SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

SPONSORED CHEMICAL

FYROL 6 (CAS No: 2781-11-5)
[9th CI Name: Phosphonic acid,[[bis(2-hydroxyethyl)amino]methyl]-diethyl ester]

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INTERIM

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The High Production Volume (HPV) Challenge Program[1] is 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 sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do 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. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[3].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,4] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[5] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support 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. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,6]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

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[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. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

SCREENING-LEVEL HAZARD CHARACTERIZATION
Fyrol 6 (CAS No 2781-11-5)

Introduction

The sponsor, Akzo Nobel Functional Chemicals LLC., submitted a Test Plan and Robust Summaries to EPA for Fyrol 6 (CAS No. 2781-11-5; CI name: Phosphonic acid,[[bis(2-hydroxyethyl)amino]methyl]-diethyl ester) 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. The sponsor submitted updated/revised documents on August 22, 2006, which were posted to the ChemRTK website September 21, 2006.

This screening-level hazard characterization is based primarily on the review of the test plan and robust summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. 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. A summary table of SIDS endpoint data with the structure(s) of the sponsored chemical(s) is included in the appendix. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Summary-Conclusion

The log K_{ow} of Fyrol 6 indicates that its potential to bioaccumulate is expected to be low. Fyrol 6 is not readily biodegradable, indicating that it has the potential to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of Fyrol 6 to aquatic organisms is low.

Acute oral and dermal toxicity of Fyrol 6 is low. Fyrol 6 is not irritating to skin but is mildly irritating to eyes. Repeated exposures via oral route caused decreased red blood cells and discoloration of lungs, liver, kidney and thymus. Enlarged liver with hepatocellular hypertrophy and cytoplasmic eosinophilia of centrilobular hepatocytes were seen, but these were considered adaptive changes rather than toxic responses to Fyrol 6. Fyrol 6 did not produce reproductive or developmental effects in rats. Fyrol 6 was not mutagenic in bacterial cells; however, in a mouse lymphoma cell line it was weakly mutagenic and caused structural and numerical chromosomal aberrations. Fyrol 6 did not cause delayed neurotoxicity in hens.

The potential health hazard of Fyrol 6 is low. Available data suggest that Fyrol 6 has the potential to be genotoxic.

No data gaps were identified under the HPV Challenge Program.

1. Physical-Chemical and Environmental Fate Properties

A summary of physical-chemical and environmental fate data submitted is provided in the Appendix. For the purpose of the screening-level hazard characterization, the review and summary of these data were limited to the octanol-water partition coefficient and biodegradation endpoints as indicators of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

Log K_{ow}: -0.72 (measured)

Biodegradation

In a modified Sturm test using activated sludge from a municipal sewage treatment plant as inoculum, 19% of Fyrol 6 had degraded after 28 days.
Fyrol 6 is not readily biodegradable.

Conclusion: The log K_{ow} of Fyrol 6 indicates that its potential to bioaccumulate is expected to be low. Fyrol 6 is not readily biodegradable, indicating that it has the potential to persist in the environment.

2. Environmental Effects- Aquatic Toxicity

Toxicity to Fish

Rainbow trout (*Salmo gairdneri*) were exposed to Fyrol 6 at nominal 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_{50} = > 10,000 mg/L

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_{50} > 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_{50} > 86 mg/L

Conclusion: The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates the potential acute hazard of Fyrol 6 to aquatic organisms is low.

3. Human Health Effects

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. Mild depression, piloerection, alopecia and red facial stains were observed following dosing. All animals appeared normal by day 2.
LD_{50} > 5000 mg/kg-bw

Acute Dermal Toxicity

Stauffland albino rabbits (5/sex) were administered a single dermal dose of Fyrol 6 at 2000 mg/kg bw and were observed for 14 days. No mortality occurred. Mild depression was observed following dosing and all animals appeared normal by day 2. Local dermal effects included mild erythema and edema and necropsy revealed no adverse effects.
LD_{50} > 2000 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. The control group received corn oil only. Mortality observed in the study was attributed to dosing accidents. Alopecia was the major clinical sign at all doses; darker coloration of eyes and chromorhinorrhea (bloody noses) was seen at the high dose. Increases in white blood cells and lower hemoglobin and hematocrit values were seen at the high dose. In the mid- and low- doses, a decrease in red blood cells was observed. Discoloration of lungs, liver, kidney and thymus (only at high dose) and enlarged liver were seen at all dose levels. Absolute and relative weights of liver and kidney were also evident at mid- and high- doses. Slight hepatocellular hypertrophy and cytoplasmic eosiophilia of centrilobular hepatocytes was present at 100 and 500 mg/kg-bw/day.
LOAEL = 20 mg/kg-bw/day (based on changes in blood chemistry parameters)
NOAEL = Not established

Reproductive Toxicity

In a combined reproductive/developmental toxicity screening test, Sprague-Dawley rats (12/sex/dose) were administered Fyrol 6 via 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 clinical signs of toxicity. Parental body weights and food consumption were unaffected. No effects were seen on parental reproductive organ weights (ovaries, testes, and epididymides). No histopathological changes were seen in reproductive organs. Absolute and relative liver weights were increased in a dose-related manner in male rats but were not statistically significant. There was no effect on pup survival, litter size or total pups born and offspring body weights were comparable to control group.
LOAEL (systemic toxicity) > 750 mg/kg-bw/day
NOAEL (systemic toxicity) = 750 mg/kg-bw/day (based on no effects at the highest tested dose)
LOAEL (reproductive toxicity) > 750 mg/kg-bw/day
NOAEL (reproductive toxicity) = 750 mg/kg-bw/day (based on no effects at the highest tested dose)

