HAZARD ASSESSMENT
FORMAT EVALUATION REVIEW DRAFT
Primene™ 81-R Amines (CAS No. 68955-53-3)

Introduction

The sponsor, Rohm and Haas Company, submitted a test Plan and robust summaries to EPA, dated April 25, 2003, for amines, C12-C14-tert-alkyl (Primene™ 81-R Amines, CAS No. 68955-53-3). EPA posted the submission on the RTK HPV Challenge Website on August 19, 2003. EPA comments were posted to the HPV Challenge Website on December 19, 2003 and the sponsor's response (revised documents) was submitted to EPA on March 18, 2004.

Primene™ 81-R Amine is a primary aliphatic amine with highly branched alkyl chains in which the amino nitrogen atom is linked to a tertiary carbon (C12 – C14 t-alkyl amines). The amount of C12 amine in Primene™ 81-R Amines is at least 70% and C11 to C14 t-alkyl amines are more than 80%.

Group Assignment from Tier I Screening Process and Tier II Screening Level Hazard Characterization[1]

Group 1 Assignment

Triggered by: Human Health (Repeated-Dose Toxicity, Group 1)
Supported by Reproductive Toxicity, Ecotoxicity and Biodegradation data.

Tier 1 Screening: Primene™ 81-R Amines was placed into Group 1 based on an inhalation LOAEL of approximately 0.129 mg/L/day (129 mg/m^3) in a 4-week study according to GHS hazard classification criteria. Low values in acute aquatic toxicity studies also support the chemical's placement into **Group 1.** Positive evidence in the reproductive toxicity and evidence of chronic aquatic toxicity lend further support to Group 1 placement. In addition, the chemical is not readily biodegradable, further confirming its Group1 designation.

Tier 2 Screening Level Hazard Characterization: The more in-depth review of the submitted data on Primene™ 81-R Amines confirmed the Tier 1 screen. The LOAEL placing the chemical into this hazard category was derived from a 4-week inhalation repeated-dose toxicity study-- a guideline, GLP study with a reliability code of 1. Based on the effects observed at low concentrations, EPA considered the study to be appropriate for use in a screening level assessment. Positive evidence from the reproductive toxicity studies provided additional support for placement into Group 1. The chemical had high acute and chronic toxicity to aquatic organisms based on low LC_{50}/EC_{50} and NOEC values. The fact that the chemical is not readily biodegradable further confirmed its placement into **Group 1**.

[1] (Explanation of Tier 1 and Tier 2 will be added here.)

Summary of Critical Studies

Human Health Effects

Repeated-Dose Toxicity (inhalation): Five groups of (5/sex/group) (Crl:CD1BR) rats were exposed (nose-only) to vapors of Primene™ 81-R Amines at 0, 2, 19, 129, or 537 mg/m^3 (0, 0.002, 0.019, 0.129, or 0.537 mg/L) 6 hours/day, 5 days/week for 4 weeks. The control group received filtered air only. OECD TG 412 was followed. All animals exposed to 537 mg/m^3 died by exposure day 11. Prior to death animals exposed to 537 mg/m^3 exhibited treatment-related labored breathing, respiratory noise, gasping, unstable gait, tremors, salivation, and lacrimation. At 129 mg/m^3 transient occurrences of unstable gait, respiratory noise, salivation, and lacrimation were observed. At 2 and 19 mg/m^3 no treatment-related clinical signs were noted. Statistically significant decreases in body weight and body weight change occurred in males and females dosed at 129 and 537 mg/m^3. Effects on body weight and body-weight changes were seen in females at 2 and 19 mg/m^3. Organ weights revealed no treatment-related effects. At the end of the four week exposure period, neurological evaluations of all surviving animals showed no signs of a cumulative toxic effect on the nervous system of any group. No treatment-related effects on clinical chemistry or hematology parameters were observed in any group.

