

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### Phosphonic acid, P-[[bis(2-hydroxyethyl)amino]methyl]-, diethyl ester (Fyrol 6, CASRN 2781-11-5)

The High Production Volume (HPV) Challenge Program<sup>1</sup> 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<sup>1,2</sup>) 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<sup>2,3</sup> 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

---

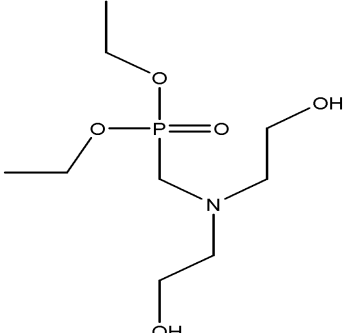
<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> 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 information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>	<p><b>2781-11-5</b></p>
<p><b>Chemical Abstracts Index Name</b></p>	<p><b>Phosphonic acid, [[bis(2-hydroxyethyl)amino]methyl]-, diethyl ester</b></p>
<p><b>Structural Formula</b></p>	
<p style="text-align: center;"><b>Summary</b></p> <p>CASRN 2781-11-5 is a liquid with high water solubility and low vapor pressure. It is expected to have moderate mobility in soil. Volatilization of this chemical is considered low. The rate of hydrolysis is considered negligible at acidic and neutral pH; however, the rate of hydrolysis is rapid under alkaline conditions. The rate of atmospheric photooxidation is considered rapid. It is expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral toxicity of CASRN 2781-11-5 to rats and acute dermal toxicity to rabbits is low. CASRN 2781-11-5 is slightly irritating to rabbit eyes, and not irritating or sensitizing to rabbit skin. Repeated oral exposure of rats to CASRN 2781-11-5 for 13 weeks showed no systemic toxicity up to 500 mg/kg-bw/day (highest dose tested). An oral combined developmental/reproductive toxicity screening test in rats showed no maternal, reproductive or developmental (prenatal and limited postnatal) toxicity up to 750 mg/kg-bw/day (highest dose tested). CASRN 2781-11-5 did not induce gene mutations in bacteria. It did induce some gene mutations in an <i>in vitro</i> mouse lymphoma assay and was positive in an <i>in vitro</i> chromosomal aberrations assay. It did not cause acute delayed neurotoxicity in hens when tested up to 10 g/kg-bw.</p> <p>For CASRN 2781-11-5, the measured 96-hour LC<sub>50</sub> for fish is &gt; 10,000 mg/L, the measured 48-hour EC<sub>50</sub> for aquatic invertebrates is &gt; 936 mg/L, and the measured 96-hour EC<sub>50</sub> for aquatic plants is &gt; 86 mg/L.</p> <p>No data gaps were identified under the HPV Challenge Program.</p>	

The sponsor, Akzo Nobel Functional Chemicals LLC., submitted a Test Plan and Robust Summaries to EPA for phosphonic acid, P-[[bis(2-hydroxyethyl)amino]methyl]-, diethyl ester (Fyrol 6, CASRN 2781-11-5) on December 19, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on February 10, 2004 (<http://www.epa.gov/chemrtk/pubs/summaries/phsacdb2/c14938tc.htm>). EPA comments on the original submission were posted to the website on June 13, 2004. Public comments were also received and posted to the website. Supresta U.S. LLC purchased the Akzo Nobel Functional Chemicals LLC. phosphorus chemicals flame retardant operations in July 2004 and assumed responsibility for submitting a response and revised summaries on August 22, 2006, which were posted to the ChemRTK website on September 21, 2006.

## 1. Chemical Identity

### 1.1 Identification and Purity

No information on purity of Fyrol 6 is indicated in the Test Plan (2003); however, where indicated in the revised robust summaries, the purity of the test substance was approximately 75-97% (2006).

### 1.2 Physical-Chemical Properties

The physical-chemical properties of Fyrol 6 are summarized in Table 1.

Fyrol 6 is a liquid with high water solubility. The reported moderate vapor pressure is due to the low molecular weight component partial pressure because the test substance vapor pressure is estimated to be low ( $< 1 \times 10^{-7}$  mm Hg).

