201-14639

100 INDEPENDENCE MALL WEST PHILADELPHIA, PA 19106-2399 U.S.A.
TELEPHONE (215) 592-3000 CABLE ADDRESS: ROHMHAAS CENTRAL FAX (215) 592-3377

REPLY TO:
RESEARCH LABORATORIES
727 NORRISTOWN ROAD
P.O. BOX 904
SPRING HOUSE, PA 19477-0904
(215) 641-7000
(215) CH 2-0400

ROHM AND HAAS COMPANY

July 30, 2003

Ms. Linda Fisher
Acting Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

ATTN: Chemical Right-to-Know Program

RE: HPV CHEMICAL CHALLENGE PROGRAM for
Primene™ 81-R Amines (CAS 68955-53-3)
Rohm and Haas Company

Dear Ms. Fisher:

On behalf of Rohm and Haas Company, I am pleased to submit the test plan and robust summaries for Primene™ 81-R Amines (C12 to C14 t-alkyl amines, CAS 68955-53-3). My company has agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003.

We have electronically submitted via email, the test plan and IUCLID robust summaries (both the Export file and the .rtf printout), as well as this cover memo.

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the address below.

Best regards,

James E. McLaughlin, PhD
Toxicology Department
Rohm and Haas Company
727 Norristown Road
P.O. Box 0904
Spring House, PA 19477-0904
Phone: 215-641-7459

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

Test Plan
For
Primene ä 81-R Amine
CAS Number 68955-53-3

PREPARED BY:

ROHM AND HAAS COMPANY

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TABLE OF CONTENTS

C. Genetic Toxicity -Mutation
D. Genetic Toxicity -Chromosomal Aberration
E. Developmental Toxicity
F. Reproductive Toxicity

OVERVIEW

The Rohm and Haas Company hereby submits for review and public comment the test plan for Primene™ 81-R Amine (CAS No.: 68955-53-3) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on Primene™ 81-R Amine in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct of any new or additional tests.

Primene™ 81-R Amine is a primary aliphatic amine with highly branched alkyl chains (C_{12} – C_{14}) in which the amino nitrogen atom is linked to a tertiary carbon. This material has unique chemical and physical properties, including unusually good resistance to oxidation, fluid character and low viscosity over a wide range of temperature, outstanding color stability, and high solubility in petroleum hydrocarbons. Primene™ 81-R Amine is used as a chemical intermediate in a wide range of applications. Primene™ 81-R Amine salts and derivatives are used to improve the stability and performance characteristics of petroleum-based industrial lubricants. Primene ™ 81-R Amine is also used to improve the storage stability and inhibit sludge formation in fuel and diesel oils, and in the production of industrial surfactants and solvent based dyes. In addition, Primene™ 81-R Amine and associated derivatives are effective in reducing fouling during the processing of crude oil.

In conclusion, an adequate assessment and summarization of all the SIDS endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests.

TEST PLAN SUMMARY

CAS No. 68955-53-3	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL –CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Density	Y	-	-	-	Y	Y	N
Vapor Pressure	Y	-	-	-	N	Y	N
Partition Coefficient	Y	-	Y	-	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
Surface Tension	Y	-	Y	-	N	Y	N
Flash Point	Y	-	Y	-	N	Y	N
Auto Flammability	Y	-	Y	-	N	Y	N
Explosive Properties	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
Chronic Toxicity to Fish	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	Y	-	-	Y	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was determined from analyses that followed the American Society for Testing and Materials (ASTM) Test Method D-97. No data on whether test was conducted in compliance with Good Laboratory Practice (GLP), but test was conducted by recognized scientific standards.

Boiling Point - A value for this endpoint was determined from analyses that followed ASTM Test Method D-1078. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Density - A value for this endpoint was determined using an Anton-Parr DMA-46 Densitometer at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Vapor Pressure - A value for this endpoint was determined from analyses that followed ASTM Test Method D-2879. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards. A value for this endpoint also was derived from measured saturated vapor concentrations during the conduct of an acute vapor inhalation LC50 study in rats. The saturated vapor concentration was determined using the same sampling and analytical methodology used to measure vapor concentration during the inhalation exposure. The quality of the acute vapor inhalation study in rats was deemed as "reliable without restrictions."

Partition Coefficient - A value for this endpoint was determined from analyses that followed 40CFR Part 792. This test was performed in accordance with GLP regulations.

Water Solubility - A value for this endpoint was determined by capillary gas chromatography at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Surface Tension - A value for this endpoint was measured on the Fisher Surface Tensiometer, Model 20 at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was

conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flash Point - A value for this endpoint was determined by the Pensky Martens Closed Cup method at the Analytical Research Department of Rohm and Haas Company in Springhouse, PA. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Auto Flammability - A value for this endpoint was determined from analyses that followed ASTM Test Method E-659. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Explosive - Properties A value for this endpoint was determined from analyses that followed ASTM Test Method E681-85. No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Conclusion: **All physicochemical endpoints have been satisfied with data from well-conducted studies using acceptable methodologies. While there is no data on whether these tests were conducted in compliance with GLP, the results are of sufficient quality to conclude that no additional testing is needed.**

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using a computer estimation model in EPI suite. The model was unable to estimate atmospheric ozone reaction rates.

Stability in Water - A value for this endpoint was obtained using a computer estimation model in EPI suite.

Biodegradation- This endpoint is filled by data from a study that followed OECD test guideline 301D and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions."

Fugacity - A value for this endpoint was obtained using the Mackay Level III steady state fugacity model.

Conclusion: **All environmental fate endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total, they are of sufficient quality to conclude that no additional testing is needed.**

C. Ecotoxicity Data

Acute Toxicity To Fish - This endpoint is filled by data from a study that followed OECD test guideline 203 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from a study that followed OECD test guideline 202 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Toxicity to Aquatic Plants - This endpoint is filled by data from a study that followed OECD test guideline 201 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Chronic Toxicity to Fish - This endpoint is filled by data from a study that followed OECD test guideline 210 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Conclusion: **All ecotoxicity endpoints have been satisfied with data from well-conducted studies that followed standardized OECD test guidelines and GLP regulations. The quality of these studies are deemed as "reliable without restrictions" and are therefore of sufficient quality to conclude that no additional testing is needed.**

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies assessing toxicity following single oral, dermal, and inhalation exposures. Acute oral toxicity was evaluated in rats and mice, while dermal and inhalation studies used only rats. In addition, studies were conducted in rabbits to assess skin and eye irritation and in guinea pigs for sensitization potential to the skin. These studies followed OECD test guidelines and were conducted under GLP regulations. The quality of these studies were deemed as "reliable without restrictions."

Repeat Dose Toxicity - This endpoint is filled by data from a 28-day dermal exposure study in rats and a 28-day inhalation exposure study in rats. These studies followed OECD test guidelines 410 and 312, respectively, and were conducted

under GLP regulations. The quality of these studies were deemed as "reliable without restrictions."

Genetic Toxicity Mutation - This endpoint is filled with data from a study that followed OECD test guideline 471 and was conducted under GLP regulations. This study utilized *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537. The quality of this study was deemed as "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vivo* mouse micronucleus test that followed OECD test guideline 473 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions".

Developmental Toxicity - This endpoint is filled by data from a percutaneous exposure study in rats that followed OECD test guideline 414 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions".

Reproductive Toxicity - This endpoint is filled by data from a dietary exposure study in rats for one-generation that followed OECD test guideline 415 and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions".

Conclusion: **All toxicological endpoints have been satisfied with data from well-conducted studies that followed standardized OECD test guidelines and GLP regulations. The quality of these studies are deemed as "reliable without restrictions" and are therefore of sufficient quality to conclude that no additional testing is needed.**

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for Primene™ 81-R Amine were obtained from actual testing of this material.

Measured and estimated environmental fate data show that Primene™ 81-R Amine will not persist in the environment. Primene™ 81-R Amine degraded up to 21.8% by day 28 in a closed-bottle test for ready biodegradability. Primary and ultimate biodegradation estimates via QSAR range from days to months, and indicate the chemical will be subject to effective biodegradative processes. Primene™ 81-R Amine is moderately volatile, the measured vapor pressure equaling 0.114 and 0.167 mm Hg at 19 and 24°C, respectively. Primene™ 81-R Amine is soluble in

water (1000 mg/l @ 25° C). QSAR estimates of Henry's Law constants show moderate tendency to partition out of the water phase into the atmosphere. Fugacity modeling suggests partitioning largely into soil, with lesser amounts in sediment and aqueous compartments and still less in the atmosphere. The estimated log K_{oc} values approximating 4.0, shows a high degree of adsorption to matrix organic carbon.

The Log P of Primene™ 81-R Amine has been measured at 2.90 and thus significant bioaccumulation in fish will not occur. Accumulation of the chemical within terrestrial species thus is unlikely to occur. The fate and behavior of Primene™ 81-R Amine in wastewater treatment facilities (WWTF) have been estimated. Model results suggest that the up to 89% of the total mass of Primene™ 81-R Amine entering a WWTF would ultimately be removed. Biodegradative losses would be low with the predominant removal mechanism being adsorption to sludge material.

Acute aquatic LC/EC_{50} tests were conducted in rainbow trout (*Oncorhynchus mykiss*), a freshwater invertebrate (*Daphnia magna*) and a freshwater algal species (*Selenastrum capricornutum*). Of these three test organisms, the algae were the most sensitive (72 hour E_rC_{50} = 0.43 mg/L). The 96-hour LC_{50} for trout (1.3 mg/L) and the 48-hour EC_{50} (4.1 mg/L) are qualitatively similar. In a test conducted to estimate the potential chronic toxicity of Primene™ 81-R Amine to the early life-stages of the rainbow trout, the maximum acceptable toxicant concentration (MATC), based on growth was 0.11 mg/L. Therefore, Primene™ 81-R Amine can be classified as toxic (moderate concern) to fish and aquatic invertebrates (appropriate LC/EC_{50} values are greater than 1 mg/L and less than 10 mg/L) and is categorized as very toxic (high concern) to algae (EC_{50} value is less than 1 mg/L).

Primene™ 81-R Amine is considered moderately toxic following acute oral, dermal and inhalation exposures. The oral LD_{50} of rats was 1177 mg/kg for males and 612 mg/kg for females. The oral LD_{50} of mice was 522 mg/kg. The inhalation 4-hr LC_{50} of rats was >231 ppm (> 1.75 mg/L) for males and 157 ppm (1.19 mg/L) in females. The dermal LD_{50} of rats was 251 mg/kg compared to a dermal LD_{50} of 1120 mg/kg in rabbits. Data from skin and eye irritation studies in rabbits indicate that Primene™ 81-R Amine is corrosive to skin and eyes. Signs of central nervous system effects were seen by the oral, dermal, and inhalation routes of administration. Primene™ 81-R Amine was shown to produce skin sensitization in guinea pigs in a non-adjuvant study (i.e. Buehler) with acetone/ethanol as vehicles. However, use of mineral oil as the vehicle instead of acetone/ethanol, as well as a salt form of Primene™ 81-R Amine in mineral oil, did not produce skin sensitization.

In a 28-day repeated dose study, Primene™ 81-R Amine was administered to rats by dermal application at doses of 0, 5, 20, and 60 mg/kg body weight/day. There were no treatment-related mortalities, clinical signs, or effects on feed consumption. Body weight and cumulative body weight gain were not affected in females of any treatment group. Treatment-related effects on body weight and cumulative body weight gain were observed in high dose males at the end of weeks 1 and 2. Other statistically significant changes in body weight and body weight gain were attributed to solvent exposure. There was no treatment-related effect on any hematologic or clinical chemistry parameters. Increased absolute and relative adrenal weights were observed in both males and females in the high dose group (60 mg/kg/day). Other statistically significant

changes in absolute and relative organ weights were attributed to solvent exposure or judged incidental. Local skin irritation was observed at all dose levels, the duration and severity of which were dose-dependent. Treatment-related gross and histopathologic effects were confined to the skin (epidermis and dermis) and underlying subcutaneous tissues at the treatment site. The NOEL for systemic toxicity was 20 mg/kg/day. The minimum effect level was 60 mg/kg/day.

In a four week repeated dose study, the chemical was given to rats via nose-only inhalation for 6 hr per day, 5 days a week for four weeks to vapors of Primene™ 81-R Amine at concentrations of 2, 19, 129, and 537 mg/m^3. No significant clinical signs were observed at 2 or 19 mg/m^3. All animals at 537 mg/m^3 died by exposure day 11. These animals as well as those at the 129 mg/m^3 dose level showed signs of CNS effects (tremors, salivation and lacrimation). After 4 weeks of exposure, none of the survivors showed any effects of CNS effects. Male and female rats exposed to 129 mg/m^3 showed slight focal lesions of the nasal cavity. Microscopic changes at 537 mg/m^3 consisted of effects in the nasal cavity, larynx, trachea, and lung. The NOEL was 19 mg/m^3.

A one-generation reproductive toxicity study of rats was conducted by dietary exposure at 250, 750, and 1500 ppm, approximately equivalent to 20, 59, and 116 mg/kg/day, respectively. Continuous exposure of the chemical in the diet for one generation had a NOEL for parental toxicity of 250 ppm (~20 mg/kg). The reproductive and developmental NOEL was 250 ppm due to decreased pup body weight at both 750 and 1500 ppm and delayed sexual maturation in females at 750 ppm and in both sexes at 1500 ppm. No developmental toxicity was seen in rats treated percutaneously with 5, 15, or 45 mg/kg/day Primene™ 81-R Amine on gestation days 6-20. The developmental NOEL was 45 mg/kg/day and the maternal NOAEL was 5 mg/kg/day. Adverse clinical observations, skin reactions and reductions in body weights and feed consumption were observed in the 15 and/or 45 mg/kg/day dose groups.

Results from mutagenicity and chromosomal aberration studies indicate that Primene™ 81-R Amine is not genotoxic. The chemical was not mutagenic in an Ames mutagenicity assay and did not induce micronuclei in mouse bone marrow in vivo.

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on Primene™ 81-R Amine that either followed established protocols under GLP regulations or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to workers and the general population as well as the environment.

EVALUATION OF DATA FOR OUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance and the systematic approach described by Klirnisch *et al*. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their

usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation. The codification described by Klirnisch *et al*. (1997) specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in short abstracts or secondary literature (books, reviews, etc.)

REFERENCES

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.

2. USEPA. (1999). The U se of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA. (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J ., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacal.* 25:1-5.

5. USEPA. (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

I U C L I D

D a t a S e t

Existing Chemical ID: 68955-53-3
CAS No. 68955-53-3
EINECS Name Amines, C12-C14-tert-alkyl
EC No. 273-279-1
TSCA Name Amines, C12-C14-tert-alkyl
Molecular Formula C4H2N

Producer Related Part
Company: Rohm and Haas Company
Creation date: 07-JAN-2002

Substance Related Part
Company: Rohm and Haas Company
Creation date: 07-JAN-2002

Printing date: 30-JUL-2003
Revision date:
Date of last Update: **30-JUL-2003**

Number of Pages: **102**

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: cooperating company
Name: Rohm and Haas Company
Contact Person: Wendy W. Bingaman **Date:**
Street: 100 Independence Mall West
Town: 19106-2399 Philadelphia, PA
Country: United States
Phone: (215) 619-5531
Telefax: (215) 619-1657

Source: Rohm and Haas Company, Spring House, PA, USA
30-JUL-2003

Type: cooperating company
Name: Rohm and Haas Company
Contact Person: James E. McLaughlin **Date:**
Street: 727 Norristown Road
Town: 19477 Spring House, PA
Country: United States
Phone: (215) 641-7459
Telefax: (215) 619-1618

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.0.2 Location of Production Site, Importer or Formulator

Type: manufacturer
Name of Plant: Houston Plant
Street: 1900 Tidal Road
Town: 77536 Deer Park, TX
Country: United States
Phone: 1-281-228-8100
Telefax: 1-281-228-8684

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.0.3 Identity of Recipients

-

1.0.4 Details on Category/Template

-

1.1.0 Substance Identification

Mol. Formula: C12H27N to C14H31N

Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (1) valid without restriction
31-JAN-2002

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: = 100 - % v/v
Colour: Light colored
Odour: Amine odor

Source: Rohm and Haas Company, Spring House, PA, USA
01-FEB-2002

1.1.2 Spectra

Type of spectra: NMR

Method: NMR Equipment and Conditions
Pure solutions of Primene 81-R Amine was submitted for 1H and 13C NMR analysis to Spectral Data Services, Inc. The samples were run on a Modified NT-360 spectrometer with a Nicolet console. The 1H spectra was collected using the following parameters:

One pulse Sequence
P2 3.00 usec
D5 1.00 sec

NA 100
SIZE 32768
AT 1.36 sec
QPD ON 1
ABC ON
Butterworth Filter On
DB ATT 3
ADC 12 Bits
AI 5
SW +/- 3012.04
DW 166
RG 10 usec
DE 166 usec
TL High Power On
F2 360.006546
BB Modulation On
OF 2471.84

SF 360.007001
EM 0.20
PA 261.6
PB 35.7
T2 8000

Sample Preparation
The samples were mixed in approximately a 10% (v/v) ratio with CDCl3 and placed in an NMR tube along with a trace of tetramethylsilane (TMS) as a chemical shift reference (0 ppm).

Result: The 13C NMR spectrum shows that Primene 81-R Amine consists of a mixture of branched (primary, secondary and tertiary) alkyl amine species. The resonances observed between 55 and ~ 47 ppm are due to primary, secondary, and tertiary carbons bearing nitrogen as well as some highly branched alkyl species. Excess overlap of the amine and alkane resonances in the NMR spectrum prohibit calculation of the quantity of specific species.
The 1H NMR spectrum confirms that Primene 81-R Amine consists of a mixture of branched (primary, secondary and tertiary) alkyl amine species. Since all of the resonances observed are between 1.8 and 0.8 ppm, this also suggests that the amines found in the sample are tertiary alkyl based amines. (The general chemical shifts of protons on a carbon atom adjacent to an amine are 2.5 for methyl, 2.7 for methylene, and 3.1 for methine.)

Source: Rohm and Haas Company, Spring House, PA, USA

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (4)

Type of spectra: IR

Method: FTIR Analytical Equipment and Conditions
The instrument employed was a Perkin-Elmer Model Spectrum 2000. Primene 81-R Amine was run as a neat sample. The spectrum is obtained by running a background of the KBr liquid sample holder followed by the Primene 81-R Amine sample at 4 cm-1 resolution.

Sample Preparation
The Primene 81-R Amine sample was run as a neat liquid in a KBr liquid sample holder.

Result: The FTIR spectrum of Primene 81-R Amine is not available but the absorbance of the amine bands were observed at 815 cm-1 (-NH2 wag) and a doublet around 3,365 - 3,305 cm-1 (-NH2 stretch).

Source: Rohm and Haas Company, Spring House, PA, USA

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with

GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (3)

Type of spectra: GC

Method: Chromatographic Equipment and Conditions
The instrumentation used consisted of a Hewlett-Packard Model 5890 Gas chromatograph with FID and Split/Splitless injector equipped with a Hewlett-Packard Pascal Series Chem Station. Capillary GC analyses were conducted using the following conditions:

Column:	Ultra-1 50 meter X 0.2 mm X 0.33 mm Film Thickness
Carrier Gas:	Helium
Column Head Pressure:	27 PSI
Split Vent Flow Rate:	77 mL/min
Septum Purge Vent Flow Rate:	3 mL/min
Injector Temperature:	250 °C
Injection Volume:	1 mL, split injection
Detector temperature:	300 °C
Detector Attenuation/Range:	attn = 3, range = 2
Oven Parameters:	
Initial Temperature:	35 °C
Initial Hold:	0 min
Rate:	4 °C /min
Final Temperature:	250 °C
Final Hold:	20 min

Sample Preparation
Primene 81-R Amine was injected as a 1 uL neat sample for GC analysis.

Result: Results of GC Analysis
It has been of great interest to identify individual components of Primene 81-R Amine. The Methods Development Analytical Group of Rohm Haas, Texas has developed a capillary GC method, which can be used to separate most of the components present in the product. Using this method, it was noticed that Primene 81-R Amine samples contain approximately 200 components. Most of the components are C11-C14 isomers of tertiary alkyl primary amines (major C12; 66%).