In both sexes, histological changes at 537 mg/m^3 included nasal cavity (moderate to severe desquamation of respiratory and olfactory epithelium, epithelial necrosis), larynx and trachea (epithelial necrosis and submucosal inflammation), and lungs (foci of inflammation of bronchi, bronchioles and/or alveoli in two females). Histological changes seen at 129 mg/m^3 were primarily in the nasal cavity (necrosis of respiratory and olfactory epithelium, inflammation in the mucosa and submucosa, foci of respiraotory epithelial hyperplasia and squamosas metaplasia). The olfactory epithelium and underlying Bowman's gland epithelium were atrophied.

NOAEL = 19 mg/m^3 (0.019 mg/L) based on body weight effects, clinical signs and histological changes seen at 129 mg/m^{3}and above.
LOAEL = 129 mg/m^3 (0.129 mg/L)

Supporting Studies

Reproductive/Developemntal Toxicity: In a one generation reproductive toxicity study, rats (Crl:CD1BR) were administered Primene™ 81-R Amines in the diet at 0, 250, 750, or 1500 ppm (corresponding to 0, 19.1, 55.6, or 107.3 mg/kg/day, respectively, for males and 0, 21, 62.8, or 124.1 mg/kg/day, respectively, for females). The parental animals were offered the treated diet 10 weeks prior to mating, during mating and for females continued throughout gestation, lactation and until terminal necropsy. Significant effects on parental body weight and body weight changes were seen at 750 and 1500 ppm. Decreased food consumption was seen in both sexes at 1500 ppm and in males at 750 ppm. In pups, decreased body weights were seen at 750 and 1500 ppm throughout the lactation period. In addition, in pups, treatment-related delayed

sexual maturity was seen (delayed vaginal opening in females at 750 and 1500 ppm and delayed preputial separation in males at 1500 ppm).

NOAEL (parental toxicity) = 250 ppm (19.1 and 21.0 mg/kg/day for males and females, respectively, based on body weight effects)
NOAEL (reproductive and developmental toxicity) = 250 ppm (19.1 and 21.0 mg/kg/day for males and females, respectively, based on body weight effects and delayed sexual maturation)

Other Information

Developmental Toxicity: In a developmental toxicity study, groups of pregnant female rats were dermally administered Primene™ 81-R Amines at 5, 15, or 45 mg/kg/day through days 6-20 of presumed gestation. Maternal toxicity (effects on body weight, food consumption, clinical signs, and skin reactions) was evident at the 15 and 45 mg/kg/day dose levels. No treatment-related developmental effects were seen at any dose level.

NOAEL (maternal toxicity) = 5 mg/kg/day
NOAEL (developmental toxicity) = 45 mg/kg/day (highest dose tested)

Genetic Toxicity (Gene mutations and Chromosomal aberrations): The submitted data are negative for genetic toxicity.

Primene™ 81-R Amines is acutely toxic via inhalation, corrosive to rabbits skin and eyes and causes delayed contact hypersensitivity in guinea pigs.

Conclusion: The target organ after repeated inhalation exposure to Primene™ 81-R Amines via inhalation is the respiratory tract (nasal cavity, larynx, trachea and lungs). Oral exposure to Primene™ 81-R Amines also affected body weights in parental animals and pups and caused delayed sexual maturity in pups. Gene mutation and chromosomal aberration tests indicated negative results.

Environmental Effects:

Fish: 96h LC_{50} = 1.3 mg/L (*Oncorhynchus mykiss*, nominal*)*
Invertebrates: 48h EC_{50} = 4.1 mg/L (*Daphnia magna*, nominal*)*
Algae: 72h ErC_{50} = 0.20 mg/L (*Pseudokirchneriella subcapitata*, nominal*)*

Chronic Fish Toxicity: 96-day NOEC < 0.1 (*Oncorhynchus mykiss*, measured*)*

In a static OECD TG 201 acute algal toxicity study, *Pseudokirchneriella subcapitata* was exposed to nominal concentrations of Primene™ 81-R A for 72 hours. Concentrations tested were 0.05, 0.10, 0.20, 0.40, and 0.80 mg/L. Three replicates were tested at each concentration. Acetone was used as a vehicle/solvent with the final concentration being 0.10 ml/L. At 72-hours, the cell density data for each concentration tested was: 110 mg/L, 110 mg/L, 120 mg/L,

62 mg/L, 55 mg/L, 33 mg/L, and 0 mg/L for the control, solvent control, 0.05, 0.10, 0.20, 0.40, and 0.80 mg/L sample concentrations, respectively.

