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TELEPHONE [illegible] CABLE ADDRESS ROHMHAAS [illegible]

REPLY TO:
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201-15627

ROHM AND HAAS COMPANY

04L-024

September 30, 2004

Mr. Mike Leavitt, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

04 OCT -5 PM 1:20

ATTN: Chemical Right to Know Program

RE: HPV CHEMICAL CHALLENGE PROGRAM for
Hexaoxatricosane (CAS 143-29-3)
Rohm and Haas Company

Dear Mr. Leavitt:

On behalf of Rohm and Haas Company, I am pleased to submit the test plan, robust summaries, and SIAP for hexaoxatricosane (CAS 143-29-3). My company has agreed to sponsor this chemical and provide the Agency with the enclosed information.

We have electronically submitted via email, the test plan (.doc and .pdf), IUCLID robust summaries (.exp, .rtf, and .pdf), the SIAP (.doc and .pdf), and 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 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
Hexaoxatricosane
CAS Number 143-29-3

04 OCT -5 PM 1:20

PREPARED BY:

ROHM AND HAAS COMPANY

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OVERVIEW

The Rohm and Haas Company hereby submits for review and public comment the test plan, robust summaries, and SIDS Initial Assessment Profile (SIAP) for hexaoxatricosane (CAS No.: 143-29-3) 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 hexaoxatricosane 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.

Hexaoxatricosane, sold by Rohm and Haas Company as TP-90B Rubber Chemical (95-99% a.i.), is used to develop optimum low-temperature flexibility characteristics in fuel hose, wire jacketing, cellular rubber goods, friction compounds, and a wide variety of molded and extruded products. Used in only moderate concentrations (usually 20-30 parts per hundred resin (phr)), it functions effectively without seriously degrading the rubber's characteristic physical properties. This is accomplished by its reducing of the viscosity of rubber sterically, thereby reducing the transition temperature of the plasticized rubber. Because of its rapid plasticizing action, hexaoxatricosane is also useful for softening slightly scorched stocks with little effect on their ultimate physical properties.

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. 143-29-3	Information	OECD Study	Other	Estimation using EPI Suite™ v3.11	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	-	-	Y	N
Boiling Point	Y	Y	-	-	Y	Y	N
Density	Y	Y	-	-	Y	Y	N
Vapor Pressure	Y	Y	-	-	Y	Y	N
Partition Coefficient	Y	Y	-	-	Y	Y	N
Water Solubility	Y	Y	-	-	Y	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	-	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
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 - No value was determined for this endpoint, as the substance is a liquid below 0 °C.

Boiling Point - A value for this endpoint was determined from analyses that followed OECD test guideline 103 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Density - A value for this endpoint was determined from analyses that followed OECD test guideline 109 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Vapor Pressure - A value for this endpoint was determined from analyses that followed OECD test guideline 104 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Partition Coefficient - A value for this endpoint was determined from analyses that followed OECD test guideline 117 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Water Solubility - A value for this endpoint was determined from analyses that followed OECD test guideline 105 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Conclusion: All physicochemical endpoints have been satisfied, except for melting point, 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. The test for melting point is not required because hexaoxatricosane is a liquid below 0 °C.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using a computer estimation model in EPI Suite™ v3.11. The model was unable to estimate atmospheric ozone reaction rates.

Stability in Water - Experimental measurement of the hydrolysis rate of hexaoxatricosane at pH 5, 7, or 9 was not measured in an OECD 111 guideline study. Because of the insolubility of hexaoxatricosane in water, experimental parameters could not be accurately measured. Subsequent efforts to accurately predict the hydrolysis rate by means of structural activity relationships were not productive. EPI Suite™ v3.11 was not able to predict a hydrolysis rate for this class of compound. Literature searches yielded no alternative structural activity relationship models for this class of compound. The rate of hydrolysis of hexaoxatricosane could not be accurately measured, nor estimated using quantitative structure activity relationship modeling.

Because alcohols and ethers are generally resistant to hydrolysis, it is predicted that TP-90B Rubber Chemical should not undergo hydrolysis in aquatic environments, and will be stable at pH values of 5, 7, or 9.