Source: Rohm and Haas Company, Spring House, PA, USA

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (3)

Type of spectra: mass spectrum

Method: MS Analytical Equipment and Conditions

In continuation of the work to identify individual components of Primene 81-R Amine, a sample of 81-R was analyzed on the HP-5989 MS-Engine, using methane chemical ionization mass spectrometry. The separation was done on a 50 meter X 0.32 MM X 0.17 um film thickness, HP-1 column programmed from 35 °C to 250 °C at 3 °C/min. The Primene 81-R Amine was dissolved in methylene chloride and injected into split injection port at 250 °C. Since methane chemical ionization tends to protonate most compounds it was assumed that all of the molecular ions produced in MS were the protonated molecular ions. Mass spectrometric analysis was conducted under the following conditions:

MS System:

Ionization Mode:	CI
Run Time:	50 minutes
Helium Pressure:	10 psi
Source Temperature:	170 °C
Analyzer Temperature:	100 °C
Scan Range:	60 to 400 amu
Injection Volume	1 uL

Sample Preparation

The sample was prepared by dissolving and diluting Primene 81-R Amine in spectroscopic grade CH2Cl2, resulting in a Primene 81-R Amine concentration of 10% w/w.

Result: A sample of the Primene 81-R Amine was analyzed via GC/MS. Based on this analysis, it is concluded that the amount of C12 amine in Primene 81-R Amine is at least 70% and C12 - 14 t-alkyl amines are at more than 80%.

This data was calculated based on the total area of the protonated molecular ion for each amine, and then divided by the sum of the areas for all of the amines. It is also assumed that response factors for all amines are the same and no other components are present in the product. This assumption may not be correct, as other chemical analysis have shown presence of minor amounts of olefins and formamide (2-4%) in the product. This method cannot detect these components. It is most likely that the low molecular weight amines (C9-11) detected here are either incorrect or at a much lower actual concentration than reported.

Primene 81-R Amine Distribution

Amine	MH Ion	Area	Percent
C8	130	16511	Trace
C9	144	29437	.1
C10	158	1625985	5.28
C11	172	4399977	14.29
C12	186	21694458	70.47

C13	200	1656980	5.38
C14	214	1360935	4.42
C15	228	----	----

Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (3)

Type of spectra: UV

Method: The instrumentation employed was a Varian DMS100 UV/VIS Spectrophotometer. The analysis was conducted with the following conditions:

Mode:	Absorbance
Bandwidth	1.0 nm
Time Constant	0.3 sec
Scan Speed	50 nm/min
Upper Wavelength	580.1 nm
Lower Wavelength	190.0 nm
Cell Length	10 mm
Solvent	MeCN

Sample Preparation
The sample was prepared by diluting Primene 81-R Amine 0.0143 g to 250 mL in Spectophotometric grade Acetonitrile, resulting in a concentration of 0.3 mM.
Result: A sample of the test material was analyzed by UV/VIS spectroscopy. A peak at wavelength 196 nm was detected.
Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (3)

1.2 Synonyms and Tradenames

Amines, C12-C14-tert-alkyl; t-Alkyl (C12-C14) primary amines

Source: Rohm and Haas Company, Spring House, PA, USA
29-JAN-2002

Primene (TM) is a trademark of Rohm and Haas Company or one of its subsidiaries or affiliates.

Source: Rohm and Haas Company, Spring House, PA, USA
30-JAN-2002

Primene 81-R Amine

Source: Rohm and Haas Company, Spring House, PA, USA
30-JAN-2002

1.3 Impurities

Remark: Complex mixture with multiple isomers; no known impurities.
Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (1) valid without restriction
01-FEB-2002

1.4 Additives

Remark: Not applicable
Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (1) valid without restriction
01-FEB-2002

1.5 Total Quantity

Quantity: > 500 tonnes produced in 2001

Remark: Product is classified as a High Production Value (HPV) chemical.
Source: Rohm and Haas Company, Spring House, PA, USA
30-JUL-2003

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (T) toxic
(C) corrosive
(N) dangerous for the environment
R-Phrases: (22) Harmful if swallowed
(23/24) Toxic by inhalation and in contact with skin
(34) Causes burns
(43) May cause sensitization by skin contact
(48/23) Toxic: danger of serious damage to health by prolonged exposure through inhalation
(50/53) Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases: (36/37/39) Wear suitable protective clothing, gloves and eye/face protection

Remark: Additional S-phrases:
S36/37/39 - Wear suitable protective clothing, gloves, and eye/face protection.

S26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S28 - After contact with skin, wash immediately with plenty of soap and water.
S45 - In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S60 - This material and/or its container must be disposed of as hazardous waste.
S61 - Avoid release to the environment.

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: other: toxic; corrosive; hazardous to the environment
R-Phrases: (22) Harmful if swallowed
(23/24) Toxic by inhalation and in contact with skin
(34) Causes burns
(43) May cause sensitization by skin contact
(48/23) Toxic: danger of serious damage to health by prolonged exposure through inhalation
(50/53) Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.6.3 Packaging

Memo: Packaged in either drums, railcars, tank car or deck tanks.

Source: Rohm and Haas Company, Spring House, PA, USA
30-JUL-2003

1.7 Use Pattern

Type: industrial
Category: other: Fuel and Lubricant Additive, Surfactants, Dyes, Refinery Processes, Metal Working Fluids

Source: Rohm and Haas Company, Spring House, PA, USA
Flag: confidential
30-JUL-2003

1.7.1 Detailed Use Pattern

Industry category: 15/0 other
Use category: 55/0 other
Extra details on use category: No extra details necessary
No extra details necessary
Emission scenario document: not available

Remark: Industry Category:
Fuel and Lubricants, Surfactants, Dyes, Refinery and Processing, Metal Working Fluids
Source: Rohm and Haas Company, Spring House, PA , USA
Flag: confidential
01-FEB-2002

1.7.2 Methods of Manufacture

Type: Production

Remark: Primene 81-R Amine is manufactured in batch operations in kettles. All the product is hard-piped to temporary storage to either railcars, tank car or deck tanks.
Source: Rohm and Haas Company, Spring House, PA, USA
30-JUL-2003

1.8 Regulatory Measures

-

1.8.1 Occupational Exposure Limit Values

Type of limit: other: Rohm and Haas Company
Limit value: 1 other: ppm
Short term exposure
Limit value: 2.5 other: ppm

Remark: Risk of skin sbsorption associated with occupational exposure limit value.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.8.2 Acceptable Residues Levels

-

1.8.3 Water Pollution

-

1.8.4 Major Accident Hazards

Remark: Evacuate the spill area. Floor may be slippery, use care to avoid falling. Contain spills immediately with inert materials (e.g. sand, earth). Transfer liquids and solid diking material to separate suitable containers for recovery or disposal. Flush cleaned area with water to a sewage treatment facility. Avoid all contact.
WARNING: KEEP SPILLS AND CLEANING RUNOFFS OUT OF MUNICIPAL SEWERS AND OPEN BODIES OF WATER.
Reliability: (1) valid without restriction
01-FEB-2002

1.8.5 Air Pollution

Remark: Estimated partitioning of Primene 81-R Amine into the atmosphere will be negligible. Estimated degradation rats in atmosphere are rapid (i.e. 4 hrs). Volatization from water bodies expected to be moderate. Fugacity modeling would indicate partitioning into the atmosphere would be minimal.
Source: Rohm and Haas Company, Spring House, PA, USA
Reliability: (1) valid without restriction
30-JUL-2003

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: This product is in compliance with the inventory listing requirements of the Chemical Control Laws in the following countries:
United States of America
Canada
European Union
Japan
Australia
Korea
Philippines

Source: Rohm and Haas Company, Spring House, PA, USA
01-FEB-2002

1.9.1 Degradation/Transformation Products

Remark: This material is considered stable under specified conditions of storage, shipment and/or use. There are no known hazardous decomposition products for this material. Product will not undergo polymerization.
Source: Rohm and Haas Company, Spring House, PA, USA
01-FEB-2002

1.9.2 Components

-

1.10 Source of Exposure

Source of exposure: Human: exposure by production
Exposure to the: Substance

Remark: Inhalation: Inhalation of vapor or mist can cause irritation of nose, throat, and lungs.
Eye Contact: Material can cause severe irritation and permanent eye injury.
Skin Contact: Material is harmful if absorbed through the skin. Material can cause the following: - corrosion to the skin - burns - skin sensitization in susceptible individuals.
Ingestion: Material is harmful if swallowed. Material can be fatal in large amounts. Material can cause the following: - burning and severe swelling of the mouth, throat and digestive tract.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

1.11 Additional Remarks

-

1.12 Last Literature Search

-

1.13 Reviews

-

2.1 Melting Point

Value: = -65 degree C
Sublimation: no

Method: other: ASTM method D 97
Year: 1994
GLP: no data

Method: ASTM method D 97
The pour point of a petroleum sample is an index of the lowest temperature of its utility for certain applications. The pour point of t-Alkyl (C12-C14) primary amine was determined via ASTM D 97 method. After preliminary heating, the sample is cooled and examined at intervals of 3°C for flow characteristics. The lowest temperature at which movement of the test material is observed is recorded as the pour point.
Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine, lot No. 50025-92)
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
01-FEB-2002 (2)

2.2 Boiling Point

Value: = 217 - 231 degree C
Decomposition: no

Method: other: ASTM Method D-1078
Year: 1992
GLP: no

Method: ASTM Method D-1078
The boiling range or boiling temperature of a material is the temperatures at which the substance changes its physical state from a liquid to a gas. Environmentally, this physical property is important for identification purposes and is one factor influencing the states in which the substance will exist. The distillation range of Primene 81-R Amine is determined via ASTM Method D-1078. Primene 81-R Amine (100 mL) is distilled under conditions equivalent to a simple batch differential distillation. The temperature of the mercury thermometer is equilibrated with that of the refluxing liquid before the distillate is taken over. Temperatures are corrected to standard atmosphere pressure to give true boiling temperatures.
Year: 1992 to 1996
Remark: Boiling point determination was done following ASTM D 1078

test method at QAL (Rohm and Haas, Deer Park. ISO 9002)
Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine, lot # 350025-92)
Reliability: (2) valid with restrictions
Not conducted in compliance with GLP, but by recognized scientific standards.
Flag: Critical study for SIDS endpoint
25-JAN-2002 (1)

2.3 Density

Type: density
Value: = .8076 g/cm³

Method: other: Anton-Parr DMA-46 Densitometer
Year: 1994
GLP: no data

Method: Using Anton-Parr DMA-46 densitometer
The density of a substance is its mass per unit of volume. Relative density (specific gravity) is the ratio of the density of substance to the density of a reference substance. For liquids or solids it is the ratio of the density of the substance to the density of water at a specified temperature. A pure sample of Primene 81-R Amine was submitted for density analysis to Rohm and Haas, Analytical Research Department in Springhouse, PA. The density of Primene 81-R Amine was measured on an Anton-Parr DMA-46 densitometer. Each sample was measured in duplicate to insure accurate data. Air and water references were taken before and after the Primene 81-R Amine samples were measured. These air and water values were within predetermined specifications.
Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine, lot # 50025-92)
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (1)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: = 25.27 hPa at 10 degree C
Decomposition: no

Method: other (measured): ASTM D 2879
Year: 1999
GLP: no data

Method: Using an isoteniscope as described in ASTM D 2879
The vapor pressure of pure liquids is the pressure exerted by the vapors of said liquid. If the substance is in an enclosed space, the vapor pressure will reach a maximum value that depends only on the nature of the substance and the temperature. A sample of Primene 81-R Amine was measured for vapor pressure - temperature relationship. The data was obtained using an isoteniscope as described in ASTM D 2879. Dissolved and entrained fixed gases are first removed by heating a thin layer of the test sample at a reduced pressure. This process should remove the minimum amount of volatile constituents from the sample. The vapor pressure is then determined at selected temperatures by balancing the pressure due to the vapor of the sample against a known pressure of an insert gas. The manometer section of the isoteniscope is used to determine the pressure equality.

Result: Vapor Pressure by Isoteniscope (ASTM D2879)

Temperature (°C)	Vapor Pressure (Pa)
10	25.27
20	47.88
37.8	133.0
65.6	598.5
93.3	1968.4
121.1	5586.0
148.9	14231.0
176.7	31920.0
204.4	65170.0
218.3	90440.0

Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
25-JAN-2002 (1)

Value: = 15.16 hPa
Decomposition: no

Method: other (calculated)
Year: 2001
GLP: yes

Method: Vapor pressure of Primene 81-R Amine was derived from measured saturated vapor concentrations during the conduct of an acute vapor inhalation LC50 study in rats. The saturated vapor concentration of Primene 81-R Amine was determined using the same sampling and analytical methodology used to measure vapor concentration during the inhalation exposure.

Primene 81-R Amine vapor concentrations in Tedlar gas sampling bags and in inhalation toxicity chambers were determined using gas chromatography with flame ionization detection (GC-FID). The method for determining the saturated vapor concentration of Primene 81-R Amine was validated by measuring the saturated vapor concentration of several reference compounds and comparing the measured values to literature values. All of the measuered values were within 20% of the literature values.

Remark: Other estimates of vapor pressure were considered, since they were measured according to an isoteniscopic method recommended by an internationally recognized testings organization-American Society for Testing and Materials (ASTM). However, this method (ASTMD2879) acknowledges that even an ideal mixture will show a progressive decrease in vapor pressure as the lighter component is removed, and that this is vastly accentuated in complex mixtures such as Primene 81-R Amine. Such a mixture may well exert a pressure in a closed vessel of as much as 100 times that calculated from its average composition, and it is the closed vessel which is simulated by the isoteniscope. Therefore, use of the vapor pressure, as calculated from the saturated vapor concentrations measured in the acute inhalation toxicity study, is considered appropriate for Human Health Effects Assessment.

Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)
Conclusion: The average saturated vapor concentration of Primene 81-R Amine at 19°C was 150 ppm. The average saturated vapor pressure of Primene 81-R at 24°C was 220 ppm. These saturated vapor concentrations are equivalent to 0.114 and 0.167 torr at temperatures of 19°C and 24°C, respectively.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
29-JAN-2002 (12)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = 2.9 at 23 degree C

Method: other (measured): 40CFR Part 792
Year: 1994
GLP: yes

Method: Shake flask tests performed in accordance with Good Laboratory Practice Regulations 40 CFR Part 792. The values obtained by two methods - GC/NPD and titration.
Remark: The values obtained by two methods are not statistically different (P = 0.05, n = 22). The average log p is 2.9.
Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
01-FEB-2002 (7)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 1000 ppm at 25 degree C

Year: 1994
GLP: no data

Method: Solubility is measured as follows:
Spectrophotometric Equipment and Experimental Conditions
The water solubility of Primene 81-R Amine was determined via capillary gas chromatography at the Analytical Research Department of Rohm and Haas in Springhouse, PA. A HP-5890 GC with flame ionization detector was employed. The experimental conditions are given below:

Column	J&W DB-1 (100% dimethyl polysiloxane) 30 meter X 0.25 mm X 0.25 mm Film Thickness
Carrier Gas	Helium
Linear Flow Rate	27 cm/sec
Injector Temperature	75 °C
Injection Volume	1 mL, split injection
Detector temperature	350 °C
Oven Parameters	
Initial Temperature	35 °C
Initial Hold	0 min
Rate	8 °C/min
Final Temperature	320 °C
Run Time	50 min

Sample Preparation
The sample was prepared by adding 1 part Primene 81-R Amine

in 4 parts water. The two components were mixed for one hour at 55 °C. The mixture was placed in a separatory funnel and allowed to cool overnight. The clear bottom layer was centrifuged for 30 minutes at 25 °C (bench-top centrifuge). Afterwards, the clear water solution was ready for analysis by GC/FID.

Result: Results of water solubility and stability
The Primene 81-R Amine content in water was calculated using a 1000-ppm standard solution of THF. The total areas between 9 and 16 minutes were compared.
The water solubility of Primene 81-R Amine is 1000 mg/L at 25 °C. The Primene 81-R Amine is stable in water at 25 °C for two weeks. Two items were not considered when these measurements were done: 1) The pH of the tap water was not measured and 2) the effect of CO2 in the water. These effects may change the value; however, to what extent is unknown. Primene 81-R Amine's lower molecular weight fraction (<C12) is more soluble in water than the higher molecular weight fraction (C12-C14).

Source: Rohm and Haas Company, Spring House, PA, USA

Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JUL-2003 (1)

2.6.2 Surface Tension

Value: = 30 mN/m at 20 degree C

Year: 1994

GLP: no data

Method: Surface tension values were measured on the Fisher Surface Tensiometer, Model 20. Two measurements were performed and the values shown are averages. The instrument was calibrated using hexane and the values obtained were within 2 dynes/cm from theoretical as given in CRC handbook.

Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (34)

2.7 Flash Point

Value: = 75.5 degree C
Type: closed cup

Method: other: Pensky Martens Closed Cup
Year: 1994

Source: Rohm and Haas Company, Spring House, PA USA
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (28)

2.8 Auto Flammability

Value: = 247 degree C

Method: other: ASTM E 659
Year: 1995
GLP: no data

Source: Rohm and Haas Company, Spring House, PA USA
Test substance: t-Alkyl (C12-C14) primary amines (Primene 81-R Amine)
Conclusion: With auto-ignition temperature of 247 °C, t-Alkyl (C12-C14) primary amines (Primene 81-R Amine) is not considered as highly auto-flammable.
Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.
Flag: Critical study for SIDS endpoint
30-JAN-2002

2.9 Flammability

-

2.10 Explosive Properties

Method: other:ASTM E681-85

Method: Measurements are carried out in a glass reaction vessel having a volume of 5.00 dm3. A high voltage power supply was used to produce a high energy ignition source. The spark gap was located at the center of the reaction vessel, which was housed within a temperture controlled enclosure. A K-type thermocouple was located within the reaction vessel to monitor the temperature of the contents. The vessel was

fitted with a magnetic stirrer. After a period of equilibration at the desired temperature, different volumes of sample were injected into the vessel and the atmosphere agitated for 2 minutes to allow thermal equilibrium and total vaporization of the sample to occur. A spark was then passed through the sample for 2 seconds. The results are quoted as cm3 of liquid required per cubic meter of air.

The quantity of liquid injected was increase such that the lower limit was determined as the smallest injected quantity to form a flammable mixture. Determinations were then continued until a maximum flammable concentration was obtained. This point was the upper flammable limit, beyond this point the mixtures were over-rich and would not ignite.

Result: Lower explosible limit: 0.64% v/v @ 150 °C
Upper explosible limit: 5.05% v/v @ 150 °C

Source: Rohm and Haas Company, Spring House, PA, USA

Reliability: (2) valid with restrictions
No data on whether test was conducted in compliance with GLP, but test was conducted by recognized scientific standards.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (14)

2.11 Oxidizing Properties

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2.12 Dissociation Constant

-

2.13 Viscosity

30-JAN-2002

2.14 Additional Remarks

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3.1.1 Photodegradation

Type: air

Remark: Photodegradation information is not available. However, with regard to atmospheric oxidation the AOPWIN estimated half-lives equaled 3.05 and 3.13 hours for the C12 and C14 isomers, respectively. The model was unable to estimate atmospheric ozone reaction rates.
Source: Rohm and Haas Company, Spring House, PA, USA
Flag: Critical study for SIDS endpoint
01-FEB-2002

3.1.2 Stability in Water

Type: abiotic

Remark: Both measured and estimated environmental fate data indicate that Primene 81-R Amine will not persist in the environment. Measured data indicate that Primene 81-R Amine exhibits moderate volatility, the measured vapor pressure equalling 0.114 and 0.167 mm Hg at 19 and 24 °C, respectively. The QSAR estimated Henry's Law constants equal 1.71E-04 and 3.01E-04 atm-m3/mole for the C12 and C14 isomers, respectively, indicating that Primene 81-R Amine will exhibit a moderate tendency to partition out of the water phase into the atmosphere. Primary and ultimate biodegradation estimates are weeks to months, respectively, and indicate therefore that the chemical remaining in the aqueous compartment will be subject to effective biodegradative processess and thus will not tend to be persistent in the environment. Half-lives in modeled rivers and lakes indicate a similar rapid to moderately rapid removal from water bodies. River systems are estimated to have a more rapid rate of removal of Primene 81-R Amine when compared to that in lakes likely due to increase in turbulent flow influenced increases in volatilization.
Source: Rohm and Haas Company, Spring House, PA, USA
Flag: Critical study for SIDS endpoint
01-FEB-2002

3.1.3 Stability in Soil

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3.2.1 Monitoring Data (Environment)

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3.2.2 Field Studies

-

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III

Remark: For the C12 and C14 Primene 81-R Amine isomers, the Mackey level III steady state fugacity model indicates that for a given unit volume release of Primene 81-R Amine 72.4 and 53.4% of the material would partition into the soil (C12 and C14 isomers, respectively). The tendency to partition into the soil compartment is corroborated by the QSAR estimated log Koc of 3.7 and 4.1 which are indicative of high degree of adsorption to matrix organic carbon. Of the remaining C12 isomer, estimates suggest that 9.9 and 17.1% would partition into the sediment and water column compartments, respectively. For the C14 isomer, 36.1 and 10% would partition into the sediment and water column compartments, respectively. For the C12 and C14 isomers, according to the Mackey level III fugacity model partitioning into the air would account for a small amount of applied material equaling 0.65 and 0.47%, respectively.

