

SCREENING-LEVEL HAZARD CHARACTERIZATION

Sponsored Chemical

2H-Benzimidazole-2-thione, 1,3-dihydro-, 4(or 5)-methyl-, zinc salt (2:1)

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.

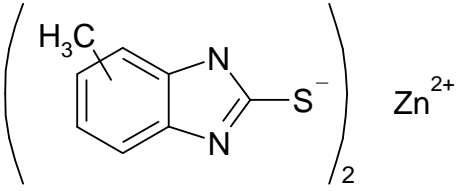
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment 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 information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>61617-00-3</p>
<p>Chemical Abstracts Index Name</p>	<p>2H-Benzimidazole-2-thione, 1,3-dihydro-4(or 5)-methyl-, zinc salt (2:1)</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>CASRN 61617-00-3 is a solid with moderate water solubility and negligible vapor pressure. It is expected to have moderate mobility in soil. Volatilization is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photo-oxidation is considered rapid; however, this compound is unlikely to exist in the vapor phase in the atmosphere. CASRN 61617-00-3 is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p> <p>The acute oral, inhalation and dermal toxicities of CASRN 61617-00-3 are low in rats. It is not irritating to rabbit eyes or skin. A combined repeated-dose reproductive/developmental toxicity study showed both systemic and reproductive toxicity in orally exposed rats. Significant decrements in body weight gain and organ weights were observed at all levels of treatment, including the lowest dose tested (45-50 mg/kg/day). Female reproductive toxicity, as evidenced by increased gestation length, occurred at all doses. The NOAEL for male reproductive toxicity was approximately 275-338 mg/kg/day, based on no effects at the highest dose tested. Developmental toxicity could not be evaluated due to a high incidence of mortality in the dams. This chemical did not induce bacterial gene mutations <i>in vivo</i> or chromosomal aberrations in mammalian cells <i>in vitro</i>.</p> <p>The 96-hour LC₅₀ of CASRN 61617-00-3 to fish is 5.6 mg/L. The 48-hour EC₅₀ of CASRN 61617-00-3 to aquatic invertebrates is 1.4 mg/L, and the 96-hour EC₅₀ to aquatic plants is 6.6 mg/L.</p> <p>No data gaps were identified for this chemical under the HPV Challenge Program.</p>	

The sponsor, R.T. Vanderbilt Company, submitted a Test Plan and Robust Summaries to EPA for 2H-benzimidazole-2-thione,1,3-dihydro-4(or 5)-methyl-,zinc salt (2:1) (CASRN 61617-00-3) on January 2, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on January 31, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/zincmerc/c14230tc.htm>). EPA comments on the original submission were posted to the website on June 17, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revise documents on November 3, 2006, which were posted to the ChemRTK website on January 30, 2008.

1. Chemical Identity

1.1 Identification and Purity

The Robust Summaries submitted by the sponsor state that the purity of CASRN 61617-00-3 ranges from 95-97%.

1.2 Physical-Chemical Properties

The physical-chemical properties for CASRN 61617-00-3 are summarized in Table 1. This chemical is a solid with moderate water solubility and negligible vapor pressure.

Table 1. Physical-Chemical Properties of 2H-Benzimidazole-2-thione, 1,3-dihydro-,4 (or 5)-methyl-, zinc salt (2:1)¹	
Property	Value
CASRN	61617-00-3
Molecular Weight	393.85
Physical State	Solid
Melting Point	≥700°C (measured)
Boiling Point	No data ²
Vapor Pressure	4.64×10 ⁻¹⁴ mm Hg at 25°C (estimated)
Water Solubility	32 mg/L at 20°C (measured)
Dissociation Constant (pK _a)	Not Applicable
Henry's Law Constant	8.69×10 ⁻¹⁵ atm-m ³ /mole (estimated)
Log K _{ow}	3.07 at 20.5°C (measured)

¹R.T. Vanderbilt Company, Inc. November 3, 2006. Robust and Revised Robust Summary for 2H-Benzimidazole-2-thione, 1,3-dihydro-, 4 (or 5)-methyl-, zinc salt (2:1). <http://www.epa.gov/chemrtk/pubs/summaries/zincmerc/c14230tc.htm>.