Biodegradation- This endpoint is filled by data from a study that followed OECD test guideline 301B and was conducted under GLP regulations. 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. Details of the studies can be found in the co-submitted robust summaries.**

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."

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. Details of the studies can be found in the co-submitted robust summaries.**

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, while dermal studies used rats and rabbits. Acute inhalation studies were evaluated in rats, mice and guinea pigs. 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." The inhalation studies were performed before the advent of GLP regulation. One set of these studies, where the animals were exposed to aerosols, was deemed "valid with restrictions." The other set, in which the animals were exposed to a heated vapor, was deemed "invalid" due to the lack of reported exposure concentration, as well as the unknown identity of the decomposition volatiles to which the animals were exposed. Details of the studies can be found in the co-submitted robust summaries.

Repeat Dose Toxicity - This endpoint is filled by data from an oral Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats. This study followed OECD test guideline 422 and was conducted under GLP regulations. The quality of this study was 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, *Escherichia coli* strain WP2*uvr*A. 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 474 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 an oral Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats. This study followed OECD test guideline 422 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 an oral Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats. This study followed OECD test guideline 422 and was conducted under GLP regulations. The quality of this study was deemed as "reliable without restrictions."

Conclusion: **All toxicological endpoints, with the exception of the acute inhalation studies, 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. Although the inhalation studies were conducted prior to GLP regulations, they are deemed as "valid with restrictions". Since hexaoxatricosane is a liquid with a low vapor pressure, further inhalation testing is not needed. Details of the studies can be found in the co-submitted robust summaries.**

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (boiling point, vapor pressure, density, partition coefficient, and water solubility) for hexaoxatricosane were obtained from actual testing of this material.

Measured and estimated environmental fate data show that hexaoxatricosane will not persist in the environment. Hexaoxatricosane degraded up to 55.5% by day 28 using the CO_2 evolution method for testing ready biodegradability. Primary and ultimate biodegradation estimates via QSAR range from days to weeks, and indicate the chemical will be subject to effective biodegradative processes. Hexaoxatricosane has a low volatility, the measured vapor pressure being less than 7.34×10^{-7} mm Hg at 25° C. Hexaoxatricosane has a very low water solubility (< 96 ng/l @ 20º C). Fugacity modeling suggests partitioning largely into sediment and soil, with lesser amounts in the aqueous compartment and very little in the atmosphere.

The Log P of hexaoxatricosane has been measured at 6.2, indicating the potential to bioaccumulate in fish. It is unlikely that this bioaccumulation will occur, though, as the very low water solubility of the substance would cause it to aggregate and precipitate out of solution upon entering the aquatic environment. These aggregations make it more difficult for organisms to take up the substance, as well as for the substance to cross cell membranes. Accumulation of the chemical within terrestrial species thus is unlikely to occur. The fate and behavior of hexaoxatricosane in wastewater treatment facilities (WWTF) have been estimated. Model results suggest that the up to 93% of the total mass of hexaoxatricosane 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 (96 hour EC_{50} = 26 mg/L). The 96-hour LC_{50} for trout (491 mg/L) and the 48-hour EC_{50} (87 mg/L) for invertebrates indicate trout to be the least sensitive species. Therefore, hexaoxatricosane can be classified as low concern to fish, and as moderate concern to aquatic invertebrates and algae.

Based on lethality alone, hexaoxatricosane is considered practically non-toxic via the acute dermal and inhalation routes, and slightly toxic via the acute oral route. The oral LD_{50} of rats was greater than 2000 mg/kg. One death occurred at this dose. Central nervous system effects were also noted at this dose (and at 550 mg/kg), including convulsions, lethargy, lachrymation, and salivation (see robust summaries for details). The inhalation 1-hr LC_{50} of rats, mice and guinea pigs exposed to aerosolized hexaoxatricosane was greater than 200 mg/L. In a study that was deemed invalid, rats and mice exposed to hexaoxatricosane decomposition volatiles all died (9/10 guinea pigs survived). The identity and the concentration of the decomposition volatiles is unknown (see robust summaries for details). The dermal LD_{50} of rats was greater than 2000 mg/kg. Data from skin and eye irritation studies in rabbits indicate that hexaoxatricosane is not irritating to the skin or eyes. Hexaoxatricosane was shown to not act as a skin sensitizer in guinea pigs in a non-adjuvant study (i.e. Buehler).

A Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422) was performed in 12 week old rats given hexaoxatricosane by gavage at concentrations of 0, 10, 100, or 800 mg/kg/day. The no-observed-adverse-effect-level (NOAEL) in this study was 100 mg/kg/day. Multiple effects were seen at the high dose, including treatment-related signs of intoxication (e.g., ataxia, semi-closed eyes, hunched posture), a statistically significant decrease in food consumption in females, and statistically significant increases in absolute and relative liver weights in males. In females these liver effects were not significant. These liver weight effects were corroborated by histopathology showing treatment-related diffuse hepatocellular hypertrophy to have occurred in males and females (see robust summaries for details).

Fertility effects in this study included a treatment-related decrease in the fertility index (7/10 females in the high-dose group were not pregnant). Though not statistically significant, an increased incidence in the number and percentage of pre-birth loss was noted. Related to this, a decrease in mean pup weight and the average number of pups per litter was observed at birth,

and on day 4 *post-partum* in the high-dose group. Furthermore, a statistically significant increase in pup mortality (females and total) from days 0 to 4 was noted (see robust summaries for details).

Developmental effects in this study were also noted at the high dose. Six pups in one litter of the high-dose group showed fore/hindlimb digits missing or not defined during pre-weaning observations and/or necropsy. Necropsy examination of four of these pups confirmed the diagnoses of agenesis and/or microdactily. The other two pups were not available for necropsy. One pup from a different litter had flexure of the hindlimbs. These findings were considered treatment-related since they are rare findings in this species (see robust summaries for details).

Results from mutagenicity and chromosomal aberration studies indicate that hexaoxatricosane 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 hexaoxatricosane 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 QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance and the systematic approach described by Klimisch *et al*. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The codification described by Klimisch *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 3.11, Syracuse Research Corporation, Syracuse, New York.

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

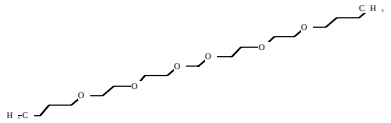
3. USEPA. (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

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.

SIDS INITIAL ASSESSMENT Profile

Hexaoxatricosane (CAS No. 143-29-3)

CAS No.	143-29-3
Chemical Name	Hexaoxatricosane
Structural formula	

RECOMMENDATIONS

The substance is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health:

Based on lethality alone, hexaoxatricosane is considered practically non-toxic via the acute dermal and inhalation routes, and slightly toxic via the acute oral route. The oral LD_{50} of rats was greater than 2000 mg/kg. One death occurred at this dose. Central nervous system effects were also noted at this dose (and at 550 mg/kg), including convulsions, lethargy, lachrymation, and salivation (see robust summaries for details). The inhalation 1-hr LC_{50} of rats, mice and guinea pigs exposed to aerosolized hexaoxatricosane was greater than 200 mg/L. In a study that was deemed invalid, rats and mice exposed to hexaoxatricosane decomposition volatiles all died (9/10 guinea pigs survived). The identity and the concentration of the decomposition volatiles is unknown (see robust summaries for details). The dermal LD_{50} of rats was greater than 2000 mg/kg. Data from skin and eye irritation studies in rabbits indicate that hexaoxatricosane is not irritating to the skin or eyes. Hexaoxatricosane was shown to not act as a skin sensitizer in guinea pigs in a non-adjuvant study (i.e. Buehler).

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and/or necropsy. Necropsy examination of four of these pups confirmed the diagnoses of agenesis and/or microdactily. The other two pups were not available for necropsy. One pup from a different litter had flexure of the hindlimbs. These findings were considered treatment-related since they are rare findings in this species (see robust summaries for details).

