

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICAL

Carbonothioic dihydrazide (CASRN 2231-57-4)

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, EXTTOXNET, 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

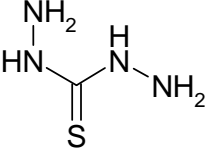
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

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 Registry Number (CASRN)</p>	<p>CASRN 2231-57-4</p>
<p>Chemical Abstract Index Name</p>	<p>Carbonothioic dihydrazide</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>Carbonothioic dihydrazide is a solid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of carbonothioic dihydrazide is considered low based on its Henry's Law constant. The rate of hydrolysis was not available and could not be estimated for this compound. The rate of atmospheric photooxidation is considered rapid. Carbonothioic dihydrazide is expected to have moderate persistence (P2) based on the slow rate of biodegradation of a structurally similar compound (thiosemicarbazide) and low bioaccumulation potential (B1).</p> <p>Acute oral and inhalation toxicity of this chemical is high. There are no available repeated-dose, developmental or reproductive toxicity tests. It induced gene mutations in bacteria and unscheduled DNA synthesis <i>in vitro</i>. There are no available tests for the chromosomal aberrations endpoint.</p> <p>The estimated 96-hour LC₅₀ for fish is 30 mg/L, the estimated 48-hour EC₅₀ for aquatic invertebrates is 12 mg/L, and the estimated 96-hour EC₅₀ for aquatic plants is 15 mg/L.</p> <p>Data gaps for biodegradation, repeated-dose, reproductive and developmental toxicity, chromosomal aberrations, acute toxicity to fish, aquatic invertebrates, and toxicity to aquatic plants endpoints were identified under the HPV Challenge Program.</p>	

The sponsor, Bayer Corporation, submitted a Test Plan and Robust Summaries to EPA for carbonothioic dihydrazide (CASRN 2231-57-4; CA Index name: carbonothioic dihydrazide) on December 29, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on February 25, 2004

(<http://www.epa.gov/chemrtk/pubs/summaries/crbndhyd/c14999tc.htm>). EPA comments on the original submission were posted to the website on January 19, 2005. Public comments were also received and posted to the website.

The sponsor proposed reduced health effects testing, claiming that carbonothioic dihydrazide is a closed-system intermediate (CSI). EPA's evaluation of the submitted information indicated that the chemical does not meet the criteria to fully support the CSI claim for this chemical. Therefore, EPA has determined that carbonothioic dihydrazide does not qualify for reduced testing and data for the repeated-dose and reproductive toxicity endpoints are needed for the purposes of the HPV Challenge Program.

1 Chemical Identity

1.1 Identification and Purity

There is no discussion of the identification and purity of this chemical in the sponsor's Test Plan.

1.2 Physical-Chemical Properties

The physical-chemical properties of carbonothioic dihydrazide are summarized in Table 1. Carbonothioic dihydrazide is a solid with high water solubility and moderate vapor pressure.

Property	Value
CASRN	2231-57-4
Molecular Weight	106.15
Physical State	Solid
Melting Point	170°C (decomposes)
Boiling Point	decomposes
Vapor Pressure	0.002 mm Hg at 25°C (estimated)
Water Solubility	5,500 mg/L at 24.7°C ² 1,800 mg/L at 0°C ²
Dissociation Constant (pK _a)	0.29 (estimated) ³
Henry's Law Constant	2.76×10 ⁻¹² atm·m ³ /mole (estimated)
Log K _{ow}	-2.04 (estimated)

¹Bayer CropScience LP. January 6, 2004. Robust Summary for Carbonothioic Dihydrazide. <http://www.epa.gov/chemrtk/pubs/summaries/crbndhyd/c14999tc.htm>.

²Beilstein, E4, Vol 3, part 1, page 388.

³SPARC. 2008. Online pKa and Property Calculator v. 4.2.1405-s4.2.1408. Accessed October 30, 2008. <http://ibmlc2.chem.uga.edu/sparc/index.cfm?CFID=32727&CFTOKEN=65477992>.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical had an aggregated production and/ or import volume in the United States between 1 million and 10 million pounds during calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates in the manufacturing of pesticides and other agricultural chemicals. The HSDB information states that the chemical is primarily used in electron microscopy to produce electron-opaque deposits for ultrastructural analysis. It is also used in veterinary medicine. The HPV submission states that the chemical is primarily used as an intermediate in the production of an agricultural herbicide and, in limited quantities, as an intermediate in the production of a “fine” chemical.

