

SCREENING-LEVEL HAZARD CHARACTERIZATION

Propanoic Acid, 2-hydroxy-, compound with 3-[2-(dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3-phenylene)bis[carbamate] (1:1) (CASRN 68227-46-3)

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

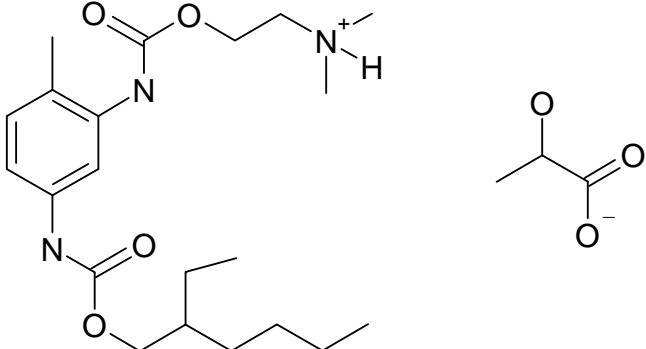
¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

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>.

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>68227-46-3</p>
<p>Chemical Abstract Index Name</p>	<p>Propanoic acid, 2-hydroxy-, compd. with 2-ethylhexyl N-[3-[[[2-(dimethylamino)ethoxy]carbonyl]amino]-4-methylphenyl]carbamate (1:1)</p>
<p>Structural Formula</p>	

Summary

Propanoic acid (CASRN 68227-46-3) is a solid that can be dispersed in water and has negligible vapor pressure in its pure form. It is expected to have low mobility in soil. Volatilization of this chemical is considered low since this is an ionic compound. The rate of hydrolysis for the bis[carbamate] moiety of the compound is considered moderate to rapid under alkaline conditions and moderate at neutral pH. The rate of atmospheric photooxidation is considered rapid; however, this compound is not expected to exist in the vapor phase in the ambient atmosphere. This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The acute oral toxicity of this chemical in rats is low. In an oral repeated-dose study, rats exhibited a decrease in body weight gain at 7.5 mg/kg-bw/day; the NOAEL was 2.0 mg/kg-bw/day. An oral combined reproductive/developmental toxicity screening test in rats showed decreased pup body weight at 7.5 mg/kg-bw/day; the NOAEL was 2.0 mg/kg-bw/day for developmental (pre- and limited postnatal) toxicity. In the same study, there was a decrease in the number of implants at 7.5 mg/kg-bw/day; the NOAEL for female reproductive toxicity was 2.0 mg/kg-bw/day. Male rats exhibited a decrease in testes weights with seminiferous epithelial degeneration at 50 mg/kg-bw/day; the NOAEL for male reproductive toxicity was 7.5 mg/kg-bw/day. This chemical did not induce gene mutations nor induce chromosomal aberrations *in vitro*.

The estimate 96-hour LC₅₀ of CASRN 68227-46-3 to fish is 2.5 mg/L, the measured 48-hour EC₅₀ to aquatic invertebrates is 4.2 mg/L, and the measured 96-hour EC₅₀ to aquatic plants is 0.07 mg/L (biomass). The 21-day NOEC for daphnia is 0.365 mg/L

No data gaps were identified under the HPV Challenge Program.

The sponsor, PPG Industries, Inc., submitted a Test Plan and Robust Summaries to EPA for Propanoic Acid, 2-hydroxy-, compound with 3-[2-(dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3-phenylene)bis[carbamate] (1:1)(CASRN 68227-46-3; 9th CA Index name: propanoic acid, 2-hydroxy-, compd. with 2-ethylhexyl [[3-[[2-(dimethylamino)ethoxy] carbonyl]amino]-4-methylphenyl]carbamate (1:1) on June 28, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 19, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/prop2hyd/c13863tc.htm>). EPA comments on the submission were posted to the website on May 2, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on February 14, 2003, June 30, 2003 and December 17, 2004, which were posted to the ChemRTK website on February 28, 2003, July 24, 2003 and January 13, 2005, respectively.

1. Chemical Identity

1.1 Identification and Purity

The following description is taken from the final Test Plan (2005). CASRN 68227-46-3 is produced commercially as 75% solids [Propanoic acid, 2-hydroxy-, compound with 3-[2-(dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3-phenylene)bis[carbamate] (1:1)] in the presence of Methyl Isobutyl Ketone (MIBK) solvent (2-3%), 2-butoxy ethanol (6-7%), and water (15-17%). At this concentration in this solvent system, the test substance is a clear, light yellow, liquid.

1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 68227-46-3 are summarized in Table 1.