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Environment:
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Exposure:
Since end-use products contain only low (20-30 parts per hundred resin) levels of hexaoxatricosane, consumer exposure to the chemical is likely to be negligible. Human exposure can potentially occur only during its manufacture and formulation into rubber. Worker exposure is limited by closed systems, industrial hygiene controls and personal protective measures. Due to those protection measures, independently of the toxic properties of the substance, no risk to workers is expected.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

201-15627B

I U C L I D

D a t a S e t

04 OCT -5 PM 1:20

Existing Chemical	ID: 143-29-3
CAS No.	143-29-3
EINECS Name	Hexaoxatricosane
EC No.	205-598-9
Molecular Formula	C17-H36-O6

Producer Related Part

Company:	Rohm and Haas Company
Creation date:	06-MAY-2003

Substance Related Part

Company:	Rohm and Haas Company
Creation date:	06-MAY-2003

Printing date:	22-SEP-2004
Revision date:	
Date of last Update:	**22-SEP-2004**

Number of Pages:	**81**

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: Dr. Jim McLaughlin **Date:**
Street: 727 Norristown Road
Town: Spring House, PA 19477-0904
Country: United States
Phone: 215-641-7459
Telefax: 215-619-1618
Email: jmclaughlin@rohmhaas.com

10-SEP-2004

1.0.2 Location of Production Site, Importer or Formulator

-

1.0.3 Identity of Recipients

-

1.0.4 Details on Category/Template

-

1.1.0 Substance Identification

IUPAC Name: Hexaoxatricosane (TP-90B Rubber Chemical)
Smiles Code: O(CCOCCOCCCC)COCCOCCOCCCC
Mol. Formula: C17-H36-O6
Mol. Weight: 336.47

Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: 95 - 99 % w/w
Colour: Amber
Odour: Mild

Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.1.2 Spectra

-

1.2 Synonyms and Tradenames

bis(2-(2-butoxyethoxy)ethoxy)methane

Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

TP-90B(TM) Rubber Chemical

21-SEP-2004

10-SEP-2004

1.3 Impurities

Purity type: typical for marketed substance
CAS-No: 50-00-0
EC-No: 200-001-8
EINECS-Name: formaldehyde
Mol. Formula: C-H2-O
Contents: < .1 % w/w

Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

Purity type: typical for marketed substance
CAS-No: 7664-93-9
EC-No: 231-639-5
EINECS-Name: sulphuric acid
Mol. Formula: H2-S1-O4
Contents: < .0035 % w/w

12-AUG-2004

Purity type: typical for marketed substance
CAS-No: 112-34-5
EC-No: 203-961-6
EINECS-Name: 2-(2-butoxyethoxy)ethanol
Mol. Formula: C8-H18-O3
Contents: 1 - 5 % w/w

12-AUG-2004

1.4 Additives

Remark: Not applicable
Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.5 Total Quantity

Quantity: > 800 tonnes produced

Remark: Product is classified as a High Production Volume (HPV) chemical.
Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (Xn) harmful
R-Phrases: (22) Harmful if swallowed
S-Phrases: (60) This material and/or its container must be disposed of as hazardous waste

Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed

Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.6.3 Packaging

Memo: Packaged in either pails, drums, totes, or tank trucks.

Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.7 Use Pattern

Type: industrial
Category: other: rubber industry

Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.7.1 Detailed Use Pattern

-

1.7.2 Methods of Manufacture

Type: Production

Remark: TP-90B is manufactured in batch operations in kettles. It is then transferred to pails, drums, totes, or tank trucks.
Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.8 Regulatory Measures

-

1.8.1 Occupational Exposure Limit Values

Type of limit: other: Rohm and Haas Company
Limit value: .5 other: ppm
Short term exposure
Limit value: 1.5 other: ppm

Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.8.2 Acceptable Residues Levels

-

1.8.3 Water Pollution

-

1.8.4 Major Accident Hazards

Remark: Evacuate personnel to a safe areas. Ventilate the area. Floor may be slippery; use care to avoid falling. Soak up the spill with inert absorbent material (e.g., sand, silica gel, acid binder, universal binder, sawdust). Sweep or vacuum up the spillage and collect in a suitable container for disposal. Avoid breathing vapor.
Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.8.5 Air Pollution

Remark: Estimated partitioning of TP-90B Rubber Chemical into the atmosphere will be negligible. Estimated degradation rates in atmosphere are rapid (i.e., 1.5 hours). Volatilization from water bodies is expected to be negligible. Fugacity modeling indicates that partitioning into the atmosphere would be negligible.
Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: All components of this product are in compliance with the inventory listing requirements of the chemical control laws in the following countries:
USA (TSCA)
Canada (DSL)
EU (EINECS)
Japan (ENCS)
Australia (AICS)
Korea (ECL)
China (IECS)

