

SCREENING-LEVEL HAZARD CHARACTERIZATION Carbamate Hydrochloride (CASRN 65086-85-3)

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.

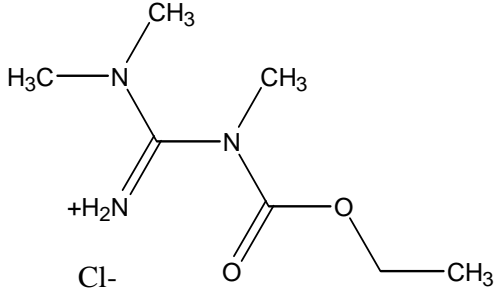
OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental 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 provide information previously not readily available to the public.

<p>Chemical Abstract Service Registry Number (CASRN)</p>	<p>65086-85-3</p>
<p>Chemical Abstract Index Name</p>	<p>Carbamic acid, N-(aminoiminomethyl)-N-methyl-, dimethyl deriv., ethyl ester, hydrochloride (1:1)</p>
<p>Structural Formula</p>	
<p style="text-align: center;">Summary</p> <p>This chemical is a solid with high water solubility and negligible vapor pressure. It is expected to have moderate mobility in soil. Carbamate hydrochloride underwent 2% biodegradation over the course of a 21-day incubation period using an activated sludge inoculum and the modified Sturm test (OECD 301B). Volatilization of carbamate hydrochloride is negligible since this substance is a salt. The rate of hydrolysis is considered negligible to slow. The rate of atmospheric photooxidation is considered moderate. Carbamate hydrochloride is expected to have moderate persistence (P2), due to the presence of the carbamate and ester groups, and low bioaccumulation potential (B1).</p> <p>Acute oral toxicity of this chemical in rats is low. An oral combined repeated-dose/reproductive/developmental screening study in rats showed no adverse effects; the NOAEL for systemic toxicity was 1000 mg/kg-bw/day. In the same study, there was no maternal, reproductive or developmental toxicity and the respective NOAELs were 1000 mg/kg-bw/day for each. Carbamate hydrochloride did not induce gene mutations or chromosomal aberrations when tested <i>in vitro</i>.</p> <p>The acute hazard of this chemical to fish, aquatic invertebrates and aquatic plants is >100 mg/L.</p> <p>No data gaps were identified for the HPV Challenge Program.</p>	

The sponsor, E.I. du Pont de Nemours & Company, submitted a Test Plan and Robust Summaries to EPA for carbamate hydrochloride (CASRN 65086-85-3; CA index name: carbamic acid, N-(aminoiminomethyl)-N-methyl-, dimethyl deriv., ethyl ester, hydrochloride (1:1)) on December 17, 2002. EPA posted the submission on the ChemRTK HPV Challenge website on June 26, 2003 (<http://www.epa.gov/chemrtk/pubs/summaries/carbhydr/c14499tc.htm>). EPA comments on the original submission were posted to the website on November 5, 2003. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on June 14, 2006 and October 26, 2006 which were posted to the ChemRTK website on June 26, 2008 and February 1, 2007, respectively.

The sponsor proposed reduced health effects testing, claiming that carbamate hydrochloride is a closed-system intermediate (CSI) under the HPV Challenge Program. EPA's evaluation of the original and revised/updated information indicated that the chemical does not meet the criteria to fully support the CSI claim for this chemical and that the chemical does not qualify for reduced testing. Therefore, the sponsor conducted and submitted data for the combined repeated-dose/reproductive/developmental toxicity screening test to address these endpoints for the purposes of the HPV Challenge Program.

The sponsor's original submission noted the CASRN as 65206-90-8. However, the resubmission listed the CASRN as 65086-85-3. CASRN 65086-85-3 is associated with a more specifically-described name and structure. It is assumed that these two CASRNs refer to the same chemical substance.

1. Chemical Identity

1.1 Identification and Purity

As stated in the sponsor's 2006 resubmitted documents, carbamate hydrochloride is shipped by the manufacturer as a formulated mixture which contains carbamate hydrochloride (35–51%), water (34–40%), dimethylamine hydrochloride (5–14%), and trimethylguanidine hydrochloride (1–5%).