Developmental Toxicity

In the combined reproductive/developmental toxicity screening test described previously, no effects were noted on mortality, maternal body weights and food consumption. There were no significant differences in mean corpora lutea, implantation sites, litter size, total pups born and pup survival between treated and control animals. There was no effect on offspring body weights. No effects on offspring development were noted.
LOAEL (maternal/developmental toxicity) > 750 mg/kg-bw/day
NOAEL (maternal/developmental toxicity) = 750 mg/kg-bw/day (based on no effects at the highest tested dose)

Genetic Toxicity – Gene Mutation

In vitro
(1) In Ames assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA 1538 and *Saccharomyces cerevisiae* D4, were exposed to Fyrol 6 at concentrations ranging from 0.01 to 10 µL/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 (L5178Y) 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 Aberration

In vitro
Mouse lymphoma cells (L5178Y) were exposed to Fyrol 6 at concentrations ranging from 0.25 – 2.0 µL/mL with metabolic activation and 0.0313 – 0.5 µL/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 or edema was not present at any observation period.
Fyrol 6 was not irritating to skin.

Eye Irritation

Fyrol 6 (0.1 mL) 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 6 rabbits were not washed. Irritation was scored using Draize scoring method at 24, 48, 72 hours and 4 and 7 days following exposure. No effects were seen in the 3 rabbits with washed eyes. The six rabbits with unwashed eyes, showed mild conjunctival irritation. By 72 hours, the irritation had cleared.
Fyrol 6 was mildly irritating to eyes.

Neurotoxicity
Acute delayed neurotoxicity 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 1 or 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: Acute oral and dermal toxicity of Fyrol 6 is low. Fyrol 6 is not irritating to skin but is mildly irritating to eyes. Repeated exposures via oral route caused decreased red blood cells and discoloration of lungs, liver, kidney and thymus. Enlarged liver with hepatocellular hypertrophy and cytoplasmic eosinophilia of centrilobular hepatocytes were seen, but these were considered adaptive changes rather than toxic responses to Fyrol 6. Fyrol 6 did not produce reproductive or developmental effects in rats. Fyrol 6 was not mutagenic in bacterial cells; however, in a mouse lymphoma cell line it was weakly mutagenic and caused structural and numerical chromosomal aberrations. Fyrol 6 did not cause delayed neurotoxicity in hens.

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4. Hazard Characterization

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produce reproductive or developmental effects in rats. Fyrol 6 was not mutagenic in bacterial cells; however, in a mouse lymphoma cell line it was weakly mutagenic and caused structural and numerical chromosomal aberrations. Fyrol 6 did not cause delayed neurotoxicity in hens.

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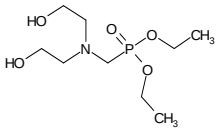
5. Data Gaps

No data gaps were identified under the HPV Challenge Program.

APPENDIX

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **Fyrol 6** **(2781-11-5)**
Structure	
Summary of Physical-Chemical Properties and Environmental Fate Data	
Melting Point (°C)	Substance is a liquid
Boiling Point (°C)	196
Vapor Pressure (hPa at 25°C)	0.39 at 20 °C
Log K_{ow}	-0.72
Water Solubility (mg/L at 25°C)	9.00×10^{5}
Direct Photodegradation	—
Indirect (OH^-) Photodegradation Half-life ($t_{1/2}$)	0.898 h (estimated)
Stability in Water (Hydrolysis) ($t_{1/2}$)	Half-lives at 15 and 25 °C are 5159 and 179 days, respectively, at pH 4; 87 and 26 days, respectively, at pH 7; 38 and 14 hours, respectively, at pH 9.
Fugacity (Level III Model) **Air (%)** **Water (%)** **Soil (%)** **Sediment (%)**	 6.8% 35% 58.2% 0.0645%
Biodegradation at 28 days (%)	15 – 19 Not readily biodegradable
Summary of Environmental Effects – Aquatic Toxicity Data	
Fish 96-h LC_{50} (mg/L)	> 10,000
Aquatic Invertebrates 48-h EC_{50} (mg/L)	> 936
Aquatic Plants 72-h EC_{50} (mg/L) (growth) (biomass)	> 86
Summary of Human Health Data	
Acute Oral Toxicity LD_{50} (mg/kg-bw)	> 5000
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	> 2000
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)	LOAEL = 20 NOAEL = Not established

Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program	
Endpoints	**SPONSORED CHEMICAL** **Fyrol 6** **(2781-11-5)**
Reproductive Toxicity **NOAEL/LOAEL** **(mg/kg-bw/day)** **Systemic/Reproductive Toxicity**	LOAEL > 750 NOAEL = 750
Developmental Toxicity **NOAEL/LOAEL** **(mg/kg-bw/day)** **Maternal and Developmental Toxicity**	LOAEL > 750 NOAEL = 750
Genetic Toxicity – Gene Mutation ***In vitro***	Positive
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Positive
Additional Information Acute Delayed Neurotoxicity	NOAEL = 10 g/kg (hen)

— indicates endpoint was not addressed for this chemical.