Table 1. Physical-Chemical Properties of Propanoic Acid, 2-hydroxy-, compound with 3-[2-(dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3-phenylene)bis[carbamate] (1:1)¹	
Property	Value
CASRN	68227-46-3
Molecular Weight	483.61
Physical State	Solid (pure material); Clear, light yellow, liquid (commercial product)
Melting Point	164°C (estimated) ²
Boiling Point	444°C (estimated) ²
Vapor Pressure	2.6×10 ⁻⁸ mm Hg (estimated)
Water Solubility	281,000 mg/L at 20°C (measured for dispersion)
Dissociation Constant (pK _a)	No data
Henry's Law Constant	1.6×10 ⁻¹² atm-m ³ /mole (estimated) ²
Log K _{ow}	4.38 (estimated)

¹PPG Industries. December 22, 2004. Revised Robust Summary and Test Plan for Propanoic Acid, 2-Hydroxy-, Compound with 3-[2-(Dimethylamino)ethyl] 1-(2-Ethylhexyl) (4-Methyl-1,3-phenylene)bis[carbamate] (1:1). <http://www.epa.gov/chemrtk/pubs/summaries/prop2hyd/c13863tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

2. General Information on Exposure

2.1 Production Volume and Use Pattern

This chemical has an aggregated production volume in the United States of 500,000 to 1 million pounds.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates in the manufacture of paint and coatings. The HPV submissions for this chemical state it is primarily used as an isolated intermediate to subsequently produce a resin that is a component of paint. However, this compound is completely consumed during the preparation of the OEM (Original Equipment Manufacture) coating therefore, this chemical no longer exists in the final paint/coating product.

2.2 Environmental Fate Characterization

No quantitative information is available on releases of this chemical to the environment. The environmental fate properties are provided in Table 2. CASRN 68227-46-3 is expected to have low mobility in soil. The rate of volatilization from water and moist soil is considered low since this is an ionic compound. The test material did not pass a modified Sturm (OECD 301B) test and was deemed not readily biodegradable. However, the rate of hydrolysis for the bis[carbamate] moiety of the compound is considered moderate to rapid under alkaline

conditions, and moderate at neutral pH, based on modeling (EPI Suite HYDROWIN). This chemical is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of Propanoic Acid, 2-hydroxy-, compound with 3-[2-(dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3-phenylene)bis[carbamate] (1:1)¹	
Property	Value
Photodegradation Half-life	1.1 hours (estimated)
Hydrolysis Half-life	14 hours at pH 8 (estimated); 6 days at pH 7
Biodegradation	10.6% after 28 days (not readily biodegradable)
Bioconcentration	BCF = 472 (estimated) ²
Log K _{oc}	5 (estimated) ²
Fugacity (Level III Model)	Air = 0.0032% Water = 14.4% Soil = 79.1% Sediment = 6.52%
Persistence ³	P1 (low)
Bioaccumulation ³	B1 (low)

¹PPG Industries. December 22, 2004. Revised Robust Summary and Test Plan for Propanoic Acid, 2-Hydroxy-, Compound with 3-[2-(Dimethylamino)ethyl] 1-(2-Ethylhexyl) (4-Methyl-1,3-phenylene)bis[carbamate] (1:1). <http://www.epa.gov/chemrtk/pubs/summaries/prop2hyd/c13863tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

³Federal 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 Effects

Acute Oral Toxicity

Sprague-Dawley rats (15 females) were administered CASRN 68227-46-3 via oral gavage at 175 (one rat), 550 (five rats) or 2000 mg/kg-bw (nine rats) and observed for 15 days. Individual animals were treated 2 days apart, with dose selections based on survival of animals treated previously. Mortality occurred only at 2000 mg/kg-bw. Five/nine animals died on days two and three. Clinical signs of toxicity were reported at 500 and 2000 mg/kg-bw.

LD₅₀ = 2000 mg/kg-bw

Repeated-Dose Toxicity

Sprague-Dawley rats (5/sex/dose) were administered CASRN 68227-46-3 via oral gavage at 0, 2, 7.5 or 30 mg/kg-bw/day for 28 days. Rats treated with 7.5 mg/kg-bw/day exhibited decreased body weight gain; and at 30 mg/kg-bw/day decreased body weight through day 7 and testes and sperm effects. Treatment did not affect neurotoxicity observations, motor activity, functional observations, water consumption, hematology, clinical chemistry, urinalysis or organ weights.

Histology examination revealed tubular atrophy of the testes in 3/5 high-dose males and 1/5 low-dose males. Sloughing of spermatogenic cells was observed in the epididymides of 2/5 high-dose males and 1/5 low-dose males (the latter also had spermatid retention in the testes). Similar histopathology was not noted in the testes or epididymides of males at 7.5 mg/kg-bw/day. Organ weight data were reported to confirm the histology, but details were not given. No other histopathology findings were noted.