Source: Rohm and Haas Company, Spring House, PA, USA

Flag: Critical study for SIDS endpoint

01-FEB-2002

3.3.2 Distribution

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3.4 Mode of Degradation in Actual Use

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3.5 Biodegradation

Type: aerobic
Concentration: mg/l
Contact time: 28 day(s)
Degradation: ca. 22 % after 28
Result: other: not readily biodegradable
Kinetic: 28 day(s) ca. 22 %

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1992
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Source: Rohm and Haas Company, Spring House, PA USA
Test condition: Type: aerobic
Inoculum: secondary effluent from an activated sludge treatment plant.
Degradation: approximately 22% after 28 days.
Result: not readily biodegradable.
Control substance: other: sodium acetate
Degradation Product: no
Method: OECD Guideline 301D Ready biodegradability in closed bottle test.
Year: 1994
GLP: yes
Result: approximately 93.0% of the sodium acetate was biodegraded in the 28-day test period, which verified that the microbial inoculum in the systems was viable and active. Approximately 21.8% of the Primene 81R was biodegraded in the 28-day test period. Two criteria were used to define the acceptability of the study results: the inoculum check (sodium acetate), and the inoculated blank (control + inoculum). The inoculum check was the system containing the reference substance with inoculation. If the BOD is greater than or equal to 60% of its ThOD (or COD) within 28 days, then the viability of the inoculum is acceptable in this test. The inoculum was shown to be viable since 93.0% of the reference substance biodegraded by 28 days.

The oxygen depletion in the inoculated blanks was 0.4 mg O2/L after 28 days. The values in these blanks were within the criteria limits recommended by the guideline.
Conclusion: The test substance, Primene 81-R Amine, degraded approximately 22% in 28 days and is not considered readily biodegradable according to the testing guidelines.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
25-JAN-2002 (20)

3.6 BOD5, COD or BOD5/COD Ratio

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3.7 Bioaccumulation

-

3.8 Additional Remarks

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AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = .56 - measured/nominal
LC50: = 1.3 - measured/nominal
Limit Test: no

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 1992
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED
- Nominal/measured concentrations: nominal
- Effect data (Mortality):
24 hr LC50 = 1.3 mg/L
48 hr LC50 = 1.3 mg/L
72 hr LC50 = 1.3 mg/L
96 hr LC50 = 1.3 mg/L
(95% confidence limits were: 1.0 to 1.8)
NOEC = 0.56 mg/L
- Concentration / response curve: not applicable
- Effect concentration vs. test substance solubility: the 3.2 mg/L test solutions had an oily surface film at 0-hour, which had dissipated by the 24 hour observation. All other test concentrations had no signs of surface films.
- Other effects: no abnormal effects or mortality were observed in the 0.32 and 0.56 mg/L test concentrations during the 96-hour exposure period. The abnormal effect of dark discoloration was observed in the 1.0 mg/L test concentration. No mortality was observed at 1.0 mg/L. The 1.8 and 3.2 mg/L test concentrations elicited 100% mortality within 24 hours.
RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: none
- Nature of adverse effects: none
RESULTS: TEST WITH REFERENCE SUBSTANCE
- Concentrations: not applicable
- Results: not applicable

Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS
- Strain: Rainbow Trout, Oncorhynchus mykiss
- Supplier: Mount Lassen Trout Farm, Red Bluff, CA, USA
- Wild caught: No
- Age/size/weight/loading: ± 17 weeks old fish with a mean wet weight of 0.95 0.19 g and a mean standard length of 42 ± 3 mm, and a mean total length of 49 ± 3 mm were used. This gave a test chamber biomass loading of 0.32 g/L for the definitive study.

- Feeding: fed newly hatched brine shrimp (Artemia sp) and/or a commercially available fish food daily.
- Pretreatment: held for 14 days prior to test initiation
- Feeding during test: no

STOCK AND TEST SOLUTION AND THEIR PREPARATION

- Dispersion: the working standard was prepared by weighing 320 mg (total product) of Primene 81R into a 10 ml volumetric flask. The flask was then brought to volume with acetone, for a final concentration of 32 mg/ml.
- Vehicle, solvent: acetone
- Concentration of vehicle/ solvent: 1.5 ml aliquot of acetone in each vehicle blank chamber and in each test concentration chamber.
- Other procedures: No

STABILITY OF THE TEST CHEMICAL SOLUTIONS: not described.
REFERENCE SUBSTANCE: No
DILUTION WATER

- Source: blending naturally hard well water with well water demineralized by reverse osmosis.
- Aeration: No
- Alkalinity: 160 mg/L (as CaCO3)
- Hardness: 148 mg/L (as CaCO3)
- TOC: <1.0 mg/L
- TSS: 0.3 mg/L
- pH: 8.1
- Oxygen content: 8.8 mg/L
- Conductance: 380 uM hos/cm
- Holding water: water quality measurements for hard blended dilution and holding water were made daily. A daily record of fish observations during the holding period, along with any prophylatic or therapeutic disease treatments, was maintained.

TEST SYSTEM

- Test type: static
- Concentrations: 0.32, 0.56, 1.0, 1.8, 3.2 mg/L
- Dosing rate: not applicable
- Renewal of test solution: not applicable
- Exposure vessel type: 5 gallon glass vessels containing 15 L of hard blended water
- Number of replicates, fish per replicate: 2 replicates per control and test concentrations with 5 fish per test vessel for a total of 10 fish per concentration.
- Test temperature: 15-17 degrees C
- Dissolved oxygen: 4.8-8.8 mg/L
- pH: 7.6-8.5
- Adjustment of pH: no
- Intensity of irradiation: 68 foot candles (732 lux)
- Photoperiod: 16 hour daylight

DURATION OF THE TEST: 96 hours
TEST PARAMETER: biological observations were made at test initiation and at each 24 hour interval.
SAMPLING: not performed
MONITORING OF TEST SUBSTANCE CONCENTRATION: all results were based on the nominal concentrations of 0.32, 0.56, 1.0,

1.8 and 3.2 mg/L. No analytical measurements of test concentrations were made.

Conclusion: The 24-, 48-, and 96-hour LC50 values for Primene 81-R Amine were all 1.3 mg/L (95% confidence limits of 1.0 to 1.8 mg/L). All results were based on the nominal concentrations of 0.32, 0.56, 1.0, 1.8 and 3.2 mg/L. The 96-hour no-observed effect concentration (NOEC) was 0.56 mg/L based on the lack of mortality or observed abnormal (sublethal) effects at this concentration. The slope of the 96-hour dose-response line was 18.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (33)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = .55 - measured/nominal
EC50: = 4.1 - measured/nominal
Limit Test: no

Method: OECD Guide-line 202
Year: 1981
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS
- Strain: Daphnia magna
- Source/supplier: in house daphnia culture maintained by ABC Laboratories since 1977. The primary culture was obtained from the Columbia National Fisheries Research Laboratory (CNFRL), Columbia, MO in 1977.
- Breeding method: not described.
- Age: first in star, < 24 hr old.
- Feeding: algae plus a supplement consisting of fish food and active dry yeast.
- Pretreatment: none
- Feeding during test: no
- Control group: solvent control

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: not described.
- Vehicle, solvent: acetone
- Concentration of vehicle/ solvent: 0.1 ml/L

STABILITY OF THE TEST CHEMICAL SOLUTIONS: not described.
REFERENCE SUBSTANCE: none
DILUTION WATER
- Source: reverse osmosis water and ABC Laboratories well water
- Aeration: no

- Alkalinity: 168 mg/L (as CaCO3)
- Hardness: 154 mg/L (as CaCO3)
- TOC: < 1.0 mg/L
- TSS: 0.1 mg/L
- pH: 8.4
- Oxygen content: 7.8-8.0
- Conductance: 320 uMhos/cm
- Holding water: water chemistry parameters of temperature dissolved oxygen and pH in all replicates of all test concentrations at 0 hour.

TEST SYSTEM
- Test type: static
- Concentrations: 0.55, 0.99, 1.8, 3.2 and 5.8 mg/L nominal.
- Renewal of test solution: not described.
- Exposure vessel type: 250 ml glass beakers containing 200 ml test volume.
- Number of replicates, individuals per replicate: 4 replicates per test concentration with 5 daphnids per replicate for a total of 20 daphnids/concentration.
- Test temperature: 20 ± 2 degrees C
- Dissolved oxygen: 6.6-8.4 mg/L
- pH: 8.2-8.6
- Adjustment of pH: not described.
- Intensity of irradiation: 71 foot candles (764 lux)
- Photoperiod: 16 hour light per day

DURATION OF THE TEST: 48 hours
TEST PARAMETER: biological observations were made at test initiation at each 24 hour interval.
SAMPLING: not performed.
MONITORING OF TEST SUBSTANCE CONCENTRATION: all results were based on nominal concentrations of 0.55, 0.99, 1..8, 3..2 and 5.8 mg/L. No analytical measurements of test concentrations were made.

Conclusion: The 24- and 48-hour EC50 values were > 3.2 and 4.1 mg/L, respectively, based on the nominal concentrations of Primene 81-R Amine. The 95% confidence limits for the 48-hour EC50 were 0.55 and 0.58 mg/L. The abnormal effects of immobility, quiescence, and/or daphnids on bottom of the test chamber were noted in the 0.99-, 1.8-, 3.2- and 5.8-mg/L test concentrations. All daphnids in the control, vehicle blank, and 0.55 mg/L based on the lack of immobility and/or abnormal/sublethal effects at that concentration. All control, vehicle blank, and exposure solutions were clear throughout the test.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (32)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = .05 - measured/nominal
EC10: - measured/nominal
EC50: = .2 -
Limit Test: no

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1981
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED
- Nominal/measured concentrations: nominal concentrations 0.05, 0.10, 0.20, 0.40 and 0.80 mg/L
- Effect data/Element values:

Time Period	EC50 (95% Confidence Limits) mg/L
0-48 hr	0.24 (0.20-0.29)
0-72 hr	0.20 (0.15-0.25)

- Cell density data: mg/L

Nominal Concentrations	24 Hr	48 Hr	72 Hr
Control	5.1	30	110
Solvent Control	5.3	30	110
0.05	5.2	31	120
0.10	4.4	23*	62*
0.20	3.9*	17*	55*
0.40	2.9*	11*	33*
0.80	1.3*	0.74*	0*

* denotes a significant ($p < 0.05$) inhibition effect from the control as calculated using transformed (square root) cell counts by Dunnett's test.
RESULTS CONTROL: no significant inhibition of growth in either the water or solvent control.
RESULTS: TEST WITH REFERENCE SUBSTANCE
- Concentrations: none
- Results: none
STATISTICAL RESULTS:
Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS
- Strain: Selenastrum capricornutum Printz
- Source/supplier: Department of Botany, Culture Collection of Algae, The University of Texas at Austin, TX, USA
- Laboratory culture: yes, parent culture received on April 19, 1994
- Method of cultivation: the parent culture was divided into individual lots by adding single scrapings to sterile culture tubes containing agar. The prepared lots were stored at room temperature
- Pretreatment: cultures are maintained under the same

conditions used for testing. The algal culture used for this toxicity test was 5 days old.
- Controls: water, solvent control (acetone)
- Initial cell concentration: 1.0 x 104 cells/ml
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: for definitive testing, an 8.0 mg/ml primary standard was prepared by weighing 0.0800 g of the test material in a 10ml volumetric flask and then brought to volume with acetone. The 8.0 mg/ml primary standard was then used to prepare the 0.80 mg/L working standard (level 5) by injecting a 0.20 ml aliquot into approximately 1800 ml media in a 2-liter volumetric flask and then brought to volume with algae nutrient medium. The 0.80 mg/L working standard was used to prepare test levels 1-4. This was accomplished by transferring aliquots of 62.5, 125, 250 and 500 mL of the 0.80 mg/L working standard to 1-L volumetric flasks. Each 1-L volumetric flask was then brought to volume with algae nutrient medium.
- Vehicle, solvent: acetone
- Concentration of vehicle/ solvent: 0.10 ml/L
- Other procedures: none
STABILITY OF THE TEST CHEMICAL SOLUTIONS: not described.
REFERENCE SUBSTANCE: none
DILUTION WATER
- Source: autoclaved reverse osmosis/deionized water passed through carbon, ion exchange, and organic adsorption cartridges and filtered through a 0.2 um hollow fiber final filter to produce 16-18 megaohm cm water.
- Aeration: not described.
GROWTH/TEST MEDIUM CHEMISTRY
- Alkalinity: not described.
- Hardness: not described.
- Salinity: not described.
- TOC: not described.
- EDTA: yes, the nutrient solution contained 300 ug/L.
- TSS: not described.
- pH: 7.7 ± 0.3 using 0.10 N NaOH and resterilized by passage through Milluipore 0.45-um filters.
- Dissolved oxygen: not described.
TEST SYSTEM
- Test type: static
- Concentrations: 0.05, 0.10, 0.20, 0.40 and 0.80 mg/L (based on total product)
- Renewal of test solution: none
- Exposure vessel type: 250 ml Erlenmeyer flasks
- Number of replicates: 3 for each test concentrations and controls.
- Test temperature: 24 to 25 degrees C
- pH: 7.7 to 8.1
- Intensity of irradiation: 800 ± 10% foot candles
- Photoperiod: continuous cool-white fluorescent lighting
TEST PARAMETER: 50% algal growth inhibition (EC50)
MONITORING OF TEST SUBSTANCE CONCENTRATION: All results were based on the nominal concentrations of 0.05, 0.10, 0.20,

0.40 and 0.80 mg/L total product. No analytical measurements of test concentrations were made.

Conclusion: The EC50 (0-48 hr) value for Primene 81-R Amine was estimated to be 0.24 mg/L (95% confidence limits = 0.20 and 0.29 mg/L) and the EC50 (0-72 hr) was 0.20 mg/L (95% confidence limits = 0.15 and 0.25 mg/L). The EC50 24-48 hr) was estimated to be 0.42 mg/L with (95% confidence limits = 0.39 and 0.44 mg/L). the 72-hour no-observed effect concentration (NOEC) was estimated to be 0.050 mg/L.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (16)

4.4 Toxicity to Microorganisms e.g. Bacteria

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4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species: Oncorhynchus mykiss (Fish, fresh water)
Endpoint: other: egg hatchability; survival; standard length; growth
Exposure period: 96 day(s)
NOEC: < .1 - measured/nominal

Method: other: OECD Guideline 210
Year: 1996
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Primene™ 81-R was administered for 96 days (62 days post-hatch) to rainbow trout (Oncorhynchus mykiss) under flow-through conditions. Fifteen rainbow trout embryos were exposed in each of four replicates to the following nominal concentrations: 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product. Mean measured concentrations were <MQL (control), <MQL (acetone control), 0.078, 0.16, 0.29, 0.59, and 1.4 mg/L. The recoveries in the two lower test substance treatments were estimated based on a mean recovery of 83% in the top three test substance treatments. All test solutions were clear and colorless with no visible surface films or precipitates. Water quality parameters of temperature (8.9 to 11.2EC), dissolved oxygen concentration (76 to 100% of saturation), and pH (7.8 to 8.4) were measured weekly during the course of the test.

Result: RESULTS: RANGE FINDING TEST: A 37-day (35 days post-hatch) flow-through range-finding test was conducted at nominal concentrations of 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product. Ten heavily eyed rainbow trout embryos were added to incubation cups in two replicates in each treatment. Egg hatch began on day 1 and was complete on day 2. After 37 days of exposure, percent mortality was 0, 0, 10, 5, 30, and 95% in the control, acetone control, 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L treatments, respectively. Mean standard length in the control, acetone, 0.094, 0.19, 0.38, and 0.75 mg/L treatments was 30, 30, 30, 30, 30, and 28 mm, respectively. Mean blotted wet weight in the control, acetone control, 0.094, 0.19, 0.38, and 0.75 mg/L treatments was 0.346, 0.350, 0.344, 0.357, 0.339, and 0.262 g, respectively. Sublethal behavioral effects consisted primarily of fish resting on the bottom of the test chamber in the 1.5 mg/L treatment. Test solutions were clear and colorless with no visible particulate material, surface film, undissolved test substance, or precipitate throughout the test.

Based on the results of the range-finding test, nominal concentrations selected for the definitive exposure were 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product.

RESULTS: EXPOSED
- Nominal/measured concentrations: nominal concentrations were 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product. Mean measured concentrations (estimates for the two lowest treatments) of Primene 81-R were <MQL (control), <MQL (acetone control), 0.078, 0.16, 0.29, 0.59, and 1.4 mg/L.
- Effect data: No effects on egg hatchability were observed at any concentration tested. Survival was significantly reduced at concentrations of 0.59 and 1.4 mg/L when compared to the pooled control. At 61 days post-hatch, a statistically significant reduction in standard length was detected at a concentration of 0.29 mg/L when compared to the pooled control. A statistically significant reduction in blotted wet weight was detected at concentrations of 0.16 and 0.29 mg/L when compared to the pooled control. The no-observed-effect concentration (NOEC) for egg hatchability was 1.4 mg/L. The NOEC for survival was 29 mg/L. The NOEC for growth (blotted wet weight) was 0.078 mg/L. The maximum acceptable toxicant concentration (MATC) based on growth (blotted wet weight) is estimated to be 0.11 mg/L.
- Concentration / response curve:
- Effect concentration vs. test substance solubility:
- Other effects:
RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: Egg fertilization averaged 94% in the lot of eggs fertilized for use in the test. Egg hatch began on day 28 and was 100% complete on day 34. Percent hatch was based on the number of embryos present after thinning on day 19 and the number of dead embryos and live fry accounted for on day 34. Hatching success in the control, vehicle control, and levels 1 through 5 was lOO, lOO, 98, 100, 100, 100, and 100%, respectively. No differences were detected between the control and acetone control and they were pooled. No statistically significant reduction in hatch was detected at any concentration when compared to the pooled control.

Normal swim-up behavior began on day 44 and was complete on day 55. The primary morphological abnoffi1alities that were observed during the study were fish resting on the bottom of the test chamber and abnormal development of the jaw. These observations were made in one to three individuals in the control, acetone control, 0.16, 0.29, 0.59, and 1.4 mg/L treatments and were first observed on day 48.

Post-hatch survival was based on the initial number of embryos present after thinning on day 19 and the number of fish accounted for at test teffi1ination. Percent survival in the control, vehicle control, and levels 1 through 5 was 98, 97, 95, 97, lOO, 80, and 0%, respectively. No differences were detected between the control and acetone control and they were pooled. A statistically significant reduction in survival was detected at concentrations of 0.59

and 1.4 mg/L when compared to the pooled control.