Source: Rohm and Haas Company, Spring House, PA, USA
21-SEP-2004

1.9.1 Degradation/Transformation Products

Remark: This material is considered safe under specified conditions of storage, shipment and/or use. There are no known hazardous decomposition products for this material. Product will not undergo polimerization.
Source: Rohm and Haas Company, Spring House, PA, USA
22-SEP-2004

1.9.2 Components

-

1.10 Source of Exposure

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

Remark: Eyes: Material can cause slight irritation

Skin: Material can cause slight irritation

Ingestion: Material is possibly harmful if swallowed. Material can cause abdominal pain, vomiting, nausea, diarrhea, central nervous system effects, salivation, convulsions, and difficulty in breathing.

Inhalation: Inhalation of vapor mist can cause irritation of nose, throat and lungs, nausea, dizziness, and difficulty in breathing.

Source: Rohm and Haas Company, Spring House, PA, USA
16-AUG-2004

1.11 Additional Remarks

-

1.12 Last Literature Search

-

1.13 Reviews

-

2.1 Melting Point

Remark: No value was determined for this endpoint, as the substance is a liquid below 0 °C.
Source: Rohm and Haas Company, Spring House, PA, USA
Flag: Critical study for SIDS endpoint
21-SEP-2004

2.2 Boiling Point

Value: = 285.2 degree C at 1000 hPa
Decomposition: ambiguous

Method: OECD Guide-line 103 "Boiling Point/boiling Range"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: TP-90B Rubber Chemical was added to three boiling point tubes to a height of 15-18 mm. Boiling capillaries were inserted into the boiling point tubes until the capillaries rested on the base of each tube. The tubes were analyzed individually by inserting the tube into the center slot of the instrument. These samples were analyzed starting at 280 degrees C, and increasing at +0.2 degrees C per minute until the boiling point was reached. The boiling points recorded were calculated by the instrument using the actual boiling temperatures and barometric pressure (100 kPa) measurements.
Source: Rohm and Haas Company, Spring House, PA, USA
Conclusion: The boiling point of TP-90B Rubber Chemical was determined to be 285.2 +/- 1.1 degrees C (558.4K). There were no known circumstances that may have adversely affected the quality or integrity of the data.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
13-AUG-2004 (17)

2.3 Density

Type: density
Value: = .967 g/cm³ at 20 degree C

Method: OECD Guide-line 109 "Density of Liquids and Solids"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: The calibrated 25-ml glass pycnometer was filled with test substance and immersed inside the water bath, and the contents of the pycnometer were equilibrated to just below the test temperature of 20 degrees C. The pycnometer, assembled with the pycnometer thermometer, was then removed from the water bath, dried, and weighed on the analytical balance. The procedure was repeated until three successive weighings were within 5 mg. The three successive weighings were then avergaed to attain the weight of the pycnometer filled with test substance. The specific gravity and density values were calculated based on these measurements.
Source: Rohm and Haas Company, Spring House, PA, USA
Conclusion: The density of TP-90B Rubber Chemical was determined to be 0.967 +/- 0.000 g/ml at an average temperature of 20.0 +/- 0.0 degrees C. There were no known circumstances that may have adversely affected the quality or integrity of the data.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
13-AUG-2004 (17)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: < .00978 hPa at 25 degree C
Decomposition: no

Method: OECD Guide-line 104 "Vapour Pressure Curve"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: TP-90B Rubber Chemical-dosed sand was distributed evenly into three vapor saturator columns labeled Test 1, 2, and 3. A control vapor saturator column was previously filled with a similar amount of sand that was not coated with test substance. The saturator columns containing the dosed sand and the saturator column containing the control sand were placed inside glass water jackets, and attached to a flow-controlled glass manifold. Nitrogen gas was passed through each saturator column overnight.