<b>Table 1. Physical-Chemical Properties of Fyrol 6 (Phosphonic Acid, P-[[Bis(2-hydroxyethyl)amino]methyl]-, Diethyl Ester<sup>1</sup>)</b>	
<b>Property</b>	<b>Value</b>
CASRN	2781-11-5
Molecular Weight	255.25
Physical State	Liquid
Melting Point	Liquid at room temperature
Boiling Point	196°C (meas. for mixture); 379 °C (est. EPIWIN)
Vapor Pressure	0.43 mm Hg at 20°C (meas. for mixture); < 1E <sup>-7</sup> (est. EPIWIN)
Water Solubility	900,000 mg/L at 25°C (measured)
Dissociation Constant (pK <sub>a</sub> )	5.6 (estimated) <sup>2</sup>
Henry's Law Constant	1.6×10 <sup>-7</sup> atm·m <sup>3</sup> /mole (estimated) <sup>2</sup>
Log K <sub>ow</sub>	-0.72 (measured)

<sup>1</sup>Supresta U.S. LLC. September 21, 2006. Revised Robust Summary and Test Plan for Phosphonic Acid, [[Bis(2-Hydroxyethyl)Amino]Methyl]-, Diethyl Ester (Fyrol 6<sup>3</sup>). <http://www.epa.gov/oppt/chemrtk/pubs/summaries/phsacdb2/c14938tc.htm>.

<sup>2</sup>HSDB. 2008. Hazardous Substances Data Bank. Accessed August 22, 2008. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.

<sup>3</sup>Fyrol 6 product used for testing P-Chem properties was only 70 – 90% pure containing many impurities & solvents.

<http://www.supresta.com/pdfs/FYROL%206-MSDS.pdf>

## 2. General Information on Exposure

### 2.1 Production Volume and Use Pattern

This chemical had an aggregated production and/or imported volume in the United States of less than 500,000 pounds in 2005. It was an HPV chemical in previous reporting years. Both the HSDB and the HPV submission indicate that the chemical is primarily used as a flame retardant for urethane and electronic laminate resin systems. The HPV submission states that this chemical reacts with, and becomes, an integral part of the resin system during processing.

### 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. Fyrol 6 is a liquid with high water solubility and low vapor pressure. It is expected to have high mobility in soil. Volatilization of Fyrol 6 is considered low. The rate of hydrolysis is considered negligible at acidic and neutral pH; however, the rate of hydrolysis is rapid under alkaline conditions. The rate of atmospheric photooxidation is considered rapid. Fyrol 6 is expected to have low persistence (P1) and low bioaccumulation potential (B1).

<b>Table 2. Environmental Fate Characteristics of Fyrol 6 (Phosphonic acid, P-[[Bis(2-hydroxyethyl)amino]methyl]-, Diethyl Ester<sup>1</sup>)</b>	
<b>Property</b>	<b>Value</b>
Photodegradation Half-life	0.9 hours (estimated)
Hydrolysis Half-life	5,159 days at pH 4 and 15 °C (measured); 179 days at pH 4 and 25 °C (measured); 87 days at pH 7 and 15 °C (measured); 26 days at pH 7 and 25 °C (measured); 38 hours at pH 9 and 15 °C (measured); 14 hours at pH 9 and 25 °C (measured)
Biodegradation	15–19% in 28 days (not readily biodegradable)
Bioconcentration	BCF = 3 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	1.0 (estimated) <sup>2</sup>
Fugacity (Level III Model)	Air = 0.2% Water = 58.3% Soil = 41.4% Sediment = 0.1%
Persistence <sup>3</sup>	P1 (low)
Bioaccumulation <sup>3</sup>	B1 (low)

<sup>1</sup>Supresta U.S. LLC. September 21, 2006. Revised Robust Summary and Test Plan for Phosphonic Acid, [[bis(2- Hydroxyethyl) Amino]Methyl]-, Diethyl Ester (Fyrol 6). <http://www.epa.gov/oppt/chemrtk/pubs/summaries/phsacdb2/c14938tc.htm>.

<sup>2</sup>US EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.0. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>3</sup>Federal 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**

The human health hazard data are summarized in Table 3.

#### ***Acute Oral Toxicity***

Sprague-Dawley rats (10/sex) were administered a single oral dose of Fyrol 6 in corn oil via gavage at 5000 mg/kg-bw and were observed for 14 days. No mortality occurred.