Growth was assessed at test termination (day 96, day 62 post-hatch) through standard length and blotted wet weight measurements. Although statistically significant differences with regard to length and weight were detected between the control and acetone control they were not felt to be biologically meaningful. To a large extent statistical significance is dependent on the variance of each group being evaluated. The length difference between the control and acetone control was very small at 2.7%. The statistical difference appears to be the result of tight replicate CV's (3.3 to 4.5% in the control and 3.6 to 5.4% in the acetone control). The weight difference between the control and acetone control was 7.5%. The statistical difference in the controls appears to be the result of tight replicate CV's (11 to 16% in the control and 10 to 18% in the acetone control). Three of the four acetone control replicates had CV's of lO, 13, and 13% while the fourth had a CV of 18%. These values represent relatively tight CV's for weight data. As a result even minor differences tend to be identified as statistically significant when they are not biologically meaningful. In addition hatch and survival responses indicate no effects due to the presence of acetone. Acetone is an EPA and OECD recommended solvent whose toxicological properties are well understood. The maximum amount of acetone used in this test was approximately 1~% of the maximum allowed in any test guideline. Based on this evaluation the control and vehicle control responses were pooled for comparison to the PrimeneTM 81-R treatments.
Mean standard length in the control vehicle control pooled control and levels 1 through 4 was 45.6, 46.9, 46.2, 46.2, 45.6, 44.9, and 41.7 mm respectively. The 0.59 mg/L treatment was excluded from the analysis due to significant survival effects. A statistically significant reduction in standard length was detected at a concentration of 0.29 mg/L when compared to the pooled control.
Mean blotted wet weight in the control vehicle control pooled control and levels 1 through 4 was 1.402, 1.516, 1.380, 1.459, 1.316, 1.247, and 0.966 g respectively. The 0.59 mg/L treatment was excluded from the analysis due to significant survival effects. A statistically significant reduction in blotted wet weight was detected at concentrations of 0.16 and 0.29 mg/L when compared to the pooled control.
- Nature of adverse effects:
RESULTS: TEST WITH REFERENCE SUBSTANCE
- Concentrations: see results above
- Results: see results above
STATISTICAL RESULTS: See above

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS
- Strain: Rainbow Trout, Oncorhynchus mykiss; Newly

fertilized embryos
- Supplier: Trout Lodge, Sumner, WA, USA
- Wild caught: No
- Post-hatch transfer time:
- Age/size/weight/loading: newly fertilized embryos with a mean wet weight of 0.95 0.19 g and a mean standard length of 42 3 mm, and a mean total length of 49 3 mm were used. This gave a test chamber biomass loading of 0.32 g/L for the definitive study.
- Feeding: beginning on day 46 (12 days post-hatch) fry were fed live brine shrimp (Artemia sp) nauplii and a standard commercial fish food.
- Pretreatment: held for 14 days prior to test initiation
- Feeding during test: Fed ad libitum at least three times daily during the week and twice a day on weekends and holidays. Food size and quantity were increased during testing on the basis of average fish size. The fish were not fed during the 24 hours preceding termination of the test.
- Controls:
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: diluter stock solutions were prepared at a nominal concentration of 116,550 mg/L by diluting approximately 5.8275 grams of Primene 81-R to 50 mL with acetone.
- Vehicle, solvent: acetone
- Concentration of vehicle/solvent: 1.5 ml aliquot of acetone in each vehicle blank chamber and in each test concentration chamber.
- Other procedures: No
STABILITY OF THE TEST CHEMICAL SOLUTIONS: On each sample day (-N, 0, 7 and weekly thereafter, up to and including test termination), the concentration of Primene 81-R in test solutions was determined by liquid-liquid extraction followed by GC analysis.
REFERENCE SUBSTANCE: Primene 81-R
DILUTION WATER
- Source: the dilution water was a moderately hard freshwater prepared by blending naturally hard well water with well water demineralized by reverse osmosis (RO).
- Aeration: Yes, prior to delivery to the diluter system
- Alkalinity: 150 to 162 mg/L (as CaCO3)
- Hardness: 138 to 156 mg/L (as CaCO3)
- Salinity:
- TOC: <1.0 mg/L
- TSS: 0.3 mg/L
- pH: 7.4 to 8.4
- Oxygen content: 8.1 to 10.8 mg/L
- Conductance: 285 to 347 mg/L (mS)
- Holding water: water quality measurements for hard blended dilution and holding water were made daily. A daily record of fish observations during the holding period, along with any prophylatic or therapeutic disease treatments, was maintained.

TEST SYSTEM
- Test type: flow-through
- Concentrations: 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product.
- Dosing rate: average of 7.2 volume additions per day to each test chamber
- Renewal of test solution:
- Exposure vessel type: test chambers consisted of glass aquaria measuring approximately 15 cm wide by 31 cm long by 29 cm high with a test solution depth of 22 cm. These dimensions yielded a test solution volume of approximately 10 L.
- Number of replicates, fish per replicate: 2 replicates per control and test concentrations with 5 fish per test vessel for a total of 10 fish per concentration.
- Test temperature: 8.9 to 11.2 degrees C
- Dissolved oxygen: 8.1 to 10.8 mg/L
- pH: 7.4-8.4
- Adjustment of pH: no
- Intensity of irradiation: average 539 ± 53 lux
- Photoperiod: 16 hour light:8 hour dark
DURATION OF THE TEST: 96 days (62 days post-hatch)
ENDPOINTS ASSESSED: egg hatchability, fry survival, and growth
SAMPLING: not performed
MONITORING OF TEST SUBSTANCE CONCENTRATION: On each sample day (-N, 0, 7 and weekly thereafter, up to and including test termination), the concentration of Primene 81-R in test solutions was determined by liquid-liquid extraction followed by GC analysis. Nominal concentrations of 0 (control), 0 (0.013 mL/L acetone control), 0.094, 0.19, 0.38, 0.75, and 1.5 mg/L as total product. Mean measured concentrations (estimates for the two lowest treatments) of Primene 81-R were <MQL (control), <MQL (acetone control), 0.078, 0.16, 0.29, 0.59, and 1.4 mg/L.

Conclusion: Egg hatchability was not significantly reduced at any concentration tested when compared to the pooled control. All endpoints were based on total product. No effects on egg hatachability were observed at any concentration tested. Survival was significantly reduced at concentrations of 0.59 and 1.4 mg/L when compared to the pooled control. At 62 days post-hatch, a statistically significant reduction in standard length was detected at a concentration of 0.29 mg/L when compared to the pooled control. The 0.59 mg/L treatment was excluded from the analysis due to significant survival effects. At 62 days post-hatch, s statistically significant reduction in blotted wet weight was detected at concentrations of 0.16 and 0.29 mg/L when compared to the pooled control. The 0.59 mg/L treatment was excluded from the analysis due to significant survival effects. The no-observed-effect concentration (NOEC) for egg hatchability was 1.4 mg/L and the NOEC for survival was 0.29 mg/L. The NOEC for standard length was 0.16 mg/L and the NOEC for

blotted wet weight was 0.078 mg/L. The lowest-observed-effect concentration (LOEC) for egg hatchability was >1.4 mg/L and the LOEC for survival was 0.59 mg/L. The LOEC for growth (blotted wet weight) was 0.16 mg/L. The maximum acceptable toxicant concentration (MATC) for Primene™ 81-R, based on growth (blotted wet weight), is estimated to be 0.11 mg/L.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
16-JUL-2003 (27)

4.5.2 Chronic Toxicity to Aquatic Invertebrates

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TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

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4.6.2 Toxicity to Terrestrial Plants

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4.6.3 Toxicity to Soil Dwelling Organisms

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4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

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4.7 Biological Effects Monitoring

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4.8 Biotransformation and Kinetics

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4.9 Additional Remarks

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5.0 Toxicokinetics, Metabolism and Distribution

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5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: no data
Sex: male
No. of Animals: 50
Vehicle: other: propylene glycol
Doses: 200, 250, 350, 400, 450 mg/kg
Value: = 320 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY:
- Time of death: Most deaths occurred within a few hours after dosing.
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/kg)	No. Rats Dosed	No. Rats Dying	LD50 (mg/kg)
200	10	2	
250	10	1	
350	10	4	320 ± 80
400	10	9	
450	10	10	

CLINICAL SIGNS: Death was preceeded by moderately strong convulsive movements.
NECROPSY FINDINGS: Gross necropsy showed some hyperemia of the stomach wall but no appearance of marked irritation.
POTENTIAL TARGET ORGANS: stomach
SEX-SPECIFIC DIFFERENCES: not applicable

Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS: rats
- Source: no data
- Age: young rats
- Weight at study initiation: 150 g
- Controls: none

ADMINISTRATION: test substance was prepared as a 10% solution in propylene glycol and administered by gavage
- Doses: 200, 250, 350, 400, 450 mg/kg
- Doses per time period: one
- Volume administered or concentration: not described
- Post dose observation period: not described

EXAMINATIONS: no data

Conclusion: The acute oral LD50 in male albino rats was 320 mg/kg.
Reliability: (4) not assignable
Documentation insufficient for assessment.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (19)

Type: LD50
Species: rat
Strain: other: Crl:CD BR
Sex: male/female
No. of Animals: 60
Vehicle: other: corn oil
Doses: 50, 250, 500, 750, 1000, 1500 mg/kg
Value: > 500 mg/kg bw

Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY:
- Time of death: Males - 2 at 1000 mg/kg on day 1; 1 at 1500 mg/kg 1 hr post-dosing (day 0); 3 at 1500 mg/kg on day 1; 1 at 1500 mg/kg on day 2. Females - 2 at 500 mg/kg 2 hr post-dosing (day 0); 1 at 500 mg/kg 4 hr post-dosing (day 0); 1 at 500 mg/kg on day 1; 1 at 750 mg/kg 1 hr post-dosing (day 0); 1 at 750 mg/kg 2 hr post-dosing (day 0); 5 at 1500 mg/kg 1 hr post-dosing (day 0); 1 at 1500 mg/kg 2 hr post-dosing (day 0).
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/kg)	50	250	500	750	1000	1500
Males	---	0/6	0/6	0/6	2/6	5/6
Females	0/6	0/6	4/6	2/6	---	6/6

CLINICAL SIGNS: No clinical signs related to test substance were observed in the 250-mg/kg group for males and in the 50- and 250-mg/kg groups for the females. Clinical signs indicative of neurotoxicity (abnormal gait, tremors, and convulsions) were observed at dose levels of 500 mg/kg and greater in survivors as well as decedents. Surviving animals recovered from the neurotoxic effects by day 2 of the study. Other clinical signs related to the test substance observed in survivors as well as decedents included prostration, abnormal breathing patterns, scant or no feces and ptosis. There were no apparent dose-related body weight effects in this study.
NECROPSY FINDINGS: Necropsy of the decedents revealed numerous gastro-intestinal effects related to the test substance. Necropsy of the survivors revealed no gross changes related to the test substance.
POTENTIAL TARGET ORGANS: gastro-intestinal tract
SEX-SPECIFIC DIFFERENCES: Statistically significant

sex-related difference in mortality observed.

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS: rats
- Source: Crl:CD BR
- Age: 55 days (males); 65 days (females)
- Weight at study initiation: 184-232 g (males); 187-217 g (females)
- Controls: none

ADMINISTRATION: test substance was mixed with corn oil and administered by gavage.
- Doses: 250, 500, 750, 1000, 1500 mg/kg (males); 50, 250, 500, 750, 1000 mg/kg (females)
- Doses per time period: one
- Volume administered or concentration: 10 mL/kg
- Post dose observation period: 14 days

EXAMINATIONS: 0.5, 1, 2, and 4 hr after dosing and once daily for 14 days

Conclusion: Since there was a statistically significant sex-related difference in mortality observed, the LD50 was calculated separately for males and females. The acute oral LD50 in male rats was 1177 mg/kg with 95% confidence limits of 974 and 1422 mg/kg. The acute oral LD50 in female rats was 612 mg/kg with 95% confidence limits of 442 and 848 mg/kg.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

01-FEB-2002 (24)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
No. of Animals: 15
Vehicle: no data
Doses: 100, 200, 300, 500, 750 mg/kg
Value: mg/kg bw

GLP: no

Result: MORTALITY:
- Time of death: not reported
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/kg)	100	200	300	500	750
Deaths acute	0	0	1	1	2
Deaths delayed	0	0	0	0	1
Deaths total	0/3	0/3	1/3	1/3	3/3

CLINICAL SIGNS: not reported
NECROPSY FINDINGS: not reported
POTENTIAL TARGET ORGANS: not reported
SEX-SPECIFIC DIFFERENCES: not reported

Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS: mouse
- Source: not reported
- Age: not reported
- Weight at study initiation: not reported
- Controls: not reported

ADMINISTRATION: not described
- Doses: 100, 200, 300, 500, 750 mg/kg
- Doses per time period: not reported
- Volume administered or concentration: not reported
- Post dose observation period: not reported

EXAMINATIONS: not reported
Test substance: Primene 81R was dissolved in water by the addition of dilute hydrochloric acid.
Reliability: (4) not assignable
Documentation insufficient for assessment.
Flag: Critical study for SIDS endpoint
30-JAN-2002 (26)

Type: LD50
Species: mouse
Strain: CD-1
Sex: male/female
No. of Animals: 65
Vehicle: other: corn oil
Doses: 250, 375, 500, 1000, 1500 mg/kg
Value: = 552 mg/kg bw

Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1997
GLP: yes

Result: MORTALITY:
- Time of death: Males - 1 at 375 mg/kg on day 1; 2 at 500 mg/kg 1 hr post-dosing (day 0); 1 at 500 mg/kg on day 1; 2 at 1000 mg/kg 1 hr after dosing (day 0); 2 at 1000 mg/kg 2 hr post-dosing (day 0); 2 at 1000 mg/kg on day 1; 5 at 1500 mg/kg 1 hr post-dosing (day 0); 1 at 1500 mg/kg 2 hr post-dosing (day 0). Females - 1 at 375 mg/kg 4 hr post-dosing (day 0); 1 at 500 mg/kg 1 hr post-dosing (day 0); 4 at 1000 mg/kg 1 hr post-dosing (day 0); 2 at 1000 mg/kg 4 hr post-dosing (day 0)
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/kg)	250	375	500	1000	1500
Males	0/11	1/6	3/6	6/6	6/6
Females	0/12	1/6	1/6	6/6	---
Combined Sexes	0/23	2/12	4/12	12/12	---

CLINICAL SIGNS: Clinical signs indicative of neurotoxicity were observed in male and/or female mice at 250 mg/kg and above. These signs were evident beginning at 1 hr post-dosing and were no longer evident in surviving mice by day 2 post-dosing. These signs included: tremors, hyperactivity, straub tail, passiveness and ataxia. In addition to the neurotoxicity signs, scant feces was also noted on day 1. Surviving mice were normal by day 2. Corneal opacity noted in a single female at 250 mg/kg was considered incidental. One male at 500 mg/kg was misdosed. Necropsy of this animal revealed test material in the axillary area. A female at 250 mg/kg was found dead on day 7. The clinical signs noted in this animal (i.e., wet-matted fur on the muzzle on day 0, respiratory noise and labored breathing on days 5 and 6) indicated that some test material may have been aspirated at the time of dosing. It was judged that this death was not treatment-related but rather a probable dosing error. Neither of these animals were included in the calculation of the LD50.
There were no body weight effects when compared to historical control data
NECROPSY FINDINGS: Necropsy of the decedents revealed gastro-intestinal changes: reddened intestines and clear

fluid in the stomach; carcass autolysis was also noted. Necropsy of the survivors revealed no gross changes related to the test substance.
POTENTIAL TARGET ORGANS: gastro-intestinal tract
SEX-SPECIFIC DIFFERENCES: none

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS: mice
- Source: Crl:CD-1 (ICR)BR
- Age: 7-8 weeks (males); 8-9 weeks (females)
- Weight at study initiation: 27-33 g (males); 23-31 g (females)
- Controls: none

ADMINISTRATION: test substance was mixed with corn oil and administered by gavage.
- Doses: 250, 375, 500, 1000, 1500 mg/kg (males); 250, 375, 500, 1000 mg/kg (females)
- Doses per time period: one
- Volume administered or concentration: 10 mL/kg
- Post dose observation period: 14 days

EXAMINATIONS: 1, 2, and 4 hrs after dosing and once daily for thereafter for 14 days.

Conclusion: The LD50 value was calculated from the combined male and female mortality incidence data. The acute oral LD50 for Primene 81-R Amine in male and female mice was 552 mg/kg with 95% confidence limits of 470 to 719 mg/kg.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (11)

07-JAN-2002

08-JAN-2002

09-JAN-2002

09-JAN-2002

09-JAN-2002

09-JAN-2002

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: other: Crl:CD BR
Sex: male/female
No. of Animals: 60
Doses: 0.00, 0.05, 0.63, 0.90, 0.94 mg/L
Exposure time: 4 hour(s)
Value: > .94 mg/l

Method: OECD Guide-line 403 "Acute Inhalation Toxicity"
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY:
- Time of death: Males - 1 at 0.90 mg/L during exposure period (day 0); 2 at 0.94 mg/L during exposure period (day 0); 1 at 0.94 mg/L on day 2. Females - 1 at 0.90 mg/L during exposure period (day 0); 1 at 0.90 mg/L immediately after the exposure period (day 0); 2 at 0.94 mg/L during exposure period (day 0).
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/L)	0.00	0.05	0.63	0.90	0.94
Males	0/6	0/6	0/6	1/6	3/6
Females	0/6	0/6	0/6	2/6	2/6

CLINICAL SIGNS: Signs of respiratory irritation (gasping, respiratory noise, salivation and labored breathing), were seen at 0.94, 0.90 and 0.63 mg/L, post exposure. Other clinical signs in these groups included unkempt appearance, passiveness, behavior and red-stained muzzle.
Animals exposed at concentrations of 0.94 and 0.63 mg/L showed signs of scant feces, and animals at 0.63 mg/L also had signs of yellow-stained anogenital area, red-stained dropsheets and no feces. Animals at all concentrations plus controls were noted as having wet fur post exposure. The wet fur was attributed to the nose-only restraining method and not a result of the test material exposure. All clinical signs disappeared by day 1 except for respiratory noise at 0.90 mg/L, which disappeared by day 3. Animals exposed to a concentration of 0.94 mg/L, signs disappeared by day 8, at a concentration of 0.90 mg/L, signs disappeared by day 6, at a concentration of 0.63 mg/L, signs disappeared by day 11, and at a concentration of 0.05 mg/L, signs disappeared by day1. Signs of nervous system toxicity (tremors and salivation) were observed at 0.94, 0.90 and 0.63 mg/L; however, these signs rapidly disappeared after cessation of exposure. Compared to the control animals, the body weight change on all treated groups was decreased on day 1. However, by day 7, the mean body weight change of

surviving animals of all groups had exceeded their pre-exposure body weight. By day 14 all treated groups exhibited body weight increases comparable to the controls. Necropsy observations of animals exposed to Primene 81R showed no treatment related gross lesions.
NECROPSY FINDINGS: Necropsy observations of animals exposed to vapor concentrations of Primene 81R showed no treatment related gross lesions. Scattered incidences of red foci and reddened lungs were observed in all groups, including the control group. One incidence of reddened intestines was observed in an animal found dead at 0.94 mg/L. Comparison to historical control data showed that the incidence of these lesions was not treatment related.
POTENTIAL TARGET ORGANS: lungs
SEX-SPECIFIC DIFFERENCES: none

Source: Rohm and Haas Company, Spring House, PA, USA

Conclusion: The estimated combined male and female LC50 was greater than 0.94 mg/L of Primene 81-R Amine per liter of air.

