus mykiss*) were exposed to CASRN 108-91-8 at unspecified measured concentration for 96 hours under static conditions.

96-h LC₅₀ = 44 mg/L

(2) Zebra Fish (*Danio rerio*) were exposed to unspecified nominal concentrations of CASRN 108-91-8 for 96 hours under static conditions.

96-h LC₅₀ = 470 mg/L

(3) Japanese Medaka (*Oryzias latipes*) were exposed to CASRN 108-91-8 at nominal concentrations of 0, 2.6, 4.8, 8.6, 15.4, 27.8 or 50.0 mg/L under semi-static conditions for 96 hours.

96-h LC₅₀ = 33.4 mg/L

Acute Toxicity to Aquatic Invertebrates

Cyclohexanamine (CASRN 108-91-8 supporting chemical)

Water fleas (*Daphnia magna*) were exposed to CASRN 108-91-8 at nominal concentrations of 0, 5.3, 9.5, 17.1, 30.9, 55.6 or 100 mg/L under static conditions for 48 hours.

48-h EC₅₀ = 36.3 mg/L

Toxicity to Aquatic Plants

Cyclohexanamine (CASRN 108-91-8 supporting chemical)

(1) Green Algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 108-91-8 at unspecified measured concentrations for 96 hours under static conditions.

96-hr EC₅₀ (biomass) = 20 mg/L

(2) Green Algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 108-91-8 at nominal concentrations of 0, 3.2, 5.7, 10.3, 18.5, 33.3 or 60.0 mg/L under static conditions for 72 hours.

72-h EC₅₀ (biomass) = 14.3 mg/L

Conclusion: The 96-h LC₅₀ of the supporting chemical (CASRN 108-91-8) for fish ranges from 33.4 to 470 mg/L. The measured 24-h EC₅₀ of the supporting chemical (CASRN 108-91-8) for aquatic invertebrates is 36.3 mg/L. The 72-h EC₅₀ and 96-h EC₅₀ of the supporting chemical (CASRN 108-91-8) for aquatic plants is 14.3 mg/L (biomass) and 20 mg/L (biomass), respectively.

Table 4. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program –Aquatic Toxicity Data		
Endpoints	SPONSORED CHEMICAL Cyclohexane, Isocyanato- (3173-53-3)	SUPPORTING CHEMICAL Cyclohexanamine (108-91-8)
Fish 96-h LC₅₀ (mg/L)	No Data 33.4 – 470 (RA)	33.4 - 470
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	No Data 33.4 (RA)	33.4
Aquatic Plants 72 & 96-h EC₅₀ (mg/L) (biomass) (growth rate)	No Data 14.3 and 20 (RA) –	14.3 (72-h) and 20 (96-h) –

bold = measured data (i.e., derived from testing); (RA) = read across; – indicates that endpoint was not addressed for this chemical.

5. References

Calamari, D., R.D. Gasso, S. Galassi, A. Provini, and M. Vighi: 1980 Biodegradation and Toxicity of Selected Amines on Aquatic Organisms: *Chemosphere* 9(12):753-762

Wellens, H. 1982: Comparison of the Sensitivity of *Brachydanio rerio* and *Leuciscus idus* by Testing the Fish Toxicity of Chemicals and Wastewaters: *Z.Wasser-Abwasser-Forsch.* 51(2):49-52 (GER) (ENG ABS)

The result of ecological impact test of chemical substances carried out by the Ministry of the Environment in 2006