On the following day, a primary (A) and secondary (B) vapor trap (Sep Pak Plus C18 cartidges pre-rinsed with approximately 10 ml each of methanol and ethyl acetate) were attached end-to-end to the systems on the effluent port of each of the saturator columns with the primary vapor trap before the secondary vapor trap. No test substance was added to these traps. Three spiked traps (6.0 ug) were prepared by applying 50 ul (Hamilton syringe) of a 120 ug/ml test substance solution to each trap. One spiked trap was connected to the end of each dosed saturator column after the secondary cartridge. A single vapor trap, containing no test substance, was connected to the effluent port of the control saturator column. All connections used for the test system were of Teflon or parafilm.

The nitrogen flow rate of all systems was adjusted to 10 ml/min and measured with a digital flow meter. Flow rates were confirmed and adjusted several times throughout the study. The temperature of the environmental chamber was measured at the same time the flow rates were measured.

The test systems were terminated after 31 days.

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

Conclusion: The vapor pressure of TP-90B was observed to be < 9.78 x 10-5 Pa (< 7.34 x 10-7 torr). These data indicate that TP-90B would not be expected to significantly volatilize under environmentally similar conditions.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

13-AUG-2004 (10)

2.5 Partition Coefficient

Partition Coeff.: octanol-water

log Pow: = 6.2

Method: OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"

Year: 2003

GLP: yes

Method: The test substance was analyzed in duplicate by HPLC using the equipment and conditions listed below. The calibration standard was injected both before and after the test substance injections were made. Mobile phase blanks were injected in duplicate between each standard and/or test substance injection.

Equipment:
- Controller: Agilent G1323B
- Detector: Agilent G1314A
- Pump: Agilent G1311A
- Data Acquisition: VG Multichrom

Autosampler: Agilent G1313A
Degasser: Agilent G1322A
Column Heater: Agilent G1316A
Column: Phenomenex Primesphere 5 C18 HC, 250 x 4.6 mm, 5 mm

Isocratic Mobile Phase: See Section 2.1.6

Operating Conditions:
Flow Rate: 1.5 mL/min
Column Temperature: 20°C
Injection Volume: 10 µL (for retention time identification)
50 mL (for definitive test)
Detector type: UV (l = 210 nm)

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

Conclusion: The log octanol/water partition coefficient was determined by comparing the retention time of the test substance on an HPLC column to that of compounds with known log n-octanol/water partition coefficient values. The log n-octanol/water partition coefficient of TP-90B was determined to be 6.2.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

13-AUG-2004 (16)

2.6.1 Solubility in different media

Solubility in: Water

Value: < .0001 mg/l at 20 degree C

Method: OECD Guide-line 105

Year: 2003

GLP: yes

Test substance: as prescribed by 1.1 - 1.4

Method: A nominal dosing of 0.5% (w/w) was obtained by coating 60.026 g of sand with a test substance solution in acetone containing 0.3211 g of TP-90B. The sand and test substance solution were thoroughly mixed together in a glass jar. The solvent was evaporated from the test substance and sand mixture under a gentle stream of nitrogen.

The amount of test substance initially coated on the sand was verified by removing three 0.5 g aliquots of sand. Each aliquot was extracted twice with 10 mL and once with 5 mL of methanol. After each addition of solvent, the samples were sonicated for approximately fifteen minutes, and the extracts were transferred by Pasteur pipettes into 25 mL graduated cylinders. The final volume of each extract was adjusted to 25 mL with methanol. The samples were diluted by transferring 5 mL to 10-mL flasks and bringing the flasks to volume with methanol. The samples were then analyzed by GC.

The treated sand was added to the column, and a plug of glass

wool was placed between the sand and end-fittings. The column was surrounded by a water jacket maintained at 20 ± 0.5°C by a water circulating bath. The open ends of the generator column were connected by Teflon tubing to a reservoir containing reagent water on one end and a fraction collector on the other. Reagent water was then pumped through the column in a upward direction at a flow rate of 0.4 mL/min. The system was equilibrated overnight at a flow rate of 0.4 mL/min. During the equilibration period all column eluent was discarded.

Over the next two days, fifty 50-minute eluent fractions were collected in 11-dram glass vials (0.4 mL/min x 50 minutes = 20 mL per fraction). The tare weight of each vial and the weight of each vial containing eluent were recorded. The flow rate of the water through the column was then lowered to 0.2 mL/min. After equilibrating for ~7 hours, forty-two 100 minute eluent fractions were collected in the same manner as described for the 0.4 mL/min samples (0.2 mL/min x 100 minutes = 20 mL per fraction). Note: Fifty eluent fractions were to be collected, but an instrument error prevented the collection of the last eight samples.