72-hour EC50 = 0.20 mg/L (95% confidence limits of 0.15-0.25 mg/L).
The 72-hour NOEC was 0.05 mg/L.

In a 96 day-chronic toxicity study, 15 rainbow trout embryos (*Oncorhynchus mykiss*) in each of four replicates were exposed to Primene™ 81-R A at 0 (control), 0 (acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L (nominal) or <MQL, <MQL, 0.078, 0.16, 0.29, 0.59, and 1.4 mg/L (measured) concentrations. The survival was significantly reduced at 0.59 and 1.4 mg/L. There was no effect on egg hatchability. A statistically significant reduction in standard length and growth (blotted wet weight) was seen at 0.29 mg/L. The following NOEC values were obtained:

NOEC for survival = 0.29 mg/L (LOEC = 0.59 mg/L)
NOEC for egg hatchability = 1.4 mg/L (LOEC >1.4 mg/L)
NOEC for standard length = 0.16 mg/L (LOEC = 0.29 mg/L)
NOEC for growth (blotted wet weight) = 0.078 mg/L (LOEC = 0.16 mg/L)**Conclusion:** The aquatic toxicity data indicate that Primene™ 81-R shows high acute and chronic toxicity to aquatic organisms (Group1—EC_{50} values for algae less than 1 mg/L).

Physicochemical Properties and Environmental Fate

Log Kow: 2.9

Biodegradation: **Not readily biodegradable** (22%/28d)

Other information: Primene™ 81-R Amines is a liquid at room temperature with high water solubility and relatively low vapor pressure. It will primarily distribute to soil and secondarily to water (C12 isomer) or sediment (C14 isomer). Primene™ 81-R Amines is stable to hydrolysis; however, the calculated half-life (3 hr) from reaction with OH radicals indicates that it will rapidly undergo photodegradation via indirect photolysis.

Conclusion: Based on low log Kow value, potential for Primene™ 81-R Amines to bioaccumulate will be minimal. Primene™ 81-R Amines is not readily biodegradable and is stable to hydrolysis; however, it will rapidly undergo photodegradation via indirect photolysis.

Use and Exposure

{To be developed based on exposure information submitted under 2006 Inventory Update Rule (IUR).}

OVERALL CONCLUSION

Hazard Identification

Repeated inhalation exposure to Primene™ 81-R Amines affected the respiratory tracts of rats (nasal cavity, larynx, trachea and lungs). Primene™ 81-R Amines also affected body weights in parental animals and caused delayed sexual maturity in pups in a one generation reproduction toxicity study. Gene mutation and chromosomal aberration tests indicated negative results.

Aquatic toxicity data indicate that Primene™ 81-R Amines has high acute and chronic toxicity to aquatic organisms.

The potential of Primene™ 81-R Amines to bioaccumulate will be minimal based on its low log Kow value. It has relatively low vapor pressure and will primarily distribute to soil and secondarily to sediment or water (depending on the isomer). Primene™ 81-R Amines is not readily biodegradable and is stable to hydrolysis; however, it will rapidly undergo photodegradation via indirect photolysis.

Use and Exposure

[To be developed.]

Data Gaps/Needs

All SIDS endpoints have been adequately addressed and no additional testing is needed under the HPV Challenge Program.

Primene™ 81-R Amines shows a potential inhalation hazard and, based on its exposure potential, additional testing may be necessary as a part of post-Tier II activity.