Test condition: TEST ORGANISMS:
- Source: Crl:CD BR, Charles River-Kingston, Stone Ridge, NY USA
- Age: not reported
- Weight at study initiation: 180 - 227 g (males); 182 - 241 g (females)
- Number of animals: 24 males, 24 females
- Controls: 6 males, 6 females

ADMINISTRATION:
- Type of exposure: single four-hour nose only inhalation exposures to vapors of Primene 81R
- Concentrations: 0.00, 0.05, 0.63, 0.90, 0.94 mg/L, analytical concentrations
0, 0.4, 7.0, 15.0, 16.6 mg/L, nominal concentrations

- Particle size: not applicable - study conducted with vapors, not aerosols
- Type or preparation of particles: not applicable - study conducted with vapors, not aerosols

EXAMINATIONS: All animals were observed for signs of intoxication during the exposure period and for 14 days following exposure. Examinations for neurotoxicity were conducted immediately after exposure and for seven days following the exposure. Body weights were monitored on days 0, 1, 7, and 14 during the fourteen-day observation period.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (5)

Type: LC50
Species: rat
Strain: other: Crl:CD BR
Sex: male/female
No. of Animals: 30
Doses: 91, 151, 231 ppm
Exposure time: 4 hour(s)
Value: >= 157 ppm

Method: OECD Guide-line 403 "Acute Inhalation Toxicity"
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY:
- Time of death: Males - 2 at 231 ppm during exposure period (day 0). Females - 1 at 151 ppm during exposure period (day 0); 1 at 151 ppm on day 1; 3 at 231 ppm during exposure period (day 0); 1 at 231 ppm on day 1.
- Number of deaths at each dose: (number of deaths/number treated)

Dose (ppm)	91	151	231
Males	0/5	0/5	2/5
Females	0/5	2/5	4/5

CLINICAL SIGNS: Numerous clinical signs of toxicity were noted in all exposure levels in both sexes beginning upon removal from the chamber and continuing through day 7. These clinical signs included: respiratory noise, labored breathing, gasping, abnormal gait, ataxia, tremors, passiveness, scant feces, arched back, prostration and/or yellow/brown stained anogenital area, red material surrounding the eyes and/or muzzle. There was no effect on body weight in either sex at any exposure level when compared to historical control values.
NECROPSY FINDINGS: Necropsy of the decedents revealed dark, mottled and/or reddened lungs, distended stomachs, and thymus reddened and/or having multiple red foci. Necropsy of the survivors revealed no gross changes.
POTENTIAL TARGET ORGANS: lungs
SEX-SPECIFIC DIFFERENCES: Even though the results did not indicate a statistically significant sex-related difference in mortality across dose groups for males and females, the LC50 was calculated on the female mortality incidences at each dose since at least 50% mortality was not observed in males at the highest exposure level (231 ppm).
Source: Rohm and Haas Company, Spring House, PA, USA
Conclusion: The acute inhalation LC50 for Primene 81-R Amine in female rats was 157 ppm (1.19 mg/L) with 95% confidence limits of 90 to 249 ppm. The acute inhalation LC50 for Primene 81-R Amine in male rats was greater than 231 ppm (1.75 mg/L).
Test condition: TEST ORGANISMS:
- Source: Crl:CD BR, Charles River-Kingston, Stone Ridge, NY

USA
- Age: 8 weeks (males); 10 weeks (females)
- Weight at study initiation: 234 - 274 g (males); 219 - 267 g (females)
- Number of animals: 15 males, 15 females
- Controls: none
ADMINISTRATION:
- Type of exposure: single four-hour nose only inhalation exposures to vapors of Primene 81R
- Concentrations: 91, 151, 231 ppm (0.69, 1.14, 1.75 mg/L), analytical concentrations
- Particle size: not applicable - study conducted with vapors, not aerosols
- Type or preparation of particles: not applicable - study conducted with vapors, not aerosols
EXAMINATIONS: All animals were observed for signs of intoxication during the exposure period and daily for 14 days following exposure. Body weights were recorded on days 0, 7, and 14 during the fourteen-day observation period.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
30-JAN-2002 (13)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Strain: other: Crl:CD BR
Sex: male/female
No. of Animals: 36
Vehicle: other: Neutral Oil 100 N
Doses: 50, 200, and 400 mg/kg
Value: = 251 mg/kg bw

Method: OECD Guide-line 402 "Acute dermal Toxicity"
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: - Time of death: Males - 1 at 200 mg/kg 4 hr post-dosing (day 0); 3 at 400 mg/kg 2 hr post-dosing (day 0); 3 at 400 mg/kg 4 hr post-dosing (day 0). Females - 1 at 200 mg/kg 4 hr post-dosing (day 0); 1 at 200 mg/kg on day 1; 5 at 400 mg/kg 4 hr post-dosing (day 0).
- Number of deaths at each dose: (number of deaths/number treated)

Dose (mg/kg)	50	200	400
Males	0/6	1/6	6/6
Females	0/6	2/6	5/6

CLINICAL SIGNS: No mortalities and no clinical signs related to the test substance were seen in the 50- mg/kg dose group.

A dose-related increase in mortality was observed in the 200- and 400-m/kg dose groups. Clinical signs indicative of neurotoxicity (tremors and/or convulsions) were observed in survivors as well as decedents in the 200- and 400-mg/kg dose groups. Surviving animals recovered from the neurotoxic effects by day 1 of the study. Periodically during the study, the fur surrounding the eyes and muzzle was observed to be red-stained; these effects were judged to be caused by the occluded testing methodology and by the use of collars. There was no apparent test substance related body weight effects in this study. Numerous skin irritation effects were seen in both sexes at all doses.
NECROPSY FINDINGS: Necropsy of the decedents revealed numerous skin irritation effects related to the test substance. No gross changes observed in survivors.
POTENTIAL TARGET ORGANS: skin
SEX-SPECIFIC DIFFERENCES: No statistically significant sex-related differences observed.

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS:
- Source: Crl:CD BR rats, Charles River-Kingston, Stone Ridge NY USA
- Age: 55 days (males); 65 days (females)
- Weight at study initiation: 223 - 248 g (males); 206 - 243 g (females)
- Controls: none

ADMINISTRATION:
- Area covered: clipped intact skin, entire trunk between the flank and shoulders
- Occlusion: polyethylene sheet and PEG elastic bandages secured in place with adhesive tape
- Vehicle: neutral oil 100 N
- Concentration in vehicle: none
- Total volume applied: 2.0 mL/kg
- Doses: 50, 200, or 400 mg/kg bw
- Removal of test substance: After 24 hr, the backs were wiped with water-soaked paper towels

EXAMINATIONS: Clinical signs observed 0.5, 1, 2, and 4 hr after dosing and once daily for 14 days. Body weights recorded on day 0 (prior to dosing) and on days 7 and 14.

Conclusion: The acute dermal LD50 in male and female rats (combined) was 251 mg/kg with 95% confidence limits of 190 and 322 mg/kg.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (23)

Type: LD50
Species: rabbit
Strain: New Zealand white
Sex: no data
No. of Animals: 12
Vehicle: no data
Doses: 0.625, 1.25, 2.5 g/kg
Value: = 1120 mg/kg bw

GLP: no data

Method: New Zealand White rabbits were clipped free of abdominal hair. Epidermal abrasions were made longitudinally every 2 to 3 cm over the exposed area. The abrasions were sufficiently deep to penetrate the stratum corneum but not deep enough to produce bleeding. Three groups of four were treated with doses of 0.625, 1.25, and 2.5 g/kg. The doses were applied to the exposed area. The area was covered with gauze and the trunk was wrapped with impervious material for 24 hours. At 24 hours the surviving rabbits were cleansed and dermal reactions evaluated by the Draize technique.

Result: MORTALITY:
- Time of death: 2 at 1.25 g/kg on day 1; 1 at 1.25 g/kg on day 7; 2 at 2.5 g/kg on day 0; 2 at 2.5 g/kg on day 1
- Number of deaths at each dose: (number of deaths/number treated)

Dose (g/kg)	0.625	1.25	2.5
Deaths	0/4	3/4	4/4

CLINICAL SIGNS: Clinical signs indicative of neurotoxicity were observed at all dose levels. These signs included: tremors, convulsions, dilated pupils and ataxia. Marked redness and moderate edema observed in all animals at 24 hr.

NECROPSY FINDINGS: Peritoneal wall red, kidney and liver pale in 1/4 rabbits in the 1.25 g/kg dose group. Liver and lungs dark in 1/4, liver pale and grainy in 1/4, and liver pale in 1/4 rabbits in the 2.5 g/kg dose group.
POTENTIAL TARGET ORGANS: liver, lung, kidney
SEX-SPECIFIC DIFFERENCES: not reported

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS:
- Source: New Zealand White
- Age: not reported
- Weight at study initiation: not reported
- Controls: none

ADMINISTRATION:
- Area covered: clipped free of abdominal hair
- Occlusion: covered with gauze and wrapped with impervious material
- Vehicle: not reported
- Concentration in vehicle: not reported
- Total volume applied: not reported

- Doses: 0.625, 1.25, 2.5 g/kg
- Removal of test substance: not described
EXAMINATIONS: Clinical signs observed frequently on day 0 and daily for 14 days. Body weights recorded on day 0 an in surviving rabbits on day 14.

Conclusion: The acute dermal LD50 was estimated to be 1.12 (0.83 - 1.51) g/kg.
Reliability: (3) invalid
Flag: Critical study for SIDS endpoint
30-JAN-2002 (21)

07-JAN-2002

5.1.4 Acute Toxicity, other Routes

-

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 6
PDII: 7.3
Result: corrosive
EC classificat.: corrosive (causes burns)

Method: other: 49CFR, Section 173.240(a)(2)
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: 0.5 mL of the liquid test substance, as received, was held under a patch covered with an impervious cuff in continuous 4-hr contact with the skin from which the hair had been closely clipped. After the 4-hr exposure, the patches and cuffs were removed and the application sites were wiped gently with paper towels moistened with 80% (V/V) ethanol in water.
Result: AVERAGE SCORE
- Erythema: 4.0
- Edema: 3.3
REVERSIBILITY: no
OTHER EFFECTS: On Day 21, severe erythema with eschar (in all rabbits) and eschar sloughing off with hair growth beneath it (in 5 of the 6 rabbits) was observed. Desiccation was also observed. On Day 28, no erythema or edema was observed. Three rabbits had hair growth over entire site with a small area that was hard to the touch.

The other rabbits had possible scar formation. The one remaining rabbit's skin site appeared normal. On Day 35, no erythema or edema was observed. One rabbit had a white linear striation on the application site and possible scar formation. Four of the six rabbits had a small area that was hard to the touch and hair growth covering the entire application site.

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS:
- Strain: New Zealand White rabbits
- Sex: male
- Source: Hazelton Dutchland, Denver, PA USA
- Age: 13 - 18 weeks
- Weight at study initiation: not reported
- Number of animals: 6
- Controls: none

ADMINISTRATION/EXPOSURE
- Preparation of test substance: undiluted
- Area of exposure: clipped intact skin on back
- Occlusion: entire trunk of each animal was wrapped with a polyethylene sheet and an impervious cuff secured with adhesive tape for 4 hr
- Vehicle: none
- Concentration in vehicle: not applicable
- Total volume applied: 0.5 mL
- Postexposure period: skin irritation was evaluated at 24, 48, and 72 hr and 7 and 14 days after patch removal.
- Removal of test substance: application sites wiped gently with paper towels moistened with 80% (v/v) ethanol in water

IN VITRO TEST SYSTEM
- Cell type: not applicable
- Test conditions: not applicable

EXAMINATIONS
- Scoring system: Draize et al.
- Examination time points: 24, 48, and 72 hr and 7 and 14 days after patch removal

Conclusion: Based on the severe and persisting dermal reactions, and the possible scar formation underneath the skin, the test substance is considered corrosive to the skin of rabbits.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (18)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 6
Result: corrosive
EC classificat.: corrosive (causes burns)

GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE
- Erythema:
- Edema:
REVERSIBILITY: no, study conducted for DOT Classification
OTHER EFFECTS:

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS:
- Strain: New Zealand White rabbits
- Sex: 1 (male); 5 (females)
- Source: not reported
- Age: not reported
- Weight at study initiation: 2.1 kg (male); 2.2 - 2.7 kg (females)
- Number of animals: 6
- Controls: none

ADMINISTRATION/EXPOSURE
- Preparation of test substance: undiluted
- Area of exposure: clipped intact skin on back
- Occlusion: gauze patch secured in place by hypoallergenic tape and wrapped with impervious plastic sheet
- Vehicle: none
- Concentration in vehicle: not applicable
- Total volume applied: 0.5 mL
- Postexposure period: skin irritation was evaluated at 4, 24, and 48 hr after patch removal.
- Removal of test substance: application sites wiped gently with water and non-irritating soap

IN VITRO TEST SYSTEM
- Cell type: not applicable
- Test conditions: not applicable

EXAMINATIONS
- Scoring system: Draize et al.; for DOT Classification
- Examination time points: 4, 24, and 48 hr after patch removal

Conclusion: The test material is considered corrosive. PII not determined.

Reliability: (2) valid with restrictions
Data Quality: this study was conducted in accordance with recognized scientific procedures for assessing potential skin irritation/corrosivity in mammals.

Flag: Critical study for SIDS endpoint

30-JAN-2002 (29)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
No. of Animals: 6
Result: corrosive
EC classificat.: risk of serious damage to eyes

Method: other: Draize
GLP: no

Method: Six prescreened New Zealand White rabbits were used for this study. One-tenth of a milliliter of the test material was instilled into the conjunctival sac of one eye of each rabbit on Day 0. The lids were held closed for a few seconds and released. The ocular reactions were graded at 1, 2, 3, and 7 days after instillation of the test material.

Result: AVERAGE SCORE (over 7 days)
- Cornea: 39
- Iris: 8.5
- Conjuntivae (Redness): 3.0
- Conjuntivae (Chemosis): 3.7
- Overall irritation score:

DESCRIPTION OF LESIONS:

REVERSIBILITY:

OTHER EFFECTS:

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS:
- Strain: New Zealand White
- Sex: not reported
- Source: not reported
- Age: not reported
- Weight at study initiation: not reported
- Number of animals: 6
- Controls: no

ADMINISTRATION/EXPOSURE
- Preparation of test substance: undiluted
- Amount of substance instilled: 0.1 mL of the test substance
- Vehicle: undiluted
- Postexposure period: 1, 2, 3 an 7 days after instillation of the test substance

IN VITRO TEST SYSTEM
- Cell type: not applicable
- Test conditions: not applicable

EXAMINATIONS
- Ophtalmoscopic examination: not reported
- Scoring system: Draize

- Observation period: 1, 2, 3 an 7 days post exposure
- Tool used to assess score: not reported

Conclusion: Primene 81-R Amine was found to be corrosive to the eyes.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
01-FEB-2002 (22)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
No. of Animals: 10
Result: highly irritating
EC classificat.: risk of serious damage to eyes

Method: Draize Test
GLP: yes

Method: The purpose of this study was to evaluate whether washing with distilled water or 0.85% saline would diminish or enhance the eye irritation causd by Primene 81-R Amine in the rabbit. One-tenth milliliter of undiluted Primene 81-R Amine was applied to the cornea of the left eye of male New Zealand White rabbits (2 rabbits per group). The treated eyes of one group of rabbits received no further treatment after dosing. The treated eyes of the remaining four groups of rabbits were irrigated with either distilled water or 0.85% saline beginning either 4 or 30 seconds after dosing. The degree of eye irritation for each animal was scored according to Draize's procedure at 24, 48, and 74 hr and at 7, 14, and 21 days.

Result: DESCRIPTION OF LESIONS: In rabbits dosed with Primene 81-R Amine and receiving no further treatment (i.e., unwashed eyes), both rabbits exhibited corneal, iridal, and conjunctival effects at 24 hr. Conjunctival and iridal effects were no longer present at Day 14. Corneal effects ere still present by Day 21. In addition, blood vessels extending onto the cornea, blanched nictitating membrane, eschar on eyelids, bulging of the cornea, and hair loss around the treated eye were observed during the 21-day observation period.

In groups receiving a distilled water or saline wash 4 seconds after treatment with Primene 81-R Amine, both animals in each group exhibited corneal, iridal, and conjunctival effects at 24 hr. Iridal and conjunctival effects in animals washed with distilled water 4 seconds after dosing were recovered by Day 7 and 14, respectively. Iridal and conjunctival effects in animals washed with saline 4 seconds after dosing were recovered by 72 hr and Day 14, respectively. Corneal effects were present at 21 days in both groups. In addition, blood vessels extending onto the cornea, blanched nictitating membrane, hair loss around the treated eye and eyelids pinched together at corners were observed during the 21-day observation period.

In groups receiving a distilled water or saline was 30 seconds after treatment with Primene 81-R Amine, both animals in each group exhibited corneal, iridal, and conjunctival effects at 24 hr. Iridal and conjunctival effects in animals washed with distilled water 30 seconds after dosing were recovered by Day 7 and 14, respectively. Iridal and conjunctival effects in animals washed with saline 30 seconds after dosing were recovered by Day 7 and Day 21, respectively. Corneal effects were present at 21 days in both groups. In addition, circumcorneal blood vessels, blanched nictitating membrane, hair loss around eye, eschar on eyelids, bulging of the cornea, and eyelids pinched together at corners were observed during the 21-day observation period
REVERSIBILITY:
OTHER EFFECTS:

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS:
- Strain: New Zealand White rabbits
- Sex: male
- Source: Hazleton Research Animals, Denver, PA USA
- Age: not reported
- Weight at study initiation: not reported
- Number of animals: 10
- Controls:

ADMINISTRATION/EXPOSURE
- Preparation of test substance: undiluted
- Amount of substance instilled: 0.1 mL of undiluted test substance
- Vehicle: none
- Postexposure period: 24, 48, and 72 hrs and at 7, 14, and 21 days post exposure

IN VITRO TEST SYSTEM
- Cell type: not applicable
- Test conditions: not applicable

EXAMINATIONS
- Ophtalmoscopic examination: Yes, gross examination of the eyes was performed 24 hr prior to testing (i.e., rabbit eyes were screened using 2.0% sodium fluorescein followed by distilled water rinse).
- Scoring system: Draize Test
- Observation period: 24, 48, and 72 hrs and at 7, 14, and 21 days post exposure
- Tool used to assess score: fluorescein (i.e. 2% sodium fluorescein)

Conclusion: Primene 81-R Amine produced severe eye irritation. When compared to unwashed treated eyes, washing with either water or saline 4 or 30 seconds after treatment resulted in no significant increases or decreases in the corneal, iridal, or conjunctival effects.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint
30-JAN-2002 (17)

5.3 Sensitization

Type: Buehler Test
Species: guinea pig
Concentration 1st: Induction 7.5 % other: closed patch
2nd: Challenge 2 % other: closed patch
No. of Animals: 57
Vehicle: other: mineral oil
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
Year: 1993
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS OF PILOT STUDY: Based on these results, a test article concentration of 7.5% w/v Primene 81-R Amine was considered to be appropriate for the first induction; however, due to lack of primary irritation observed after the first induction, the test article concentration was increased to 10% w/v for the second and third inductions. A test article concentration of 2.0% was considered acceptable for challenge and for both rechallenges.
RESULTS OF TEST
- Sensitization reaction:
INDUCTION

	Incidence Irrit/Sensit.	
	24 Hr	48 Hr
1st 7.5% w/v in mineral oil	0/10 (0)	0/10 (0)
2nd 10.0% w/v in mineral oil	5/10 (0.9)	2/10 (0.6)
3rd 10.0% w/v in mineral oil	7/10 (0.7)	0/10 (0)
CHALLENGE		
2% w/v in mineral oil	0/10 (0)	0/10 (0)
RECHALLENGE		
2% w/v in mineral oil	3/10 (0.3)	0/10 (0)
2nd RECHALLENGE		
2% w/v in mineral oil	1/10 (0.1)	0/10 (0)

Note: the value in parenthesis represent the mean dermal score (i.e. the intensity of the irritation response)
- Clinical signs: following challenge ± Primene 81-R Amine, no or minimal dermal reactions (scores 0 to) were observed at the test article challenge sites in both the test and challenge control animals at the 24 and 48 hour scoring intervals. Group mean dermal scores following challenge

were also comparable between test and control animals.
- Rechallenge: following rechallenge with Primene 81-R Amine, a grade 1 dermal response was noted in 3/10 test animals ± 24 hours. No or minimal dermal reactions (scores of 0 to) were noted in the remaining test animals and all control animals at both the 24 and 48 hour scoring intervals.

Following the second rechallenge, ± grade 1 dermal response was noted in 1/10 test animals at 24 hours. No or minimal dermal reactions (scores of 0 to) were noted in the remaining test animals and all control animals at both the 24 and 48 hour scoring intervals.