²An estimated value of 605°C was determined using EPI estimation software; however, this value is below the reported melting point and is unlikely to be accurate.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

CASRN 61617-00-3, previously an HPV chemical, had an aggregated production and/or import volume in the United States between 10,000 and 500,000 pounds during calendar year 2005.

There was no use information reported in the IUR submissions. The HPV submission states that it is used as an antioxidant synergist in natural and synthetic rubber.

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. CASRN 61617-00-3 is expected to have moderate mobility in soil. Volatilization is considered low based on its Henry's Law constant. The rate of hydrolysis is considered negligible. The rate of atmospheric photo-oxidation is considered rapid; however, this compound is unlikely to exist in the vapor phase in the atmosphere. It is expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of 2H-Benzimidazole-2-thione, 1,3-dihydro-4 (or 5)-methyl-, zinc salt (2:1)¹	
Property	Value
CASRN	61617-00-3
Photodegradation Half-life	1.2 hours (estimated)
Hydrolysis Half-life	Stable
Biodegradation	27% in 28 days (not readily biodegradable)
Bioconcentration	BCF = 45.7 (estimated)
Log K _{oc}	2.67 (estimated)
Fugacity (Level III Model)	Air = 0.00222% Water = 17.5% Soil = 82.1% Sediment = 0.412%
Persistence ²	P2 (moderate)
Bioaccumulation ²	B1 (low)

¹R.T. Vanderbilt Company, Inc. November 3, 2006. Robust and Revised Robust Summary for 2H-Benzimidazole-2-thione, 1,3-dihydro-, 4 (or 5)-methyl-, zinc salt (2:1).
<http://www.epa.gov/chemrtk/pubs/summaries/zincmerc/c14230tc.htm>.

²Federal 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

Sherman-Wistar rats (5 males/dose) were administered CASRN 61617-00-3 via corn oil (25% w/v) gavage at 0, 0.5, 1.0, 2.0, 4.0 or 8.0 mL/kg-bw and observed for 14 days. Mortality occurred at the highest dose.

LD₅₀ = 800 mg/kg-bw

Acute Inhalation Toxicity

Sprague-Dawley rats (5/dose; sex ratio not provided) were exposed (nose-only) to CASRN 61617-00-3 at measured aerosol concentrations of 0 or 2.12 mg/L for 4 hours. There were no mortalities.

LC₅₀ > 2.12 mg/L

Acute Dermal Toxicity

Sprague-Dawley rats (5/sex/dose) were administered CASRN 61617-00-3 via the dermal route at 2000 mg/kg-bw for 24 hours under semi-occluded conditions. There were no mortalities.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

In a combined, repeated-dose reproductive/developmental toxicity study, Sprague-Dawley rats (10/sex/dose) were administered CASRN 61617-00-3 orally in the diet at 1000, 2750 or 7500 ppm (~ 50, 138 or 375 mg/kg-bw/day). Treatment began two weeks prior to mating and continued throughout gestation, up to postnatal day 5 (~ 47 days). Doses were reduced to 900, 2500 or 6750 ppm on day 29 (~ 45, 125 or 338 mg/kg-bw/day) and on day 33, the high-dose group was further reduced to 5500 ppm (~ 275 mg/kg-bw/day) due to observed toxicity (type not specified in robust summary). Signs of systemic toxicity in adults included dose-related decreases in body weight gain and food consumption in males and females from all treatment groups (statistical significance not specified). Blood chemistry and hematological parameters of selected animals (5/sex/dose) were evaluated at a single time-point (day 14) prior to mating. Increases in serum cholesterol, plasma creatinine, phosphorous and chloride levels were reported at the highest dose. Hematology was unremarkable. Reductions in spleen and thymus weights (absolute/relative not specified) were reported in high-dose males. An increase in relative liver weight and histopathology of the liver and thyroid glands were also reported in high-dose males. The robust summary reported similar effects in the mid- and low-dose groups, with the exception of relative liver weight changes, which were not reported at the lowest dose. No organ weight or histopathological changes were reported in females; however it should be noted that one of two pregnant females in the high- dose group and eight of ten pregnant females in the mid-dose group were sacrificed *in extremis* during late gestation due to a possible impairment of parturition and therefore may not have been evaluated. No other effects were reported in the robust summary. Statistical significance was not provided for any endpoint.