Post Tier 2 Considerations/Needs

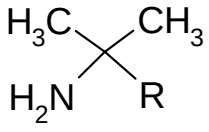
To be developed after receipt of IUR data

Regulatory History

Primene™ 81-R Amines is listed under the Clean Air Act, etc. [To be further developed.]

U.S. HPV Chemicals Data Table

(As reported in submission under the HPV Challenge Program)

CHEMICAL IDENTITY	
Chemical Name	**Amines, C12-C14-tert-alkyl**
CAS Registry Number (CAS RN)	**68955-53-3**
Structure	 R = C_9-C_{11} branched, aliphatic group
Molecular Weight	185 to 213
Molecular Formula	C12H27N to C14H31N
Physical Form	Liquid
Submitter	Rohm and Haas Company
PHYSICOCHEMICAL PROPERTIES	
Melting Point	Pour point = -65°C (Rohm and Haas)
Boiling Point	217-231 °C (Rohm and Haas)
Vapor Pressure	0.359 mm Hg at 20 °C (Rohm and Haas)
Log Kow	2.9 (Rohm and Haas)
Water Solubility	1000 mg/L at 25 ^{o}C (Rohm and Haas)
Henry's Law Constant	1.71×10^{-4} atm-m^3/mol for 2-amino-2-methylundecane (C12 isomer); 3.01×10^{-4} atm-m^3/mol for 2-amino-2-methyltridecane (C14 isomer)
ENVIRONMENTAL FATE AND TRANSPORT	
Biodegradation	22% after 28 days (Rohm and Haas)
Stability in Water (Hydrolysis)	Hydrolytically stable (technical discussion)
Photodegradation	Half-life for reaction with OH radicals (indirect photolysis) = 3.05 and 3.13 hours calculated for C12 and C14, respectively
Fugacity	Air: 0.65%, Water: 17.1%, Soil: 72.4%, Sediment: 9.9% for Primene™ 81-R Amines (C12 isomer); Air: 0.47%, Water: 10%, Soil: 53.4%, Sediment: 36.1% for 2-amino-2-methyltridecane (C14 isomer)
ECOTOXICITY	
Vertebrates (LC_{50})	= 1.3 mg/L (*Oncorhynchus mykiss,* 96h LC50, nominal)
Invertebrates (EC_{50})	= 4.1 mg/L (*Daphnia magna*, 48h EC50, nominal*)*
Algae (EC_{50})	**= 0.2 mg/L (***Pseudokirchneriella subcapitata***, 72h EC50, nominal)**
Chronic Toxicity Data	96-d NOEC < 0.1 mg/L (*Oncorhynchus mykiss*)
Terrestrial Toxicity Data	N/A

HUMAN HEALTH EFFECTS		
Acute Toxicity (LD_{50} or LC_{50})		Oral LD50 = 320 mg/kg bw (rat); 552 mg/kg bw (mouse)
		Inhalation LC50 > 0.94 mg/L (rat); >= 157 ppm (rat)
Repeated-Dose Toxicity (LOAEL/NOAEL)		Dermal 28d LOAEL = 60 mg/kg (rat)
		Inhalation 28d LOAEL = 129 mg/m3 (0.129 mg/L) (rat)
Genetic Toxicity	**Gene Mutation (positive or negative)**	Negative
	Chromosomal Aberration (positive or negative)	Negative
	Overall	Negative
Reproductive Toxicity (positive or negative)		**Positive**
Developmental Toxicity (positive or negative)		**Positive**
Other (carcinogenicity, endocrine effects, neurotoxicity)		N/A
Sponsor's Comments		The submitter states that all the test endpoints are adequate and no further testing is recommended.
EPA Comments		The submitter needs to address a few deficiencies in the robust summaries for health effects.
Sponsor's Response to EPA Comments		Done.
Public comments		Received comments from Environmental Defense. EPA considered these comments in its response.