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS: guinea pig
- Strain: Hartley Derived Albino
- Sex: male and female
- Source: Harlan Sprague Dawley, Inc., Indianapolis, IN, USA
- Age: young adult
- Weight at study initiation: 300 to 500 g
- Number of animals: 57
- Controls: non-induced challenge controls

ADMINISTRATION/EXPOSURE
- Study type: delayed contact hypersensitivity
- Preparation of test substance for induction: test material diluted in USP grade mineral oil to achieve appropriate test concentrations.
- Preparation of test substance for challenge: : test material diluted in USP grade mineral oil to achieve appropriate test concentrations.
- Induction schedule: three induction applications of 0.3 ml of the test dilution for one 6hr period per week for 3 weeks.
- Concentrations used for induction: a test concentration of 7.5% w/v of Primene 81-R Amine diluted with mineral oil was applied during the first induction and a test concentration of 10% w/v Primene 81-R Amine diluted in mineral oil was used for the second and third induction applications.
- Concentration in Freuds Complete Adjuvant (FCA): not applicable
- Challenge schedule: guinea pigs were challenged with a test concentration of 2% w/v Primene 81-R Amine diluted in mineral oil after a 2 week rest period following the last induction application.
- Concentrations used for challenge: 2% w/v Primene 81-R Amine diluted in mineral oil
- Rechallenge: ginea pigs were rechallenged twice: once 7 days following the challenge phase and once again 7 days following the rechallenge phase. A 2% w/v Primene 81-R Amine mineral oil dilution was applied to the skin at a volume of 0.3 ml test material per patch.
- Positive control: DNCB (1-chloro-2,4-nitrobenzene). The DNCB test animals received 0.5% w/v DNCB in acetone/ethanol.

EXAMINATIONS

- Grading system: according to Buehler, 1965
- Pilot study: a preliminary irritation screen was performed to determine an appropriate concentration of the test article for the standard sensitization study.

On the day prior to dose administration, the hair was removed from the dorsal trunk area of two male and two female guinea pigs with a small animal clipper. On the following day, four chambers at four different concentrations (100% as received, and 75%, 50% and 25% w/v Primene 81-R Amine in USP grade mineral oil) were applied to the clipped area of each animals (one chamber for each level of test article). A dose of 0.3 ml of the freshly prepared test solution was placed on a 25 mm Hilltop chamber backed by adhesive tape. The chambers were then applied to the clipped surface as quickly as possible. The trunk of the animal was wrapped with elastic wrap and secured with adhesive tape to prevent removal of the chamber. The animal was then returned to its cage.

Approximately six hours after dosing, the elastic wrap, tape and chambers were removed. The test sites were wiped with gauze moistened in USP grade mineral oil to remove test article residue and the animals returned to their cages. Approximately 24 and 48 hours following chamber application the test sites were graded according to Buehler.

Due to the large amount of irritation noted at the test sites during the range-finding study, additional range-finding was performed using two additional male and two additional female guinea pigs. Clipping, dosing and scoring were performed in the same manner as the initial range-finding study except the test article concentrations utilized were 10%, 5.0%, 2.5% and 1.0% w/v in USP grade mineral oil.

Conclusion: Conclusion: Under conditions of this test, Primene 81-R Amine is not considered to be a contact sensitizer in guinea pigs.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (10)

Type: Buehler Test
Species: guinea pig
Concentration 1st: Induction 75 % occlusive epicutaneous
2nd: Challenge 25 % occlusive epicutaneous
No. of Animals: 63
Vehicle: other: mineral oil
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
Year: 1993
GLP: yes
Test substance: other TS

Result: RESULTS OF PILOT STUDY: Based on these results, a test article concentration of 75% w(/v) Primene 81-R Amine was considered to be appropriate for the first induction; however, due to severe irritation observed after the first induction, the test article concentration was decreased to 50% for the second induction. However, following the second induction a significant reduction in dermal irritation was noted, and therefore, the test article concentrations was increased to 75% (w/v) for the third induction. A test article concentration of 25.0% was considered acceptable for challenge and for three rechallenges.
RESULTS OF TEST
- Sensitization reaction:

INDUCTION	Incidence Irrit/Sensit. 24 Hr	48 Hr
1st 75.0% (w/v) in mineral oil	6/10 (0.6)	7/10 (0.7)
2nd 50.0% (w/v) in mineral oil	0/10	0/10
3rd 75.0% (w/v) in mineral oil	5/10 (0.5)	3/10 (0.3)
CHALLENGE		
25% (w/v) in mineral oil	0/10	0/10
RECHALLENGE		
25% (w/v) in mineral oil	0/10	0/10
2nd RECHALLENGE		
25% (w/v) in mineral oil	9/10* (2.7)	9/10* (2.7)
3rd RECHALLENGE		
25% (w/v) in mineral oil	1/10 (0.1)	0/10

* the cause of the unusually high dermal responses in both the test and control animals could not be determined.

However, since these findings were inconsistent with the results obtained during the range-finding and challenge the results were not considered reliable and a third rechallenge was performed.

Note: the value in parenthesis represent the mean dermal score (i.e. the intensity of the irritation response)
- Clinical signs: following challenge with 25% Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, no or minimal dermal reactions (scores 0 to ±) were observed at the 24 and 48 hour scoring intervals inboth the test and challenge control animals. Group mean dermal scores following challenge were also comparable between test and control animals.
- Rechallenge: following rechallenge with 25% Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, minimal dermal reactions (scores of ±) were again noted in the test animals at the 24/48 hr scoring intervals. Dermal responses in the rechallenge control animals ranged from 0 to 1 at 24 hr and 0 to ± at 48 hr.

Following the second rechallenge with 25% Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, a grade 3 dermal response was noted in 9/10 test animals and 2/10 rechallenge control animals at both 24 and 48 hour scoring intervals. The cause of the unusually high dermal responses in both the test and control animals could not be determined. However, since these findings were inconsistent with the results obtained during range-finding an challenge, the results were not considered reliable and a third rechallenge was performed.

Following the third rechallenge with 25% Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, a grade 1 dermal response was noted in 1/10 test animals at the 24 hour scoring interval. No or minimal dermal reactions (scores of 0 to ±) were noted in the remaining test animals and in the second and third rechallenge of control animals at both 24 and 48 hours.

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ANIMALS: guinea pig
- Strain: Hartley Derived Albino
- Sex: male and female
- Source: Harlan Sprague Dawley, Inc., Indianapolis, IN, USA
- Age: young adult
- Weight at study initiation: 300 to 500 g
- Number of animals: 63
- Controls: non-induced challenge controls

ADMINISTRATION/EXPOSURE
- Study type: delayed contact hypersensitivity
- Preparation of test substance for induction: test material diluted in USP grade mineral oil to achieve appropriate test concentrations.
- Preparation of test substance for challenge: : test material diluted in USP grade mineral oil to achieve

appropriate test concentrations.
- Induction schedule: three induction applications of 0.3 ml of the test dilution for one 6hr period per week for 3 weeks.
- Concentrations used for induction: a test concentration of 75% w/v of Primene 81-R Amine/H3PO4 (85%) (1N:1P), 50% water diluted with mineral oil was applied during the first and third induction and a test concentration of 50% w/v Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, diluted in mineral oil was used for the second induction application.
- Concentration in Freuds Complete Adjuvant (FCA): not applicable
- Challenge schedule: guinea pigs were challenged with a test concentration of 25% w/v Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, diluted in mineral oil after a 2 week rest period following the last induction application.
- Concentrations used for challenge: 25% w/v Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, diluted in mineral oil
- Rechallenge: guinea pigs were rechallenged three times: once 7 days following the challenge phase, once again 7 days following the rechallenge phase and lastly, 7 days following the 2nd rechallenge. A 25% w/v Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, mineral oil dilution was applied to the skin at a volume of 0.3 ml test material per patch.
- Positive control: DNCB (1-chloro-2,4-nitrobenzene). The DNCB test animals received 0.5% w/v DNCB in acetone/ethanol.
EXAMINATIONS
- Grading system: according to Buehler, 1965
- Pilot study: a preliminary irritation screen was performed to determine an appropriate concentration of the test article for the standard sensitization study.

On the day prior to dose administration, the hair was removed from the dorsal trunk area of two male and two female guinea pigs with a small animal clipper. On the following day, four chambers at four different concentrations (100% as received, and 75%, 50% and 25% w/v Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water, in USP grade mineral oil) were applied to the clipped area of each animals (one chamber for each level of test article). A dose of 0.3 ml of the freshly prepared test solution was placed on a 25 mm Hilltop chamber backed by adhesive tape. The chambers were then applied to the clipped surface as quickly as possible. The trunk of the animal was wrapped with elastic wrap and secured with adhesive tape to prevent removal of the chamber. The animal was then returned to its cage.

Approximately six hours after dosing, the elastic wrap, tape and chambers were removed. The test sites were wiped with gauze moistened in USP grade mineral oil to remove test article residue and the animals returned to their cages. Approximately 24 and 48 hours following chamber application the test sites were graded according to Buehler.

Due to the large amount of irritation noted at the test sites during the range-finding study, additional range-finding was performed using two additional male and two additional female guinea pigs. Clipping, dosing and scoring were performed in the same manner as the initial range-finding study except the test article concentrations utilized were 10%, 5.0%, 2.5% and 1.0% w/v in USP grade mineral oil.

Test substance: Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water
Conclusion: Under conditions of this test, Primene 81-R Amine/H3PO4 (85%) (IN:1P), 50% water is not considered to be a contact sensitizer in guinea pigs.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
30-JAN-2002 (9)

Type: Buehler Test
Species: guinea pig
Concentration 1st: Induction 3 % open epicutaneous
2nd: Challenge 1 % open epicutaneous
No. of Animals: 30
Vehicle: other: ethanol
Result: sensitizing
Classification: sensitizing

GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS OF PILOT STUDY: The range-finding primary skin irritation tests results on 32 naïve guinea pigs were 3% in absolute ethanol for induction and 1% in acetone for challenge.
RESULTS OF TEST
- Sensitization reaction:

Induction	Incidence Irritation/Sensitization 24 hr	48 hr
3% (w/v) in ethanol	0/10 (0.2)	0/10 (0.1)
Challenge		
1% in acetone	15/19 (1.4)	10/19 (0.7)

Note: the value in parenthesis represents the mean dermal score (i.e., the intensity of the irritation response)
- Clinical signs: At a challenge concentration of 1% Primene 81-R Amine in acetone, 15 of the 19 guinea pigs induced with Primene 81-R Amine responded with erythema of grade 1 or greater while none of the non-induced guinea pigs responsed with erythema of grade 1 or greater.
- Rechallenge: not applicable
Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ANIMALS:
- Strain: Hartley guinea pigs
- Sex: male/female
- Source: Charles River-Kingston, Stone Ridge, NY USA

- Age: not reported
- Weight at study initiation: 426 - 632 g
- Number of animals: 30
- Controls: non-induced challenge control

ADMINISTRATION/EXPOSURE

- Study type: delayed contact hypersensitivity
- Preparation of test substance for induction: Ethanol was used in the preparation of different concentrations of Primene 81-R Amine.
- Preparation of test substance for challenge: Acetone was used in the preparation of different concentrations of Primene 81-R Amine.
- Induction schedule: Ten induction doses of 0.4 mL of 3% (w/v) test substance in absolute ethanol for three 6-hr periods per week for 3.5 consecutive weeks.
- Concentrations used for induction: 50, 25, 12.5, 6, 3, 1, 0.5, and 0.25% in ethanol (in ethanol)
- Concentration in Freuds Complete Adjuvant (FCA): not applicable
- Challenge schedule: guinea pigs were challenged with 1% (w/v) Primene 81-R Amine in acetone after a two-week rest period following the last induction application.
- Concentrations used for challenge: 1% (w/v) Primene 81-R Amine in acetone
- Rechallenge: not applicable
- Positive control: not applicable

EXAMINATIONS

- Grading system: according to Buehler, 1965
- Pilot study: Range-finding skin irritation tests were conducted on 16 naïve guinea pigs to determine the slightly irritating concentration to be used for induction and the highest non-irritating concentration to be used for challenge.

Conclusion: Under the condition of this study, Primene 81-R Amine produced delayed contact hypersensitivity in guinea pigs and Primene JM-T elicited a cross delayed hypersensitivity reaction in guinea pigs induced with Primene 81R.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

30-JAN-2002 (6)

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: 6 hrs/day
Frequency of treatment: 5 days/week for 4 weeks
Post exposure period: none
Doses: 0 (Sham Control), 0 (Solvent Control), 5, 20, 60 mg/kg/day
Control Group: other: Sham Control and Solvent Control (Neutral Oil 100N)
NOAEL: = 20 mg/kg
LOAEL: = 60 mg/kg

Method: OECD Guide-line 410 "Repeated Dose Dermal Toxicity: 21/28-day Study"
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL (NOEL), LOAEL (LOEL): NOEL 20 mg/kg/day
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX
- Time of death: 2 rats sacrificed for humane reason on day 11
- Number of deaths at each dose: 2 females at 60 mg/kg/day
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: no treatment-related mortalities
- Clinical signs: Red-stained muzzle and red-stained eyes were observed in all treatment groups and were judged to be caused by the collar. Alopecia of the forelegs and scabs on the head or neck were observed and judged unrelated to test substance exposure.
- Body weight gain: No treatment-related effect on body weight or cumulative body weight gain was evident in females at any dose level. In males, both body weight and cumulative body weight gain were statistically significantly less than the Sham control in Groups 4 (20 mg/kg/day) and 5 (60 mg/kg/day) throughout the treatment period, and in Group 3 (5 mg/kg/day) at the end of weeks 1 and 4. Body weight was also consistently less in Group 2 (Solvent Control) males throughout the treatment period. Though this difference was statistically significant only at the end of week 4. When compared to Group 2 (Solvent Control), body weight and cumulative body weight gain were significantly lower only in Group 5 males at the end of weeks 1 and 2. These results indicate that body weight effects observed in Groups 3 and 4 (5 and 20 mg/kg/day) males were attributable to Neutral Oil 100N exposure, and only in Group 5 were effects on body weights directly related to Primene 81R exposure.
- Food/water consumption: There was no treatment-related

effect on feed consumption in male or female rats at any dose level. A statistically significant reduction in feed consumption was noted in male rats at 60 mg/kg/day during week two of exposure; but this reduction was judged incidental and not test substance-related.
- Ophthalmoscopic examination: not conducted
- Clinical chemistry: No treatment-related clinical chemistry effects were observed in any group. However, numerous statistically significant changes in clinical chemistry parameters were noted but were judged to be incidental since there was a general lack of dose response or consistent pattern between endpoints and sexes, and absence of correlative histopathologic changes. Alkaline phosphatase levels were significantly increased in males at 60 mg/kg/day. Triglyceride levels were significantly reduced in males at 5 and 60 mg/kg/day groups and chloride was significantly increased in males at 20 mg/kg/day. In females, blood urea nitrogen levels were significantly increased in 60 mg/kg/day dose group, and total protein was significantly increased in Solvent Control and 20 mg/kg/day dose groups.
- Haematology: No treatment-related effect on any hematologic parameter at any dose level. A significant increase in hemoglobin concentration was observed in Group 2 (Solvent Control) females and a significant reduction in lymphocyte count was observed in females at 60 mg/kg/day dose group. These observations were judged incidental due to the minimal change observed and the lack of dose response.
- Urinalysis: not conducted
- Organ weights: The only treatment-related organ weight changes observed were significantly increased absolute and relative adrenal weights in both sexes at the 60 mg/kg/day dose group.
- Gross pathology: Treatment-related gross pathologic observations were confined to the dermal application site (treated skin) of the test material. The severity and distribution as well as the number of lesions at the application site were dose-dependent. Gross observations included scales, erosions, scabs and/or cracking fissures of the epidermis.
- Histopathology: Treatment-related histopathologic observations were confined to the dermal application site (treated skin) of the test material. The severity and distribution as well as the number of lesions at he the application site were dose-dependent. Microscopic observations included multifocal to diffuse, and moderate to severe hyperkeratosis, acanthosis and dermal inflammation. In addition, inflammation of the subcutaneous tissue underlying the skin at the application site was observed with low incidence.
- Other:
STATISTICAL RESULTS: none additional

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS
- Age: 35 days old
- Weight at study initiation: 104 - 156 g (males); 116 - 153 g (females)
- Number of animals: 60 - 30 (males); 30 (females)

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 6 hr/day, 5 days/week for 4 weeks
- Type of exposure: dermal
- Post exposure period: none
- Vehicle: Neutral Oil 100 N plus Sham Group
- Concentration in vehicle: 0.0025, 0.010, 0.030 g/mL
- Total volume applied: 2.0 mL/kg/day; 0.0 mL/kg/day (Sham Control)
- Doses: 5, 20, 60 mg/kg/day
- Area covered: the hair around the entire trunk between the flank and shoulders of each animal was closely clipped (approximately 10% of the body surface area).
- Occlusion: none
- Removal of test substance: The exposure site was washed with paper towels saturated with 1% aqueous soap solution. The exposure site was then rinsed with paper towels saturated with tap water and gently blotted dry with paper towels.

SATELLITE GROUPS AND REASONS THEY WERE ADDED: none

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes, daily
- Mortality: yes, daily
- Body weight: yes, weekly
- Food consumption: yes, weekly
- Water consumption: not monitored
- Ophthalmoscopic examination: not conducted
- Haematology: yes, all surviving rats on the day of necropsy
- Biochemistry: yes, all surviving rats on the day of necropsy
- Urinalysis: not conducted

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: Gross examination included examination of the external surface of the body, all orifices and the cranial, thoracic, and abdominal cavities and their contents.
- Microscopic: Tissues processed and examined microscopically for all control animals (Sham Control; Solvent Control (Neutral Oil 100 N)), and all animals in 60 mg/kg/day dose group included the liver, treated and untreated skin, brain, kidney, spinal cord (cervical, thoracic, lumbar), sciatic nerve, skeletal muscle, adrenals, testes, and gross lesions.

OTHER EXAMINATIONS: none

STATISTICAL METHODS: One-way analysis of covariance models were used to assess the presence or absence of a treatment effect for body weight, cumulative body weight gain and feed consumption. Separate analyses were conducted at each sampling time for each sex. Pairwise comparisons of least

square means between control and each treatment level were evaluated using Dunnett's t-test. The criterion for statistical significance for all comparisons was p-value of 0.05 or less.

Conclusion: Daily dermal application of Primene 81-R Amine to the skin of rats for four weeks (5 days/week) resulted in a No Observed Effect Level (NOEL) for systemic toxicity of 20 mg/kg/day. The minimum effect level was 60 mg/kg/day.