**LD<sub>50</sub> > 5,000 mg/kg-bw**

#### ***Acute Dermal Toxicity***

Stauffland albino rabbits (5/sex) were administered a single dermal dose of Fyrol 6 at 2000mg/kg bw for 24 hours and were observed for 14 days. No mortality occurred.

**LD<sub>50</sub> > 2,000 mg/kg-bw**

### ***Repeated-Dose Toxicity***

Sprague-Dawley rats (22/sex/dose) were administered Fyrol 6 in corn oil via gavage at doses of 0, 20, 100 and 500 mg/kg-bw/day once daily, 7 days/week, for 13 weeks. No treatment-related effects were noted.

**NOAEL = 500 mg/kg-bw/day** (based on no effects at the highest dose tested)

### ***Reproductive/Developmental Toxicity***

In a combined reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/dose) were administered Fyrol 6 via oral gavage at doses of 0, 50, 250 and 750 mg/kg bw/day for two weeks prior to mating, during mating period, through gestation, lactation (females) and until sacrifice. There were no signs of systemic, reproductive or developmental toxicity noted in either dams or pups.

**NOAEL (systemic toxicity) = 750 mg/kg-bw/day** (based on no effects at the highest dose tested)

**NOAEL (reproductive toxicity) = 750 mg/kg-bw/day** (based on no effects at the highest dose tested)

**NOAEL (developmental toxicity) = 750 mg/kg-bw/day** (based on no effects at the highest dose tested)

### ***Genetic Toxicity – Gene Mutation***

#### ***In vitro***

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA 1537, T1538 and *saccharomyces cerevisiae* D4 were exposed to Fyrol 6 at concentrations ranging from 0.01 to 10µL/plate in the presence and absence of metabolic activation. DMSO was the vehicle. No information on positive controls was presented in the robust summary.

**Fyrol 6 was not mutagenic in this assay.**

(2) In two *in vitro* forward mutation assays mouse lymphoma cells (L2178Y) were exposed to Fyrol 6 in the presence and absence of metabolic activation. The concentrations in the first assay were 0.626 -2.5 µL/mL (with metabolic activation) and 1.25-5 µL/mL (without metabolic activation). Sterile water was the vehicle. Cytotoxicity was seen at 2.5 and 5 µL/mL. In the second assay, the concentrations were 0.25 -1.0 µL/mL (with metabolic activation and 0.0313 – 0.5 µL/mL (without metabolic activation). Cytotoxicity was seen at the 0.5 µL/mL. In both assays, Fyrol 6 was weakly mutagenic in the presence and absence of metabolic activation.

**Fyrol 6 was weakly mutagenic in these assays.**

### *Genetic Toxicity – Chromosomal Aberrations*

#### *In vitro*

Mouse lymphoma cells (L5178Y) were reposed to Fyrol 6 at concentrations ranging from 0.25 - 2.0  $\mu\text{L}/\text{mL}$  with metabolic activation and 0.0313 - 0.5  $\mu\text{L}/\text{mL}$  without metabolic activation. Increases in both structural and numerical chromosomal aberrations were observed at the two highest concentrations in the presence and absence of metabolic activation.

**Fyrol 6 was clastogenic in this assay.**

#### *Additional Information*

##### *Skin Irritation*

Stauffland albino rabbits (6/sex) were dermally exposed to 0.5 mL Fyrol 6 for 4 hours. Irritation was scored using Draize scoring method at 4 and 48 hours of exposure. Neither erythema nor edema was present at any observation period.

**Fyrol 6 was not irritating to rabbit skin.**

##### *Eye Irritation*

Fyrol 6 (0.1mL) was instilled in the eyes of Stauffland albino rabbits (9/sex). Eyes of 3 rabbits were washed after 20-30 seconds of exposure. Eyes of the remaining rabbits were not washed. Irritation was scored using Draize scoring method at 24, 48, 72 hours and 4 days and 7 days following exposure. No effects were seen in the 3 rabbits with washed eyes. The 6 rabbits with unwashed eyes showed mild conjunctival irritation. By 72 hours, the irritation had cleared.