LOAEL (systemic toxicity) = 45-50 mg/kg-bw/day (based on decreased body weight gain)

NOAEL= Not established

Reproductive/Developmental Toxicity

In the combined, repeated-dose reproductive/developmental toxicity study described above, the corpora lutea and uterine implantation sites were counted in all pregnant females at necropsy. The following parameters were calculated: pre-coital interval, mating index, pregnancy index, gestation length, parturition index, live birth index, viability index and sex ratio. A marked reduction in the number of mating pairs was noted in treated animals. Only 4/10 females in the

high dose group showed evidence of mating and of those, only 2 became pregnant. Females with no evidence of mating generally showed a lack of estrous cyclicity. An increase in the pre-coital interval was also observed at this dose. One high-dose female and eight mid-dose females were sacrificed in extremis during late gestation due to a possible impairment of parturition. The robust summary did not report any evidence of prenatal developmental toxicity in these animals; however it was unclear what examinations, if any, were conducted. An increase in gestation length was observed at all doses. Reproductive organs from parental animals (testes, epididymides, ovaries) were weighed and evaluated for histological abnormalities. No evidence of toxicity to male or female reproductive organs was reported. Live offspring were evaluated on postnatal days 1 and 4 for changes in sex ratio, body weight and litter number. No significant clinical or macroscopic findings were noted; however the high incidence of mortality in the dams (9) and the limited number of viable offspring in the mid - and high-dose groups precluded meaningful evaluation, therefore effect levels for developmental toxicity could not be established.

LOAEL (female reproductive toxicity) = 45-50 mg/kg-bw/day (based on increased gestation length)

NOAEL = Not established

NOAEL (male reproductive toxicity) = 275-338 mg/kg-bw/day (based on no effects observed at the highest dose tested)

NOAEL/LOAEL (developmental toxicity) = Not established

Genetic Toxicity – Gene Mutation

In vitro

Salmonella typhimurium strains (TA1535, TA1537, TA102, TA98 and TA100) were exposed to CASRN 61617-00-3 at 0, 50, 150, 500, 1500 or 5000 µg/plate. The cytotoxic concentration was 5000 µg/plate (with and without metabolic activation). Positive controls were tested concurrently, but these data were not provided. A slight decrease in the frequency of revertant colonies was observed at the highest concentration.

CASRN 61617-00-3 was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Human lymphocytes were exposed to CASRN 61617-00-3 at concentrations of 0, 31.25, 62.5, 125, 250, 375 or 500 mg/mL for 4 hours (with and without metabolic activation) and then examined for chromosomal aberrations. No mutagenic effects were reported following a 20-hour expression period. Positive and negative controls responded appropriately.

CASRN 61617-00-3 did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

Rabbits (6; strain; sex not specified) were exposed to 0.5 g of CASRN 61617-00-3 via the dermal route for 24 hours under semi-occluded conditions. After exposure, treated areas of intact or abraded skin were examined for 48 hours. All irritation scores were zero.

CASRN 61617-00-3 was not irritating to rabbit skin in this study.