Reliability: (1) valid without restriction

30-JAN-2002 (25)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: other: Crl:CD BR
Route of administration: inhalation: vapour
Exposure period: 6 hrs/day
Frequency of treatment: 5 days/week for 4 weeks
Post exposure period: none
Doses: 2, 19, 129, 537 mg/m3
Control Group: yes, concurrent no treatment
NOAEL: = 19 mg/m³

Method: OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL (NOEL), LOAEL (LOEL): NOEL 19 mg/m3
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX
- Time of death: all animals exposed to 537 mg/m3 died by exposure day 11; 1 during week 2 of dosing
- Number of deaths at each dose: 10 at 537 mg/m3; 1 accidental death in control group
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: all animals exposed to 537 mg/m3 died by exposure day 11 and one control animal died during week 2 of exposure.
- Clinical signs: Animals exposed to 537 mg/m3 prior to death exhibited treatment-related labored breathing, respiratory noise, gasping, unstable gait, tremors, salivation, and lacrimation. At 129 mg/m3 transient occurrences of unstable gait, respiratory noise, salivation, and lacrimation were observed. Animals exposed at 19 and 2 mg/m3 showed no treatment-related signs of toxicity.
- Body weight gain: Statistically significant decreases in body weight occurred in 537 mg/m3 males during week 1, and in females during weeks 1 and 2. Males exposed to 129 mg/m3 showed statistically significant decreases in body weight and body weight change during weeks 2, 3, 4. The females exposed at 129 mg/m3 showed statistically significant decreases in body weight and body weight change during weeks 3 and 4. At 19 mg/m3 statistically significant decreases in body weight and body weight change were seen in the females

during week 2. Females in the 2 mg/m3 exposure group showed statistically significant decreases in body weight and body weight change during weeks 2, 3, and 4.
- Food/water consumption: A statistically significant decrease in feed consumption was observed in all animals in the 537 mg/m3 exposure groups during week 1. A statistically significant decrease in the feed consumption for the 129 mg/m3 males was observed during weeks 2 and 3.
- Ophthalmoscopic examination: not conducted
- Clinical chemistry: No treatment-related clinical chemistry effects were observed in any group. Statistically significant decreases in total protein and globulin in males at 129 mg/m3. At 19 mg/m3 statistically significant decreases in glutamic oxaloacetic transaminase, glutamic pyruvic transaminase in males and triglyceride in females. Males exposed at 2 mg/m3 showed a statistically significant decrease in creatinine and glutamic oxaloacetic transaminase; females in this group showed an increase in glutamic oxaloacetic transaminase. In the absence of a concentration-response relationship, none of the above changes were judged to be treatment-related.
- Haematology: No treatment-related effect on any hematologic parameter at any dose level. Animals exposed at 19 mg/m3 showed statistically significant decrease in mean cell hemoglobin and mean cell hemoglobin concentrations for the females. No changes in hematology parameters were seen at any other concentration. In the absence of a dose-response relationship, none of the above changes were judged treatment-related. No exposure-related differences in differential parameters were observed.
- Urinalysis: not conducted
- Organ weights: No treatment-related organ weight changes observed at any dose level.
- Gross pathology: Gross pathologic changes were observed only in animals exposed to 537 mg/m3. These changes consisted of partially or fully blocked nasal cavities and gas-filled stomachs.
- Histopathology: Microscopic examination of male and female rats exposed to 537 mg/m3 showed changes in the nasal cavity, larynx, trachea, and lung. The nasal cavity changes were moderate to severe desquamation of the respiratory and olfactory epithelium, epithial ncerosis and inflammation of the submucosa. In addition, all meati and primarily the dorsal meati had exudates composed of mucous, fibrin, erythrocytes, exfoliated epithelium and inflammatory cells. The larynx and trachea had epithelial necrosis, submucosal inflammation an exudates in their lumens. Two female rats had foci of inflammation of bronchi, bronchioles and/or alveoli. Specific examination of tissues from the central (brain and spinal cord) and peripheral (sciatic nerve) nervous system as well as skeletal muscle from animals exposed to 537 mg/m3 revealed no changes indicative of neurotoxicity. The nasal cavity was the only target tissue in animals exposed to 129 mg/m3. The lesions were primary

graded as slight and focal in nature. These lesions consisted of necrosis of respiratory and olfactory epithelium accompanied by inflammation in the mucosa and submucosa, as well as, exudates in meati which usually was overlying necrotic foci. Also observed were foci of respiratory epithelial hyperplasia and squamosus metaplasia (respiratory epithelium replaced by squamous epithelium). The olfactory epithelium and underlying Bowman's gland epithelium were atrophied. Rats exposed to 19 and 2 mg/m3 had not exposure-related microscopic changes.
- Other: The sentinel animal serology results were negative for the presence of adventitious virus and bacteria antibodies.
STATISTICAL RESULTS:none additional

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS
- Age: 21 - 23 days, at receipt
- Weight at study initiation: not reported
- Number of animals: 50 - 25 (males); 25 (females)
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 6 hr/day, 5 days/wk, for 4 weeks
- Type of exposure: nose-only inhalation
- Post exposure period: none
- Vehicle: none
- Doses: 0 (filtered air), 2, 19, 129, 537 mg/m3, analytical concentrations
- Particle size: study conducted with vapors, not aerosols
- Type or preparation of particles: study conducted with vapors, not aerosols
SATELLITE GROUPS AND REASONS THEY WERE ADDED: none
CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: yes, twice daily
- Mortality: yes, daily
- Body weight: yes, weekly
- Food consumption: yes, weekly
- Water consumption: not monitored
- Ophthalmoscopic examination: not conducted
- Haematology: yes, all surviving rats on the day of necropsy
- Biochemistry: yes, all surviving rats on the day of necropsy
- Urinalysis: not conducted
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: Gross examination included examination of the external surface of the body, all orifices and the cranial, thoracic, and abdominal cavities and their contents.
- Microscopic: Tissues processed and examined microscopically will be collected, saved, weighed and fixed in 10% neutral buffered formalin. Tissues included but not limited to, the nasal cavity, liver, brain, kidney, spinal cord (cervical, thoracic, lumbar), sciatic nerve, skeletal muscle, adrenals, spleen, trachea, larynx, heart, and gross lesions.

OTHER EXAMINATIONS: Neurologic evaluations were performed the day prior to the first day of exposure, and shortly after animals were removed from the chambers on the last day of exposure.
STATISTICAL METHODS: One-way analysis of covariance models were used to assess the presence or absence of an overall compound effect. Separate one-way analyses were used within the male and female data to assess overall treatment group effects. Pairwise comparisons of least square means between control and each treatment level were evaluated using Dunnett's t-test. The criterion for statistical significance for all comparisons was p-value of 0.05 or less.

Conclusion: Inhalation exposure of Primene 81-R Amine produced 100% mortality at 537 mg/m3. Prior to the death, these animals exhibited labored breathing, respiratory noise, gasping, unstable gait, tremors, salivation, lacrimation, and decresed body weight, body weight gain and feed consumption. At 129 mg/m3, transient occurrences of unstable gait, respiratory noise, salivation, lacrimation, and slight decreased body weight gains and feed consumption were observed. No treatment-related signs were observed at 19 and 2 mg/m3. Organ weights and blood analysis revealed no treatment-related effects. At the end of the four-week exposure period, neurological evalutions of all surviving animals showed no signs of a cumulative toxic effect on the nervous system in any group.

On the basis of the most sensitive indictor of toxicity, the histopathological changes seen in the nasal cavities, the NOEL for a four-week nose-only inhalation exposure of Primene 81-R Amine was 19 mg/m3.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
30-JAN-2002 (15)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537
Concentration: 20 - 5000 ug/plate
Metabolic activation: with and without

GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: GENOTOXIC EFFECTS:
- With metabolic activation: not mutagenic
- Without metabolic activation: mutagenic in strain TA1535
FREQUENCY OF EFFECTS: The test article did not induce an increase in revertants when compared to solvent controls.
PRECIPITATION CONCENTRATION: The test article did

precipitate.
MITOTIC INDEX:
CYTOTOXIC CONCENTRATION:
- With metabolic activation: mg/plate
- Without metabolic activation: mg/plate
TEST-SPECIFIC CONFOUNDING FACTORS: Results indicate that Primene 81R was mutagenic. This conclusion is based on sporadic positive responses which were statistically greater than the response observed in the negative controls, and no dose-related response was observed. Currently, the criteria for defining a positive response is a two-fold or greater response compared to negative controls. Because the response may not be biologically meaningful, the study was repeated.
STATISTICAL RESULTS: Statistical methods beyond the calculation of the mean and standard deviation are not considered necessary for the interpretation of this study.

Source: Rohm and Haas Company, Spring House, PA USA

Test condition: SYSTEM OF TESTING
- Species/cell type: Salmonella typhimurium
- Deficiences/Proficiences: not applicable
- Metabolic activation system: The S-9 used for metabolic activation was obtained from rats induced with Aroclor 1254.
- No. of metaphases analyzed: not applicable
ADMINISTRATION:
- Dosing: Dimethyl sulfoxide (DMSO) was used as the solvent for the test article and as the solvent control.
- Number of replicates: 3 plates for each dose of test article; 6 plates for each control.
- Application: For the activated portion of the assay the following were added, in order, to sterile test tubes: 2 ml of top agar, 0.1 ml of the bacteria inoculum, 0.1 ml of the test article, and 0.5 ml of phosphate buffer mix (with S-9 and NADP). For the non-activated portion of the assay, the above procedure was followed, except that the 0.5 ml of phosphate buffer mix (without S-9 or NADP) was added to the tubes directly after addition of the top agar. The contents of the test tubes were mixed and poured onto petri dishes containing approximately 19 mL of the appropriate agar. Plates were allowed to set several minutes then placed into covered plastic boxes and incubated at 37 °C for approximately 72 hr prior to colony counting.
- Positive and negative control groups and treatment: In the presence of metabolic activation, 2-anthramine was used as the positive control, for all strains. In the absence of metabolic activation, the positive controls used were: 2-nitrofluorene (TA98), sodium azide (TA100 and TA1535) and 9-aminoacridine (TA1537).
- Pre-incubation time:
DESCRIPTION OF FOLLOW UP REPEAT STUDY: Results were confirmed in an independent assay.
CRITERIA FOR EVALUATING RESULTS:

Conclusion: Primene 81-R Amine is mutagenic.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint
25-JAN-2002 (8)

Type: Ames test
System of testing: Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537
Concentration: 20 - 2000 ug/plate
Cytotoxic Concentration: 2000 ug/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: GENOTOXIC EFFECTS:
- With metabolic activation: not mutagenic
- Without metabolic activation: not mutagenic
FREQUENCY OF EFFECTS: The test article did not induce an increase in revertants when compared to solvent controls.
PRECIPITATION CONCENTRATION: The test article did precipitate.
MITOTIC INDEX:
CYTOTOXIC CONCENTRATION:
- With metabolic activation: 2,000 mg/plate
- Without metabolic activation: 2000 mg/plate
TEST-SPECIFIC CONFOUNDING FACTORS: none
STATISTICAL RESULTS: Statistical methods beyond the calculation of the mean and standard deviation are not considered necessary for the interpretation of this study.
Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: SYSTEM OF TESTING
- Species/cell type: Salmonella Typhimurium
- Deficiences/Proficiences: not applicable
- Metabolic activation system: The S-9 used for metabolic activation was obtained from rats induced with Aroclor 1254.
- No. of metaphases analyzed: not applicable
ADMINISTRATION:
- Dosing: Dimethyl sulfoxide (DMSO) was used as the solvent for the test article and as the solvent control.
- Number of replicates: 3 plates for each dose of test article; 6 plates for each control.
- Application: For the activated portion of the assay the following were added, in order, to sterile test tubes: 2 ml of top agar, 0.1 ml of the bacteria inoculum, 0.1 ml of the test article, and 0.5 ml of phosphate buffer mix (with S-9 and NADP). For the non-activated portion of the assay, the above procedure was followed, except that the 0.5 ml of phosphate buffer mix (without S-9 or NADP) was added to the tubes directly after addition of the top agar. The contents of the test tubes were mixed and poured onto petri dishes containing approximately 19 mL of the appropriate agar. Plates were allowed to set several minutes then placed into covered plastic boxes and incubated at 37 °C for

approximately 72 hr prior to colony counting.
- Positive and negative control groups and treatment: In the presence of metabolic activation, 2-anthramine was used as the positive control, for all strains. In the absence of metabolic activation, the positive controls used were: 2-nitrofluorene (TA98), sodium azide (TA100 and TA1535) and 9-aminoacridine (TA1537).
- Pre-incubation time:
DESCRIPTION OF FOLLOW UP REPEAT STUDY: Results were confirmed in an independent assay.
CRITERIA FOR EVALUATING RESULTS: A mutagenicity assay is considered valid if the following conditions are met. First, the spontaneous reversion rate, with and without metabolic activation, must be reasonably consistent with the expected range for the strain being used. Second, the positive control materials must elicit a positive response. And third, strains must maintain characteristics, i.e., nutritional requirements, crystal violet sensitivity and ampicillin resistance. A test article is considered positive (mutagenic) if it elicits in independent assays a number of revertants per plate at least 2 times that observed in the solvent control (background). A response that does not meet this criteria but elicits a potential biologically significant response (e.g., a dose related increase in revertants per plate over 3 concentrations) is considered as equivocal response and requires further evaluation. A test article is considered negative (non-mutagenic) if the criteria for a positive assay were not met and the test article was tested up to 2,000 mg/plate or the limit of solubility or toxicity, whichever was lower. Toxicity is defined as the elimination of a uniform background lawn.

Conclusion: Under the conditions of this study, Primene 81-R Amine is not mutagenic.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (30)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: CD-1
Route of admin.: gavage
Exposure period: single dose
Doses: 30, 150, 300 mg/kg
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY: there were no deaths in this study.
CLINICAL SIGNS: both male and female mice treated with 300 mg/kg of test article exhibited clinical signs of systemic toxicity which included tremors and hyperactivity within 4 hours after treatment. Hyperactivity was also observed in mice treated with 150 mg/kg of test article on day 0, after treatment. By day 1, all males exhibiting signs, with the exception of one, and all females recovered.
EFFECT ON MITOTIC INDEX OR PCE/NCE RATIO: Primene 81R was not mutagenic.
STATISTICAL RESULTS: there was no statistically significant change in the polychromatic/normochromatic ratio at either 24 or 48 hours, which is indicative of the absence of cytotoxicity. An increase in the frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow cells of male and female mice treated with 2.0 mg/kg of the positive control, mitomycin-C. When compared to the vehicle controls, the increase was greater than two-fold, indicating that the assay was sufficiently sensitive to detect induced cytogenetic damage. Statistical methods included analysis of variance followed by Dunnett's T-Test on Least Square Means.
Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ORGANISMS: CD-1 mouse
- Age: 8 weeks old
- Weight at study initiation: 22-31 g
- No. of animals per dose: 5 male and 5 females dosed per time point per treatment group. Two additional animals per time point were dosed to account for possibility of unexpected deaths.
ADMINISTRATION: oral gavage
- Vehicle: corn oil
- Duration of test: 48 hours
- Frequency of treatment: single oral dose
- Sampling times and number of samples: 24 and 48 hours post dosing. All animals from test groups and vehicle control (5/sex). Animals from the positive control groups (5/sex) at 24 hours after dosing.
- Control groups and treatment: vehicle control by oral

gavage; Mitomycin-C (MMC) (positive control) at 2.0 mg/kg administered in a single oral dose by intraperitoneal injection.
EXAMINATIONS:
- Clinical observations: recorded on days 0 and 1 and 2 post-dosing.
- Organs examined at necropsy: : bone marrow cells from both femurs were centrifuged, spread on glass slides, air-dried, fixed in methanol, stained with Acridine Orange stain and read with an epifluorescene microscope.
- Criteria for evaluating results: the test article is considered positive in this assay if it elicits a dose-response or a statistically significant increase in the number of micronucleated cells over that of the concurrent vehicle control at one or more dose levels. In the event that the test article elicits a significant increase in the number of MN-PCE due to an unusually low number of MN-PCE in the concurrent vehicle control, the data from that dose may be compared to historical vehicle control data.

The test article is considered negative in this assay if: no indication of a dose-response is observed and the treatment groups do not show a statistically significant increase in the number of MN-PCE when compared to the vehicle control.
- Criteria for selection of M.T.D.: the doses were selected after evaluation of the results of an acute oral toxicity in male and female CD-1 mice. The LD10 was selected as the high dose for this study since it was expected to produce significant toxicity, but not excessive lethality.

Conclusion: Under conditions of this study, Primene 81-R Amine was not mutagenic in the micronucleus assay in CD-1 mouse bone marrow cells.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (31)

5.7 Carcinogenicity

-

5.8.1 Toxicity to Fertility

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5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: other: Crl:CD (SD)IGS BR VAF/Plus
Route of administration: dermal
Exposure period: days 6 - 20 of presumed gestation
Frequency of treatment: once daily
Duration of test: days 6 - 20 of presumed gestation
Doses: 5, 15, and 45 mg/kg/day
Control Group: other: 0 (Sham Control), 0 (Vehicle Control)
NOAEL Maternal Toxity: = 5 mg/kg bw
NOAEL Teratogenicity: = 45 mg/kg bw
Result: No developmental effects were seen at any dose that were related to treatment with Primene 81-R.

Method: OECD Guide-line 414 "Teratogenicity"
Year: 1998
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL (NOEL), LOAEL (LOEL): 5 mg/kg/day (maternal NOAEL); 45 mg/kg/day (developmental NOEL)
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: 5, 15, 45 mg/kg/day
MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: The number of rats (eight) sacrificed for humane reasons due to adverse clinical observations (excessive vocalization, hyperactivity, and gasping) occurring immediately following test substance application in the 45 mg/kg/day dosage group was significantly increased (p£0.05) as compared to the sham control and vehicle control groups. These signs were also observed in rats that were not sacrificed; however, the extent of and the duration of the vocalization and hyperactivity did not justify sacrifice. All other rats survived until scheduled sacrifice.
8 at 45 mg/kg/day; DG 10 (2), DG 11 (3), DG 12 (2), DG 13 (1)
- Number pregnant per dose level:

Dosage Group (mg/kg/day)	0 (Sham)	0 (Veh)	5	15	45
Rats Tested	25	25	25	25	25
Pregnant	25(100)	24(96)	23(92)	23(92)	25(100)
Humane Sac.	0(0)	0(0)	0(0)	0(0)	8(32)
Rats Pregnant and Caesarean-Sectioned on Day 21 of Gestation	25	24	23	23	17
Average Maternal Body Wt. Gain (DG6-21):	+145.3 ±18.6	+136.5 ±18.8	+135 ±18.0	+129 ±9.4	+109 ±24.6
Absolute Maternal Feed Consumption (DG6-21; g/day):	29.9 ±2.0	27.6 ±2.2	26.5 ±2.2	26.4 ±1.6	25.2 ±2.4

Corpora Lutea					
	16.7 ±2.5	16.5 ±2.9	16.2 ±1.9	16.8 ±2.8	15.4 ±1.8
Implantations					
	14.6 ±2.0	14.4 ±1.7	14.5 ±1.6	14.3 ±1.4	14.0 ±1.3
Resorptions					
	0.4 ±0.5	0.7 ±1.6	0.6 ±0.8	0.5 ±1.0	0.6 ±0.8
Early Resorptions					
	9 0.4±0.5	17 0.7±1.6	15 0.6±0.8	10 0.4±1.0	11 0.6±0.8
Late Resorptions					
	1 0.0±0.2	0 0.0±0.0	0 0.0±0.0	1 0.0±0.2	0 0.0±0.0

- Number aborting:
- Number of resorptions:
- Number of implantations:
- Pre and post implantation loss:
- Number of corpora lutea:
- Duration of Pregnancy:
- Body weight:
- Food/water consumption:
- Description, severity, time of onset and duration of clinical signs: The number of rats (eight) sacrificed for humane reasons due to adverse clinical observations (excessive vocalization, hyperactivity, and gasping) occurring immediately following test substance application in the 45 mg/kg/day dosage group was significantly increased (p£0.05) as compared to the sham control and vehicle control groups. These signs were also observed in rats that were not sacrificed; however, the extent of and the duration of the vocalization and hyperactivity did not justify sacrifice. All other rats survived until scheduled sacrifice.

Additional clinical signs observed in the rats sacrificed included chromodacryorrhea, chromorhinorrhea, grade 1 and 2 flaking and grade 1 erythema and edema, brown discoloration of the skin and localized alopecia (limbs).

The number of rats in the vehicle control group with chromodacryorrhea, chromorhinorrhea and grade 1 erythema (four rats) was increased or significantly increased (p£0.05) as compared to the sham control group values. Since chromodacryorrhea and chromorhinorrhea were seen in the sham control group, these signs were considered related to the restraint procedure as well as the vehicle.

All other clinical observations in the vehicle control group were considered unrelated to the vehicle because: 1) they occurred at similar incidence to the sham control group values or 2) they occurred in only one or two rats. These

observations included localized alopecia (head, limbs and underside), a scab at the base of the tail and at the administration site, a red substance on the vagina, soft or liquid feces, no fees and grade 1 flaking.

Test substance related increases or significant increases (p£0.05) in the number or rats with hyperactivity, vocalization, gasping and brown discoloration of the skin were observed in the 15 and 45 mg/kg/day dosage groups, as compared to the sham control group and/or vehicle control group values. Signs of hyperactivity and vocalization were observed in rats that were not sacrificed; however, the extent of and duration of the vocalization and hyperactivity did not justify sacrifice.