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 2. Carbonothioic dihydrazide is expected to have high mobility in soil. No biodegradation data were submitted by the sponsor for carbonothioic dihydrazide. EPA used data for thiosemicarbazide (CASRN 79-19-6) to address the biodegradation of the sponsored chemical because the two chemicals are structurally similar chemicals and their biodegradation rates are expected to be similar. Thiosemicarbazide (CASRN 79-19-6) achieved 0% of its theoretical BOD over a 28-day incubation period using a modified MITI test (OECD 301C) and was determined to be not readily biodegradable.⁴ The rate of volatilization of carbonothioic dihydrazide from water and moist soil is considered low based on its estimated Henry’s Law constant. The rate of hydrolysis was not available and could not be estimated for this compound. Carbonothioic dihydrazide is expected to have moderate persistence (P2) based on the lack of biodegradability of thiosemicarbazide and low bioaccumulation potential (B1).

⁴National 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.

Property	Value
Photodegradation Half-life	1 hour (estimated)
Hydrolysis Half-life	Not available
Biodegradation	0% in 28 days (data for structural analog thiosemicarbazide) ²
Bioconcentration	BCF = 3.162 (estimated); BCF = 3.8–39 (measured in carp for structural analog thiosemicarbazide) ²
Log K _{oc}	1.016 (estimated) ³
Fugacity (Level III Model)	Air = <0.01% Water = 45.3% Soil = 54.6% Sediment = <0.01%
Persistence ⁴	P2 (moderate)
Bioaccumulation ⁴	B1 (low)

¹Bayer CropScience LP. January 6, 2004. Robust Summary for Carbonothioic Dihydrazide.

<http://www.epa.gov/chemrtk/pubs/summaries/crbndhyd/c14999tc.htm>.

²National 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.

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. U.S. Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

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

Conclusion: Carbonothioic dihydrazide is a solid with high water solubility and moderate vapor pressure. It is expected to have high mobility in soil. Volatilization of carbonothioic dihydrazide is considered low based on its Henry's Law constant. The rate of hydrolysis was not available and could not be estimated for this compound. The rate of atmospheric photooxidation is considered rapid. Carbonothioic dihydrazide is expected to have moderate persistence (P2) based on the slow rate of biodegradation of a structurally similar compound (thiosemicarbazide) and low bioaccumulation potential (B1).

A data gap for biodegradation was identified under the HPV Challenge Program.

3 Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 2.

Acute Oral Toxicity

(1) In two separate studies, Wistar rats (15 males/dose) were administered carbonothioic dihydrazide (in polyethylene glycol 400) via gavage at 2.5, 5, 10, 25, 35, 50, 65 (1 study only) or 100 mg/kg-bw and observed for 14 days. Deaths occurred within 3 – 24 hours in animals at and above 25 mg/kg-bw.

LD₅₀ = 35 -41 mg/kg-bw

(2) In two separate studies, Wistar rats (15 females/dose) were administered carbonothioic dihydrazide (in polyethylene glycol 400) via gavage at 2.5, 5, 10, 15 (1 study only), 17.5 (1 study only), 25, 30 (1 study only), 35, 50 or 100 mg/kg-bw and observed for 14 days. Deaths occurred within 4.5 – 24 hours in animals at and above 17.5 mg/kg-bw.

LD₅₀ = 26 - 36 mg/kg-bw

Acute Inhalation Toxicity

(1) Wistar rats (10/sex/concentration) were exposed to carbonothioic dihydrazide dust (head/nose only) at 10, 45, 50 or 60 mg/m³ (approximately 0.01, 0.045, 0.05 and 0.06 mg/L) for 4 hours and observed for 7 days. Mortality occurred 1 – 4 days post-exposure in males exposed to concentrations at and above 0.045 mg/L and in females exposed to concentrations at and above 0.05 mg/L.

LC₅₀ = 0.05 mg/L

(2) Wistar rats (10/sex/concentration) were exposed to carbonothioic dihydrazide dust (head/nose only) at 45 or 75.5 mg/m³ (approximately 0.045 and 0.076 mg/L) for 1 hour and observed for 7 days. Mortality occurred 1 – 4 days post-exposure in both males and females exposed to 0.076 mg/L (2/10 males and 1/10 females died). All 20 high dose animals showed signs of toxicity. No effects were observed in animals exposed at 0.045 mg/L. (If the toxic response is assumed to be linear, 4 hour exposure would have 12/20 mortality ~ 60%.)