Eye Irritation

Rabbits (6; strain/sex not specified) were exposed to 0.1 g of 2H-benzimidazole-2-thione, 1,3-dihydro-4 (or 5)-methyl-, zinc salt (2:1) in the conjunctival sac of the right eye; the left eye served as a control. Eyes were not washed. After exposure, eyes were examined for 7 days. All signs of irritation had subsided by the second day of exposure. The average Draize score was 0.3 on a scale of 0 – 110.

CASRN 61617-00-3 was not irritating to the rabbit eye in this study.

Conclusion: The acute oral, inhalation and dermal toxicity of CASRN 61617-00-3 is low in rats. It is not irritating to rabbit eyes or skin. A combined, repeated-dose/reproductive/developmental toxicity study showed both systemic and reproductive toxicity in orally exposed rats. Significant decrements in body weight gain and organ weights were observed at all levels of treatment, including the lowest dose tested (45-50 mg/kg-bw/day). Female reproductive toxicity, as evidenced by increased gestation length, occurred at all doses. The NOAEL for male reproductive toxicity was ~ 275-338 mg/kg-bw/day, based on no effects at the highest dose. Developmental toxicity could not be evaluated due to a high incidence of mortality in the dams. This chemical did not induce bacterial gene mutations *in vivo* or chromosomal aberrations in mammalian cells *in vitro*.

4. Hazards to the Environment

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss*) were exposed CASRN 61617-00-3 at nominal concentrations of 0.67, 1.2, 2.1, 3.8, 6.7 or 12 mg/L under static renewal conditions for 96 hours. Measured concentrations ranged from 87 to 120% of nominal concentrations.

96-h LC₅₀ = 5.6 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to CASRN 61617-00-3 at nominal concentrations of 0.08, 0.14, 0.25, 0.45, 0.8, 1.4, 2.5, 4.5 or 8 mg/L under static conditions for 48 hours. Mean measured concentrations were in excess of 120% of the nominal concentrations. Although specific measurements at each concentration were not provided, the EC₅₀ value provided is based on measured concentrations.

48-h EC₅₀ = 1.4 mg/L

Toxicity to Aquatic Plants

Green algae (*Scenedesmus subspicatus*) were exposed to CASRN 61617-00-3 at nominal concentrations of 0.69, 1.38, 2.75, 5.5 or 11 mg/L under static conditions for 72 hours. Measured concentrations ranged from 85 to 96% of nominal concentrations.

72H EC₅₀ (biomass) = 6.6 mg/L

72H EC₅₀ (growth) = 10 mg/L

Conclusion: The 96-hour LC₅₀ of CASRN 61617-00-3 to fish is 5.6 mg/L. The 48-hour EC₅₀ of CASRN 61617-00-3 to aquatic invertebrates is 1.4 mg/L, and the 96-hour EC₅₀ to aquatic plants is 6.6 mg/L.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL 2H-Benzimidazole-2-thione, 1,3-dihydro-, 4 (or 5)-methyl-, zinc salt (2:1) (CASRN 61617-00-3)
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	800
Acute Inhalation Toxicity LC₅₀ (mg/L)	> 2.12
Acute Dermal Toxicity LD₅₀ (mg/kg-bw)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	LOAEL = 45 – 50 NOAEL = Not established
Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	
Reproductive (female)	LOAEL = 45-50 NOAEL = Not established
(male)	NOAEL = 275-338 (hdt)
Developmental	NOAEL = Not established
Genetic Toxicity – Gene Mutation <i>in vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>in vitro</i>	Negative
Additional Information – Skin Irritation Eye Irritation	Not irritating Not irritating
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	5.6
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	1.4

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL 2H-Benzimidazole-2-thione, 1,3-dihydro-, 4 (or 5)-methyl-, zinc salt (2:1) (CASRN 61617-00-3)
Aquatic Plants 72H EC₅₀ (mg/L) (growth) (biomass)	10 6.6

Measured data in bold text; hdt = highest dose tested