LOAEL = 7.5 mg/kg-bw/day (based on decreased absolute body weight in both sexes)

NOAEL = 2.0 mg/kg-bw/day

Reproductive/Developmental Toxicity

In a combined reproduction/developmental toxicity screening test, Sprague-Dawley rats (10/sex/dose) were administered CASRN 68227-46-3 via oral gavage at 0, 2.0, 7.5 or 50 mg/kg-bw/day. Males were treated for 4 weeks (2 weeks pre-mating and 2 weeks cohabitation), while females were treated for 2 weeks pre-mating, throughout mating and gestation until lactation day 4. Necropsy was performed on all adults. Testes and epididymal weights were recorded. Histopathology was performed on the testes and epididymides of all males and on the ovaries of control and high-dose females. Piloerection and excessive salivation were observed in most animals treated at 50 mg/kg-bw/day; three animals exposed to 7.5 mg/kg-bw/day exhibited piloerection. Six of ten parental males exposed to 50 mg/kg-bw/day had decreased testes weights with seminiferous epithelial degeneration and mild interstitial hyperplasia. The same animals had mild to marked oligospermia and moderate to marked sloughing of spermatogenic cells in the epididymides. Mean epididymides weights were also reduced at the high dose. Two of the high-dose males failed to mate. There were no effects on testes or epididymides in males at 2.0 or 7.5 mg/kg-bw/day. At the high dose, gestation length was slightly increased, number of implants was decreased and pup mortality was markedly increased. At 7.5 mg/kg-bw/day, the number of implants was decreased and the mean litter and pup weights were decreased. Significance and magnitude not stated.

LOAEL (reproductive toxicity) = 7.5 mg/kg-bw/day (based on decreased number of implants)

NOAEL (reproductive toxicity) = 2 mg/kg-bw/day

LOAEL (developmental toxicity) = 7.5 mg/kg-bw/day (based on decreased pup weights)

NOAEL (developmental toxicity) = 2 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

Salmonella typhimurium strains TA98, TA100, TA 1535 and TA1537 and *Escherichia coli* strain WP2uvrA were exposed to CASRN 68227-46-3 in the presence and absence of metabolic activation in a direct plate assay and a pre-incubation assay. In the direct plate assay, concentrations of 1.0, 3.3, 10, 33.3, 100 and 333 µg/plate were used. In the pre-incubation assay, the same concentrations as the direct phase assay were used with metabolic activation and concentrations of 0.5, 1.7, 5, 17, 50 and 167 µg/plate were used without metabolic activation. Positive controls were tested concurrently, but control responses were not reported. In *Salmonella* strains, cytotoxicity was evident at 333 µg/plate in the presence of metabolic activation in both assays and in the absence of metabolic activation in the direct plate assay. In the pre-incubation assay without metabolic activation, cytotoxicity was observed in *Salmonella*

at 50 and 167 µg/plate. In *E. coli*, cytotoxicity was observed at 333 µg/plate without metabolic activation in the direct plate assay and at 167 µg/plate without metabolic activation in the pre-incubation assay. Cytotoxicity was not evident in *E. coli* tested in the presence of metabolic activation. No mutagenic activity was observed in any strain in either assay.

2-Hydroxypropanoic acid compound with 3-2-(dimethylamino)ethyl] 1-(2-ethylhexyl)(4-methyl-1,3-phenylene)bis[carbamate] (1:1) was not mutagenic in these assays.

Genetic Toxicity – Chromosomal Aberrations

In vitro

Chinese hamster ovary (CHO) cells were exposed to CASRN 68227-46-3 at concentrations of 5 – 40 µg/mL in the presence of metabolic activation and 5 – 80 µg/mL in the absence of metabolic activation in one test. In a second test, cells were exposed to concentrations of 10 – 30 µg/mL in the presence of metabolic activation and 5 – 25 µg/mL in the absence of metabolic activation. The vehicle in all experiments was dimethyl sulfoxide. Cells were exposed for 6 hours or 22 hours in the presence and absence of metabolic activation, respectively. Chromosomal aberrations were scored and polyploidy was assessed. Positive controls were tested concurrently, but outcome of their testing was not reported. In test 1, cytotoxicity was observed at 30 – 40 µg/mL and at 20 – 80 µg/mL in the presence and absence of metabolic activation, respectively. In test 2, cytotoxicity was evident at 22.5 – 30 µg/mL and at 10 – 25 µg/mL in the presence and absence of metabolic activation, respectively. The test material did not induce chromosomal aberrations under any of the test conditions. Slight increases in polyploidy were observed, but the number of affected cells was small, no dose-response curve was observed and the concentrations associated with this endpoint were near cytotoxic concentrations.