1.2 Physical-Chemical Properties

The physical-chemical properties of carbamate hydrochloride are summarized in Table 1. Physical/chemical properties for the formulated material were provided; however, no measured properties were provided for the carbamate hydrochloride salt.

Carbamate hydrochloride is a solid with high water solubility and negligible vapor pressure.

Table 1. Physical-Chemical Properties of Carbamic acid, N-(aminoiminomethyl)-N-methyl-, dimethyl deriv., ethyl ester, hydrochloride (1:1)] (Carbamate Hydrochloride)¹	
Property	Value
CASRN	65206-90-8
Molecular Weight	174.2
Physical State	Solid
Melting Point	-49.4°C (measured for commercial product) ² Salt (No data)
Boiling Point	105°C (measured for commercial product) ² Salt (No data)
Vapor Pressure	18 mm Hg at 21°C (measured for commercial product) ² ; Negligible (salt)
Water Solubility	>50% soluble; Miscible
Dissociation Constant (pK _a)	9.85 (estimated for the free base) ³
Henry's Law Constant	Negligible (salt)
Log K _{ow}	-3.96 (estimated) (salt)

¹E.I. du Pont de Nemours, Inc. July 3, 2006. Revised Robust Summary and Test Plan for Carbamate Hydrochloride. <http://www.epa.gov/chemrtk/pubs/summaries/carbhydr/c14499tc.htm>.

²Measured values for these endpoints are for commercial product which is a formulated mixture and likely reflect values for water since the commercial product is composed of approximately 34–40% water.

³SPARC. 2008. Online pK_a and Property Calculator v. 4.2.1405-s4.2.1408. Accessed October 27, 2008. <http://ibmlc2.chem.uga.edu/sparc/>.

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 in calendar year 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include processing as an intermediate in pesticide and other agricultural chemical manufacturing. The HPV submission for the chemical indicates use as an isolated intermediate.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties of carbamate hydrochloride are provided in Table 2. Carbamate hydrochloride is expected to have moderate mobility in soil. Carbamate hydrochloride underwent 2% biodegradation over the course of a 21-day incubation period using an activated sludge inoculum and the modified Sturm test (OECD 301B). Volatilization of carbamate hydrochloride is negligible since this substance is a salt. The rate of hydrolysis is

considered negligible to slow. The rate of atmospheric photooxidation is considered moderate. Carbamate hydrochloride is expected to have moderate persistence (P2), due to the presence of the carbamate and ester groups, and low bioaccumulation potential (B1).

Property	Value
Photodegradation Half-life	5.01 hours (estimated)
Hydrolysis Half-life	Stable at pH 7; 18.6 days at pH 9 and 20°C
Biodegradation	2% after 21 days (not readily biodegradable)
Bioconcentration	BCF = 3.16 (estimated)
Log K _{oc}	2.1 (estimated) ²
Fugacity (Level III Model)	Air = 0.005% Water = 45% Soil = 54.9% Sediment = 0.08%
Persistence ³	P2 (moderate)
Bioaccumulation ³	B1 (low)

¹E.I. du Pont de Nemours, Inc. July 3, 2006. Revised Robust Summary and Test Plan for Carbamate Hydrochloride. <http://www.epa.gov/chemrtk/pubs/summaries/carbhydr/c14499tc.htm>.

²U.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>.

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

A summary of health effects data submitted for SIDS endpoints is provided in Table 3.

Acute Oral Toxicity

Male Sprague-Dawley rats (1/dose) were administered a formulated product containing 42% carbamate hydrochloride via gavage at 670, 1000, 1500, 2250, 3400, 5000, 7500 or 11,000 mg/kg-bw and observed for 14 days. No mortality was observed.

LD₅₀ > 11,000 mg/kg-bw

Repeated-Dose Toxicity

In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/dose) were administered carbamate hydrochloride via oral gavage at 0, 50, 250 or 1000 mg/kg-bw/day for 14 days prior to mating, during mating and through gestation until lactation day 3; dams were allowed to deliver and rear their offspring until postpartum day 4. No mortality or clinical signs of toxicity were observed. There were no treatment-related effects on body weight, functional observation battery and motor activity, food consumption, hematology, gross pathology or histopathology in P1 animals. In high-dose group adult females,

a small increase in liver weight (absolute/relative not specified), a mild increase in triglycerides and a moderate increase in total bile acids were reported. Limited information on this study in the robust summary makes definitive conclusions difficult. No other effects were reported.