The number of rats in the 5, 15, 45 mg/kg/day dosage groups with chromodacryorrhea and chromorhinorrhea was significantly increased (p£0.05) as compared to the sham control group values but not the vehicle control group. These observations were therefore considered vehicle related.

All other clinical observations were considered unrelated to the vehicle or test substance.

- Skin Reactions:
The number of rats with localized alopecia on the head was significantly increased (p£0.05) in all treated groups, as compared to the sham control group and vehicle control group values. These increases were not considered test substance related because the number of rats affected did not increase in a dosage dependent manner.

The number of rats in the 5 mg/kg/day dose group with grade 1 erythema and scabs at the administration site were comparable to the vehicle control group values. These observations were therefore considered vehicle related.

Test substance related significant increases (p£0.05) in the number of rats with grade 1 flaking, edema and erythema, grade 2 flaking and scabs at the administration site were observed in the 15 and 45 mg/kg/day dose groups, as compared to the sham and vehicle control groups.

A test substance-related ulceration at the site of administration and significant increases (p£0.05) in the number of rats with grade 2 erythema and edema, grade 3 flaking occurred in the 45 mg/kg/day dose group. Although the ulceration was only observed in one rat, it is considered test substance related because it was observed in a rat that had numerous skin irritation signs.

All other skin reactions were considered unrelated to the vehicle or test substance.

- Hematological findings incidence and severity:
- Clinical biochemistry findings incidence and severity:
- Gross pathology incidence and severity: Clinical signs observed persistently during the dosage period were confirmed at necropsy; no additional gross lesions were identified.
- Organ weight changes:
- Histopathology incidence and severity:

FETAL DATA:
- Litter size and weights:
- Number viable:
-·Sex ratio:

Dosage Group (mg/kg/day)	0 (Sham)	0 (Veh)	5	15	45	
Rats Tested	25	25	25	25	25	
Pregnant	25 (100)	24 (96)	23 (92)	23 (92)	25 (100)	
Litter Sizes	14.2 ± 2.0	13.7 ± 2.4	13.9 ± 1.8	13.8 ± 1.4	13.4 ± 1.9	
Live Fetuses	354	328	319	317	228	
	14.2±2	13.7±2.4	13.9±1.8	13.8±1.4		13.4±1.9
Dead Fetuses	0		0	0	0	0
Live Male Fetuses:	179	159	169	163	118	
% Live Male Fetuses/ Litter:	50.8 ±15.8	47.3 ±15.3	53.2 ±13.2	51.4 ±13.2	51.9 ±9.8	
Live Fetal Body Wts (grams)/ Litter:	5.49 ±0.24	5.31 ±0.29	5.40 ±0.28	5.41 ±0.29	5.23	±0.38
Male Fetuses	5.65 ±0.30	5.44 ±0.30	5.55 ±0.27	5.58 ±0.28	5.30	±0.46
Female Fetuses	5.32 ±0.22	5.20 ±0.27	5.23 ±0.28	5.23 ±0.28	5.12 ±0.37	

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: TEST ORGANISMS
Presumed pregnant rats: 25/dose group
ADMINISTRATION / EXPOSURE
- Type of exposure: dermal
- Duration of test/exposure: days 6 - 20 of presumed gestation
- Treatment: Primene 81-R was administered percutaneously once daily to groups of rats on days 6 through 20 of presumed gestation (DGs 6 through 20) at dosages of 5, 15, and 45 mg/kg/day.
- Control group and treatment: 0 (Sham Control), 0 (vehicle), 5, 15, and 45 mg/kg/day
- Vehicle: Neutral Oil 100 N
- Concentration in vehicle: 0 (vehicle), 2.5, 7.5, 22.5 mg/mL

- Total volume applied: 2.0 mL/kg
- Doses: 0 (Sham Control), 0 (vehicle), 5, 15, and 45 mg/kg/day
- Concentrations: 0 (vehicle), 5, 15, and 45 mg/kg/day

MATING PROCEDURES: Virgin female rats were placed into cohabitation with breeder male rats, one male rat per female rat. The cohabitation period consisted of a maximum of five days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed in situ were considered to be at DG 0 and assigned to individual housing.

PARAMETERS ASSESSED DURING STUDY:

- Body weight gain: recorded DG 6 - 21
- Food consumption: recorded on DG 0, daily during the dosage period and on the day of sacrifice
- Clinical observations: before application and following rinsing during the dosage period and on the day of scheduled sacrifice
- Examination of uterine content: The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. Placentae were examined for size, color and shape.
- Examination of fetuses: Each fetus was weighed and examined for sex and gross lesions. Approximately one-half of the fetuses in each litter were examined for soft tissue alterations and the remaining fetuses (approximately one-half of the fetuses in each litter) were eviscerated, cleared and stained and examined for skeletal alterations. Late resorptions and dead fetuses were examined for gross external alterations to the extent possible. The body weight of each fetus was recorded. Only body weights of live fetuses were used to determine litter fetal body weight averages.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Caesaren-sectioned and gross necropsy of the thoracic, abdominal and pelvic viscera were performed. Uteri of apparently nonpregnant rats were examined while being pressed between glass plates to confirm absence of implantation sites. The number and distribution of corpora lutea were recorded. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. Placentae were examined for size, color and shape.

OTHER EXAMINATIONS: Before the first daily application, and at 24-hr intervals each day thereafter, each skin site was observed for signs of skin irritation and graded.

STATISTICAL METHODS:

Clinical observations and other proportional data (number of dams with resorptions, fetal alterations, etc.) were analyzed using the Variance Test Homogeneity of the Binomial Distribution.

Continuous data (e.g. maternal body weights, body weight changes, feed consumption values and litter averages for percent male fetuses, percent resorbed conceptuses, fetal body weights, fetal anomaly data and fetal ossification site data) were analyzed using Bartlett's Test of Homogeneity of Variances and the Analysis of Variance, when appropriate [i.e., Bartlett's Test was not significant (p>0.001)]. If the Analysis of Variance was significant (p£0.05), Dunnett's Test was used to identify the statistical significance of the individual groups. If the Analysis of Variance was not appropriate [i.e., Barlett's Test was significant (p£0.001)], the Kruskal-Wallis Test was used (£75% ties). In cases where the Kruskal-Wallis Test was statistically significant (p£0.05), Dunn's Method of Multiple Comparisons was used to identify the statistical significance of the individual groups. If there were greater than 75% ties, Fisher's Exact Test was used to analyze the data.

Count data obtained at Caesarean-sectioning of the dams were evaluated using the procedures described above for the Kruskal-Wallis Test.

Conclusion: On the basis of these data, the maternal no-observable-adverse-effect-level (NOAEL) of Primeneâ 81-R is 5 mg/kg/day. Adverse clinical observations, skin reactions and reductions in body weights and feed consumption were observed in the 15 and/or 45 mg/kg/day dose groups. An increase in the number of rats sacrificed for humane reasons was observed in the 45 mg/kg/day dose group. No developmental effects were seen at any dose that were related to treatment with Primene 81-R. The developmental NOEL is 45 mg/kg/day.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

19-MAY-2003 (35)

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: One-Generation Reproductive Study
In Vitro/in vivo: In vivo
Species: rat
Strain: other: Crl:CD BR **Sex:** male/female
Route of administration: oral feed
Frequency of treatment: continuous
Duration of test: One generation
Doses: 0, 250, 750, 1500 ppm (0, 19.1, 55.6, 107.3 mg/kg/day (males); 0, 21, 62.8, 124.1 mg/kg/day (females))
Control Group: yes, concurrent vehicle
Result: Reproductive/Developmental NOEL = 250 ppm; Vaginal opening (F) or preputial separation (M): Delayed vaginal opening in females at 750 ppm and 1500 ppm. Delayed preputial separation in males at 1500 ppm.

Method: other: OECD Guideline 415
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL (NOEL), LOAEL (LOEL): NOEL parental, males and females = 250 ppm [19.1 mg/kg/day males; 21.0 mg/kg/day females]; NOEL reproductive and developmental = 250 ppm
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX:

Dose (ppm)	male (mg/kg/day)	female (mg/kg/day)
250	19.1	21.0
750	55.6	62.8
1500	107.3	124.1

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Parental data and F1:
- Body weight: No body weight effects in parental animals at 250 ppm. Cumulative body weight gain decreased after first week of treatment in males and throughout most of premating period in females at 750 ppm. Decreased mean body weight and cumulative body weight gain during premating period in both sexes at 1500 ppm. No body weight effects on pups at 250 ppm. Decreased mean body weight in pups from postnatal day 4 on at 750 ppm and at all intervals at 1500 ppm.
- Food/water consumption: No feed consumption effects in parental animals at 250 ppm or females at 750 ppm. Decreased feed consumption in both sexes at 1500 ppm throughout premating and in males at 750 ppm from week 3 to end of premating period. No effect on feed consumption during gestation or lactation at 750 ppm or less but decreased at 1500 ppm.
- Description, severity, time of onset and duration of clinical signs: No clinical signs of systemic toxicity in parental animals of either sex during premating, females during gestation, or females and pups during lactation at any dose level.

- Fertility index: No treatment-related effects in males or females at any dose level.
- Precoital interval: No treatment-related effects at any dose level.
- Duration of gestation: No treatment-related effects at any dose level.
- Gestation index: No treatment-related effects at any dose level.
- Changes in lactation: No treatment-related effects at any dose level.
- Changes in estrus cycles: No treatment-related effects at any dose level.
- Effects on sperm: No treatment-related effects at any dose level.
- Hematological findings incidence and severity: not evaluated
- Clinical biochemistry findings incidence and severity: not evaluated
- Mortality: No treatment-related deaths at any dose level.
- Gross pathology incidence and severity: No treatment-related effects at any dose level.
- Number of implantations: No treatment-related effects at any dose level.
- Number of corpora lutea: No treatment-related effects at any dose level.
- Ovarian primordial follicle counts: No treatment-related effects at any dose level.
- Organ weight changes: No treatment-related effects at any dose level.
- Histopathology incidence and severity: No histopathology at any dose level.
- Offspring toxicity F1 and F2: No treatment-related effects at any dose level.
- Litter size and weights: No treatment-related effects at any dose level.
- Sex and sex ratios: No treatment-related effects at any dose level.
- Viability index: No treatment-related effects at any dose level.
- Post natal survival until weaning: no deaths
- Effects on offspring: No treatment-related effects at any dose level.
- Postnatal growth, growth rate: No treatment-related effects at any dose level.
- Vaginal opening (F) or preputial separation (M): Delayed vaginal opening in females at 750 ppm and 1500 ppm. Delayed preputial separation in males at 1500 ppm.
- Other observations

STATISTICAL RESULTS:

Source: Rohm and Haas Company, Spring House, PA, USA

Test condition: Parental rats: 26/sex/dose, 6-7 weeks old at initiation

ADMINISTRATION / EXPOSURE

- Type of exposure: dietary
- Duration of test/exposure: 1 generation

- Treatment: Primene 81-R Amine was administered in the diet to groups of rats at 0, 250, 750, or 1500 ppm.
- Control group and treatment: yes, Sham control
- Vehicle: none
- Doses: 0, 250, 750, or 1500 ppm
- Concentrations: 0, 19.1, 55.6, 107.3 mg/kg/day (males); 0, 21.0, 62.8, 124.1 mg/kg/day (females) - dietary concentrations

MATING PROCEDURES: Adult female rats were placed individually with an assigned male from the same treatment group, and observed daily until copulation was verified by the presence of a sperm plug in situ, multiple sperm plugs on the cage liner (at least 3), and/or sperm in a vaginal lavage sample.

STANDARDIZATION OF LITTERS: Litters were culled to 8 pups (4/sex/litter) on postnatal day 4.

PARAMETERS ASSESSED DURING STUDY P AND F1:

- Clinical observations: body weight, body weight gain, feed consumption, and clinical signs in parental animals
- Estrous cycle: Estrus cycling was evaluated in parental females for three weeks prior to mating.
- Sperm examination: Sperm evaluation was performed on all parental males at the time of necropsy.

PARAMETERS ASSESSED DURING STUDY F1 AND F2:

- Clinical observations and frequency: body weight, body weight gain, feed consumption, and clinical signs in parental animals.
- Others: Females were examined daily for vaginal opening beginning at 25 days of age. Males were examined daily for preputial separation beginning at 35 days of age. Body weights were recorded on the day sexual maturation was achieved.

OFFSPRING: Postnatal day 0 examinations included - status, sex, weight, external structural abnormalities, and clinical signs of ill health. Sex was also determined at post natal days 4, 7, 14, and 21. During lactation - mortality, morbidity, and obvious indications of a toxic effect performed daily.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Organ weights P and F1: Parental - (females) uterus, ovaries (with oviducts); (males) epididymis (single), caudia epididymis (single), seminal vesicles (with coagulating glands) with their fluids and prostate (as one unit). Offspring - none
- Histopathology P and F1: Parental - reproductive organs (vagina, uterus with cervix, ovaries with oviducts in females; testis, epididymis, seminal vesicles with coagulating glands, prostate in males), pituitary gland, stomach and gross lesions for all animals in the 1500 ppm dose group and control group, and all animals found dead or sacrificed during study. In addition, the uterus was examined in the 750 ppm dose group. Reproductive organs were examined in all 250 and 750 dose group animals suspected of reduced fertility. All tissues exhibiting

gross pathological changes were examined microscopically. The post-lactation ovary was examined for primordial and growing follicles, as well as the large corpora lutea of lactation. Offspring - none
- Histopathology F1 not selected for mating, F2:
OTHER EXAMINATIONS:
STATISTICAL METHODS: The litter (i.e., proportion of pups/litter, or litter mean) was used as the experimental unit for the purpose of statistical evaluation. The level of statistical significance selected was $p<0.05$. the statistical tests that were used to analyze the parameters studied were: Analysis of Variance (ANOVA), 2xN Chi-square test, and 2XN Kruskal-Wallis nonparametric ANOVA.

Conclusion: Continuous exposure of rats to Primene 81-R Amine in the diet through one generation had a NO Observed Effect Level (NOEL) for parental animal toxicity of 250 ppm [19.1 mg/kg/day in males; 21.0 mg/kg/day in females]. The reproductive and developmental NOEL was 250 ppm due to decreased pup weights at both 750 and 1500 ppm and delayed sexual maturation in females at 750 ppm and in both sexes at 1500 ppm.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

30-JAN-2002 (36)

5.9 Specific Investigations

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5.10 Exposure Experience

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5.11 Additional Remarks

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6.1 Analytical Methods

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6.2 Detection and Identification

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7.1 Function

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7.2 Effects on Organisms to be Controlled

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7.3 Organisms to be Protected

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7.4 User

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7.5 Resistance

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8.1 Methods Handling and Storing

Safe Handling: Do not handle material near food, feed or drinking water. This material is corrosive.
Storage Req.: Store at ambient temperatures.
Common Storage: Store in a well ventilated area.
Container: Keep container tightly closed when not in use. An atmsophere of dry Nitrogen may be used to preserve the chemical purity.
Unsuitable Cont.: Do not store this material in containers made of the following: -copper-copper alloys.
Add. Information: Empty containers retain product residue (vapors and/or liquid).

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

8.2 Fire Guidance

Hazards: Combustion generates toxic fumes of nitrogen oxides and carbon oxides.
Prot. Equipment: Wear self-contained breathing apparatus (pressure-demand NIOSH approved or equivalent) and full protective gear.

Ext. Medium: Use the following extinguishing media when fighting fires involving this material: - carbon dioxide - dry chemical - water spray.

Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

8.3 Emergency Measures

Type: injury to persons (inhalation)

Remark: Move subject to fresh air.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

Type: injury to persons (eye)

Remark: Immediately flush eyes with a large amount of water for at least 15 minutes. Get prompt medical attention.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

Type: injury to persons (skin)

Remark: Immediately get under a safety shower. Remove contaminated clothing. Wash affected skin areas thoroughly with soap and water. Get prompt medical attention. Wash contaminated clothing thoroughly before reuse. Do not take clothing home to be laundered. Discard contaminated shoes, belts and other

articles made of leather.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

Type: injury to persons (oral)

Remark: Do not induce vomiting. Give milk or water to drink. Immediately see a physician. Never give anything by mouth to an unconscious person.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

Type: other: Note to Physician

Remark: If swallowed, careful evacuation of the stomach is advisable.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

Type: accidental spillage

Remark: Personal Protection
Wear a NIOSH approved (or equivalent) self-contained breathing apparatus in the pressure demand mode or a full-facepiece airline respirator in the pressure demand mode with emergency escape provisions. Protective clothing made of the following material should be worn to avoid skin contact: - nitrile - neoprene - butyl rubber. Remove all contaminated clothing promptly. Wash all exposed skin areas with soap and water immediately after exposure.

Procedures
Evacuate the spill area. Floor may be slippery; use care to avoid falling. Contain spills immediately with inert materials (e.g. sand, earth). Transfer liquids and solid diking material to separate suitable containers for recovery or disposal. Flush cleaned area with water to a sewage treatment facility. Avoid all contact.
WARNING: Keep spills and cleaning runoffs out of municipal sewers and open bodies of water.
Source: Rohm and Haas Company, Spring House, PA, USA
31-JAN-2002

8.4 Possib. of Rendering Subst. Harmless

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8.5 Waste Management

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8.6 Side-effects Detection

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8.7 Substance Registered as Dangerous for Ground Water

Memo: Adsorption estimates suggest that Primene 81-R Amine is immobile in soil.

Source: Rohm and Haas Company, Spring House, PA, USA
01-FEB-2002

8.8 Reactivity Towards Container Material

Memo: Do not store this material in containers made of copper/copper alloys. Although stainless steel or cast iron equipment is satisfactory, mild steel is preferred.

Source: Rohm and Haas Company, Spring House, PA, USA
01-FEB-2002

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10.1 End Point Summary

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10.2 Hazard Summary

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10.3 Risk Assessment

Memo: Existing Risk Management, plus Preliminary Risk Assessment Lead with Industry, Authorities [Consultant] to provide feedback.

Remark: Existing Risk Management, plus Preliminary Risk Assessment Lead with Industry, Authorities [Consultant] to provide feedback.

Action
Rohm and Haas Company Response
For all principle routes of exposure associated with intended uses, identify all existing relevant legislative controls
Downstream users indicated that the following legislative controls applied to their intended use:
- Seveso II (96/82)
- VOC Solvent Emissions (98/8)
- Restrictions on Marketing and Use
- Classification and Labeling of Dangerous Substances (67/548)
- IPPC Directive
- Chemical Agents Directive (89/391, 98/24)
- Carcinogens Directive (90/394)

Describe the measures used to achieve compliance with these controls. Seek input from downstream organizations if necessary.
Further discussions with downstream users is necessary to address this action.
Describe the nature of the entity complying with the controls - eg professionally qualified, skilled and experienced, unskilled, consumer.
Predominantly qualified industrial users (95%) with minimal commercial and consumer users (<5%).
Identify those exposure routes where risk is not explicitly controlled by existing legislation, or where there is only low confidence in the measures/abilities of organizations to comply with existing controls.
Among the risk scenarios identified, dermal exposure to downstream users may not be controlled and could be a significant source of exposure, pending further evaluation.
Suggest further cost-effective control measures that might

be implemented. Agree these with downstream organizations if appropriate.
None identified during the pilot. Primene 81-R Amine has a long (40+ years) of safe use in industrial applications.
For the routes identified in the last activity, if the chemical is toxic or very toxic - to people - determine whether widespread consumer exposure occurs. If the chemical is toxic/very toxic to the environment, determine whether the chemical is mainly discharged to the environment in some way during its life/disposal.
Limited and somewhat undefined consumer exposure.

Based on our environmental risk scenarios, Primene 81-R Amine is either combusted upon final use or released to on-site or wastewater treatment facilities. On rare occasion if Primene 81-R is released to the environment, it will not be persistent.
If the previous activity has positive outcome(s), provide a quantitative measure (PEC/PNEC ratio etc) to indicate the risk.
See SIAR document.

Source: Rohm and Haas Company, Spring House, PA, USA

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\line Based on our environmental risk scenarios,
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