LC₅₀ > 0.075 mg/L (one hour exposure)

Acute Dermal Toxicity

Wistar rats (males and female, number not specified) were administered carbonothioic dihydrazide (in polyethylene glycol 400) dermally at 500 mg/kg-bw on to clipped, intact skin under occlusive conditions for 24 hours and were observed for 7 days. No deaths occurred. Deterioration of general physical condition was noted and lasted 3 – 4 days after treatment.

LD₅₀ > 500 mg/kg-bw (only dose tested)

Repeated-Dose, Reproductive, and Developmental Toxicity

[No data were submitted for these endpoints.]

Genetic Toxicity – Gene Mutation

In vitro

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to carbonothioic dihydrazide at concentrations of 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333 and 5000 µg/plate in the presence and absence of metabolic activation. The maximum dose tested in the preliminary toxicity determination was 5 mg/plate due to the limited solubility of carbonothioic dihydrazide. Cytotoxicity data were not provided. Positive controls were tested concurrently, but their responses were not provided. Carbonothioic dihydrazide caused a small but reproducible increase in TA1535 revertants per plate in the presence of metabolic activation (2.5 and 3.1 fold increases in 2 separate experiments). In the absence of rat liver microsomes, TA1535 did not demonstrate a positive response. All other tester strains did not demonstrate positive responses.

Carbonothioic dihydrazide was mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

Data gap

Genetic Toxicity – Other

In vitro

In an unscheduled DNA synthesis (UDS) assay, primary rat hepatocytes were exposed to carbonothioic dihydrazide at 2.2 – 666.7 µg/mL. Positive and negative controls were tested concurrently, but their responses were not provided. There was an increase in the mean number of net nuclear grain counts at the highest dose with a dose-response relationship.

Carbonothioic dihydrazide induced unscheduled DNA synthesis in this assay.

Additional Information

Skin Irritation

A single rabbit (sex and strain not specified) was administered carbonothioic dihydrazide dermally at 500 mg/kg-bw to the clipped, intact skin of the outer ear under occlusive conditions for 24 hours and was observed for 7 days. No alteration of the treated skin was observed.

Carbonothioic dihydrazide was not irritating to one rabbit skin in this study.

Eye Irritation

Carbonothioic dihydrazide (50 mg) was instilled into the conjunctival sac of the right eye of one rabbit. The test eye was not washed. Following dose administration, the animal was observed for irritation (observation period was not stated). No irritation or alterations of the eyelid, connective tissue or cornea were observed.

Carbonothioic dihydrazide was not irritating to one rabbit eye in this study.

Conclusion: Acute oral and inhalation toxicity of carbonothioic dihydrazide is high. There are no available repeated-dose, developmental or reproductive toxicity tests. Carbonothioic dihydrazide induced gene mutations in bacteria and unscheduled DNA synthesis *in vitro*. There are no available tests for the chromosomal aberrations endpoint.

Data gaps for repeated-dose, reproductive and developmental toxicity and chromosomal aberrations endpoints were identified under the HPV Challenge Program.

4 Hazards to the Environment

The sponsor did not submit measured aquatic toxicity data for carbonothioic dihydrazide. ECOSAR v1.00a was used to assess the acute toxicity of the chemical to fish, aquatic invertebrates and aquatic plants.

Acute Toxicity to Fish

A 96-hour LC₅₀ for fish estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of carbonothioic dihydrazide.

96-hr LC₅₀ = 30 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

A 48-hour EC₅₀ for Daphnia estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of carbonothioic dihydrazide.

48-hr EC₅₀ = 12 mg/L (estimated)

Toxicity to Aquatic Plants

A 96-hour EC₅₀ for algae estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of carbonothioic dihydrazide.

96-hr EC₅₀ = 15 mg/L (estimated)

Conclusion: The estimated 96-hour LC₅₀ for fish is 30 mg/L, the estimated 48-hour EC₅₀ for aquatic invertebrates is 12 mg/L, and the estimated 96-hour EC₅₀ for aquatic plants is 15 mg/L.

Data gaps for acute toxicity to fish and aquatic invertebrates, and toxicity to aquatic plants were identified under the HPV Challenge Program.

Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Carbonothioic dihydrazide (CASRN 2231-57-4)
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	35 - 41 males 26 - 36 females
Acute Inhalation Toxicity LC₅₀ (mg/L)	0.05
Repeated-dose/ Reproductive/Developmental Toxicity	No data
Genetic Toxicity – Gene Mutations <i>In vitro</i>	Positive
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	No data
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	30 (estimated)
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	12 (estimated)
Aquatic Plants 72-h EC₅₀ (mg/L)	15 (estimated)