2-Hydroxypropanoic acid compound with 3-2-(dimethylamino)ethyl] 1-(2-ethylhexyl)(4-methyl 1,3-phenylene)bis[carbamate] (1:1) did not induce chromosomal aberrations in these assays.

Conclusion: The acute oral toxicity of this chemical in rats is low. In an oral repeated-dose study, rats exhibited a decrease in body weight gain at 7.5 mg/kg-bw/day; the NOAEL was 2.0 mg/kg-bw/day. An oral combined reproductive/developmental toxicity screening test in rats showed decreased pup body weight at 7.5 mg/kg-bw/day; the NOAEL was 2.0 mg/kg-bw/day for developmental (pre- and limited postnatal) toxicity. In the same study, there was a decrease in the number of implants at 7.5 mg/kg-bw/day; the NOAEL for female reproductive toxicity was 2.0 mg/kg-bw/day. Male rats exhibited a decrease in testes weights with seminiferous epithelial degeneration at 50 mg/kg-bw/day; the NOAEL for male reproductive toxicity was 7.5 mg/kg-bw/day. This chemical did not induce gene mutations nor induce chromosomal aberrations *in vitro*.

4. Hazard to the Environmental

Acute Toxicity to Fish

A 96-hr LC₅₀ for fish was estimated using ECOSAR v1.00a to support evaluation of the acute toxicity to fish. The acute fish toxicity value estimated is consistent with the results obtained in submitted acute daphnia and algal tests.

96-h LC₅₀ = 2.5 mg/L (estimated)

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to CASRN 68227-46-3 at mean measured concentrations of 0, 0.36, 0.79, 1.72, 3.77 or 8.88 mg/L under static conditions for 48 hours. At 8.88 mg/L, 20% immobilization was observed at 24 hours and all *Daphnia* were immobilized at 48 hours. At 3.77 mg/L, 20% immobilization occurred after 48 hours.

48-h EC₅₀ = 4.2 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to CASRN 68227-46-3 at nominal concentrations of 0, 0.03, 0.06, 0.14, 0.31 or 0.67 mg/L for 96 hours. Measured concentrations were 0, 0.02, 0.03, 0.11, 0.27 and 0.61 mg/L (geometric mean of initial and 96-hour measured concentrations). The exposure period was followed by a re-inoculation phase of 9 days. The re-inoculation experiment indicated the effect of the test material to algal cells was phytostatic, not phytotoxic, as no significant differences were found in growth rate after 9 days in fresh untreated medium. However, the cells in the two test material treatments formed clumps visible to the naked eye, compared to the controls where growth was normal.

96-h EC₅₀ (biomass) = 0.07 mg/L

96-h EC₅₀ (growth) = 0.16 mg/L

Chronic Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to CASRN 68227-46-3 at nominal concentrations of 0, 0.05, 0.157, 0.498, 1.566 or 4.984 mg/L under semi-static conditions for 21 days to evaluate effects on reproduction rate. Time-weighted mean measured concentrations were 0, 0.015, 0.083, 0.365, 1.369 or 4.653 mg/L. Groups exposed to 1.369 and 4.653 mg/L died, and no reproduction data were available. Reproduction rate was not affected in surviving groups. The 21-day EC₅₀ was estimated to be 0.501 mg/L (geometric mean average of the 21-day NOEC and the calculated 7-day EC₅₀).

7-d EC₅₀ = 0.69 mg/L

21-d NOEC = 0.365 mg/L

21-d EC₅₀ = 0.501 mg/L

Conclusion: The estimate 96-hour LC₅₀ of CASRN 68227-46-3 to fish is 2.5 mg/L, the measured 48-hour EC₅₀ to aquatic invertebrates is 4.2 mg/L, and the measured 96-hour EC₅₀ to aquatic plants is 0.07 mg/L (biomass). The 21-day NOEC for daphnia is 0.365 mg/L.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Propanoic Acid, 2-hydroxy-, compound with 3-[2- (dimethylamino)ethyl] 1-(2-ethylhexyl) (4-methyl-1,3- phenylene)bis[carbamate] (1:1) (CASRN 68227-46-3)
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	LOAEL = 7.5 (28-d) NOAEL = 2.0
Reproductive /Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day)	
Toxicity Toxicity	Reproductive Developmental
	LOAEL = 7.5 NOAEL = 2.0 LOAEL= 7.5 LOAEL= 2.0
Genetic Toxicity – Gene Mutation <i>In vitro</i>	Negative
Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i>	Negative
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC₅₀ (mg/L)	3.2 (estimated)
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	4.2
Aquatic Plants 72-h EC₅₀ (mg/L)	
(growth) (biomass)	0.16 (96-h) 0.07 (96-h)
Chronic Toxicity to Invertebrates 21-day EC₅₀ (mg/L)	0.501