**Fyrol 6 was slightly irritating to rabbit eyes.**

##### *Neurotoxicity*

Acute delayed oral toxicity of Fyrol 6 was tested in White Leghorn hens. The hens were orally administered two doses, three weeks apart, of Fyrol 6 via gavage in corn oil at 10 g/kg-bw. The observation period was 43 days. Tri-ortho cresyl phosphate was used as the positive control.

**Fyrol 6 did not cause delayed neurotoxicity in hens.**

**Conclusion:** The acute oral toxicity of CASRN 2781-11-5 to rats and acute dermal toxicity to rabbits is low. CASRN 2781-11-5 is slightly irritating to rabbit eyes, and not irritating or sensitizing to rabbit skin. Repeated oral exposure of rats to CASRN 2781-11-5 for 13 weeks showed no systemic toxicity up to 500 mg/kg-bw/day (highest dose tested). An oral combined developmental/reproductive toxicity screening test in rats showed no maternal, reproductive or developmental (prenatal and limited postnatal) toxicity up to 750 mg/kg-bw/day (highest dose tested). CASRN 2781-11-5 did not induce gene mutations in bacteria. It did induce some gene mutations in an *in vitro* mouse lymphoma assay and was positive in an *in vitro* chromosomal aberrations assay. It did not cause acute delayed neurotoxicity in hens when tested up to 10 g/kg-bw.

#### 4. Hazards to the Environment

The environmental hazard data are summarized in Table 3.

##### *Acute Toxicity to Fish*

Rainbow trout (*Oncorhynchus mykiss*, 10/concentration) were exposed to Fyrol 6 at nominal test concentrations of 1000, 1800, 3200, 5600 and 10,000 mg/L under static conditions for 96 hours. There was 20% mortality at 3200 mg/L but none at the higher concentrations.

**96-h LC<sub>50</sub> > 10,000 mg/L**

##### *Acute Toxicity to Aquatic Invertebrates*

*Daphnia magna* were exposed to Fyrol 6 at nominal concentrations of 63, 125, 250, 500 and 1000 mg/L under flow-through conditions for 48 hours. No treatment-related effects were seen at any concentration tested. All test concentrations were measured, but only the measured value for the highest concentration (936 mg/L) was provided in the robust summary.

**48-h EC<sub>50</sub> > 936 mg/L**

##### *Toxicity to Aquatic Plants*

Freshwater green algae (*Pseudokirchneriella subcapitata*) were exposed to Fyrol 6 at nominal concentrations of 0, 7.5, 15, 30, 60 and 120 mg/L under static conditions for 96 hours. All test concentrations were measured, but only the measured value for the highest concentration (86 mg/L) was provided in the robust summary.

**96-h EC<sub>50</sub> > 86 mg/L**

**Conclusion:** For CASRN 2781-11-5, the measured 96-hour LC<sub>50</sub> for fish is > 10,000 mg/L, the measured 48-hour EC<sub>50</sub> for aquatic invertebrates is > 936 mg/L, and the measured 96-hour EC<sub>50</sub> for aquatic plants is > 86 mg/L.

<b>Table 3. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program</b>	
<b>Endpoints</b>	<b>SPONSORED CHEMICAL Phosphonic acid, P-[[bis(2- hydroxyethyl)amino]methyl]-, diethyl ester (Fyrol 6) (2781-11-5)</b>
<b>Summary of Human Health Data</b>	
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 5000</b>
<b>Acute Dermal Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 2000</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)</b>	<b>NOAEL = 500 (hdt)</b>
<b>Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day) Systemic/Reproductive Toxicity</b>	<b>NOAEL = 750 (hdt)</b>
<b>Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Maternal and Developmental Toxicity</b>	<b>NOAEL = 750 (hdt)</b>
<b>Genetic Toxicity – Gene Mutation <i>In vitro</i> (Bacterial) (Mammalian cells)</b>	<b>Negative Positive</b>
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i></b>	<b>Positive</b>
<b>Additional Information Acute Delayed Neurotoxicity</b>	<b>(hen) NOAEL = 10 g/kg</b>
<b>Summary of Environmental Effects – Aquatic Toxicity Data</b>	
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>&gt; 10,000</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>&gt; 936</b>
<b>Aquatic Plants 72-h EC<sub>50</sub> (mg/L)</b>	<b>&gt; 86</b>

hdt = highest dose tested; **Bold = Measured data**