NOAEL (parental systemic toxicity) = 1000 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

Reproductive Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, there were no treatment-related effects on reproductive organ weights/histopathology, mating, fertility, gestation length, corpora lutea, number of implantation sites or implantation efficiency in the P1 generation.

NOAEL (reproductive toxicity) = 1000 mg/kg-bw/day (highest dose tested)

Developmental Toxicity

In the combined repeated-dose/reproductive/developmental toxicity screening test described previously, there were no clinical observations or treatment-related effects on mean pup weight, number of pups born, number born alive, number alive on lactation day 4, sex ratio, survival indices or gross pathology of pups.

NOAEL (maternal toxicity) = 1000 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

NOAEL (developmental toxicity) = 1000 mg/kg-bw/day (highest dose tested)

Genetic Toxicity – Gene Mutations

Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA were exposed to carbamate hydrochloride at concentrations of 0, 333, 667, 1000, 3333 or 5000 µg/plate in the presence or absence of metabolic activation. Positive controls produced appropriate responses. Cytotoxicity occurred in a single activated TA98 replicate at 667 µg/plate.

Carbamate hydrochloride was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

Human peripheral blood lymphocytes (HPBL) were exposed to carbamate hydrochloride at concentrations of 0, 210, 1048 or 2097 µg/mL for 4 and 20 hours in the absence or 4 hours in the presence of metabolic activation. Positive controls produced an appropriate response. No substantial toxicity was observed at any dose level.

Carbamate hydrochloride did not induce chromosomal aberrations in this assay.

Conclusion: Acute oral toxicity of this chemical in rats is low. An oral combined repeated-dose/reproductive/developmental screening study in rats showed no adverse effects; the NOAEL for systemic toxicity was 1000 mg/kg-bw/day. In the same study, there was no maternal, reproductive or developmental toxicity and the respective NOAELs were 1000 mg/kg-bw/day

for each. Carbamate hydrochloride did not induce gene mutations or chromosomal aberrations when tested *in vitro*.

4. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 3.

Acute Toxicity to Fish

Rainbow trout (*Oncorhynchus mykiss*) were exposed to carbamate hydrochloride at measured concentrations of 0 or 114 mg/L, in a limit test, under static conditions for 96 hours. No mortality or sublethal effects were seen at either concentration.

96-h LC₅₀ > 114 mg/L

Acute Toxicity to Aquatic Invertebrates

Water fleas (*Daphnia magna*) were exposed to carbamate hydrochloride at measured concentrations of 0, 7.6, 14.9, 29.7, 59.6 or 119 mg/L under static conditions for 48 hours. No sublethal effects were seen in any test group. Immobilization occurred at the highest test concentration.

48-h EC₅₀ > 119 mg/L

Toxicity to Aquatic Plants

Green algae (*Pseudokirchneriella subcapitata*) were exposed to carbamate hydrochloride at measured concentrations of 0 or 117 mg/L, in a limit test, under static conditions for 72 hours.

72-h EC₅₀ > 117 mg/L

Conclusion: The acute hazard of this chemical to fish, aquatic invertebrates and aquatic plants is >100 mg/L.

Table 3. Summary of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	SPONSORED CHEMICAL Carbamate hydrochloride (65086-85-3)
Summary of Human Health Data	
Acute Oral Toxicity LD₅₀ (mg/kg-bw)	> 11,000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	NOAEL = 1000
Reproductive/Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Parental Systemic Toxicity Reproductive/Developmental Toxicity	NOAEL = 1000 NOAEL = 1000
Genetic Toxicity – Gene Mutations <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)	> 114
Aquatic Invertebrates 48-h EC₅₀ (mg/L)	> 119
Aquatic Plants 72-h EC₅₀ (mg/L) (growth) (biomass)	> 117 > 117