Before and after the collection of the eluent fractions at each flow rate, two 10 minute eluent fractions were collected in 7-mL scintillation vials and were reserved for pH measurements, examination for undissolved particles, and confirmation of eluent flow rate. The flow rates were measured by dividing the weight of the collected water by the collection time. The density of the water was confirmed to be 1.00 g/mL. The pH of the water before exposure to the test substance was also measured.

The eluent fractions from each flow rate were combined such that five vials were combined to form one sample (i.e., fractions 1A, 1B, 1C, 1D, and 1E were combined to form sample 1).

The recovery of TP-90B from reagent water was verified during the definitive test in concert with the definitive test samples to ensure the accuracy of the analytical method. For each flow rate test, four 96 ng/mL quality control (QC) spikes were prepared, two prior to sample collection and two after sample collection, for analysis. The spike recovery samples were processed and analyzed in the same manner as the definitive test samples. The recoveries were expressed as a percent of nominal concentration spiked into the test matrix.

For each flow rate test, a control sample was prepared prior to sample collection and after sample collection was completed. The control samples were prepared by bringing 100-mL flasks to volume with reagent water. They were then processed and analyzed in the same manner as the definitive test samples.

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

Conclusion: The water solubility of TP-90B was determined to be less than the lowest validated level of 96 ng/ml at 20 +/- 0.5 degrees C.
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
13-AUG-2004 (15)

2.6.2 Surface Tension
-

2.7 Flash Point
-

2.8 Auto Flammability
-

2.9 Flammability
-

2.10 Explosive Properties
-

2.11 Oxidizing Properties
-

2.12 Dissociation Constant
-

2.13 Viscosity
-

2.14 Additional Remarks
-

3.1.1 Photodegradation

Type: air

Remark: Photodegradation information is not available. However, with regard to atmospheric oxidation the AOPWIN estimated a half-life of 1.5 hours. 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
18-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Remark: Experimental measurement of the hydrolysis rate of TP-90B Rubber Chemical at pH 5, 7, or 9 was not possible. Because of the insolubility of TP-90B Rubber Chemical in water, experimental parameters could not be accurately measured. Subsequent efforts to accurately predict the hydrolysis rate by means of structural activity relationships were not productive. EPI Suite v3.11 was not able to predict a hydrolysis rate for this class of compound. Literature searches yielded no alternative structural activity relationship model for this class of compound. The rate of hydrolysis of TP-90B Rubber Chemical could not be accurately measured, nor estimated using quantitative structure activity relationship modeling.
Alcohols and ethers are generally resistant to hydrolysis.

Therefore, TP-90B Rubber Chemical should not undergo hydrolysis in aquatic environments, and will be stable at pH values of 5, 7, or 9.
Source: Rohm and Haas Company, Spring House, PA, USA
Flag: Critical study for SIDS endpoint
22-SEP-2004

3.1.3 Stability in Soil

-

3.2.1 Monitoring Data (Environment)

-

3.2.2 Field Studies

-

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III

Remark: To determine the partitioning properties of TP-90B Rubber Chemical in an evaluative environment, a quantitative structure activity relationship model was used. The model employed was the Level III fugacity model resident within the EPI Suite v3.11. The Level III fugacity model results are listed in the table below:

	Concentration (percent of total)	Compartment Half-Life (hr)
Air	0.323	3.05
Water	11	360
Soil	38.5	360
Sediment	50.2	1440

Source: Rohm and Haas Company, Spring House, PA, USA
Flag: Critical study for SIDS endpoint
18-AUG-2004

3.3.2 Distribution

-

3.4 Mode of Degradation in Actual Use

-

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge
Concentration: 20 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 51.3 - 55.5 % after 28 day(s)
Result: other: not readily biodegradable
Kinetic:
6 day(s) = 1 - 1.2 %
10 day(s) = 2 - 2.5 %
15 day(s) = 18.8 - 24.2 %
20 day(s) = 33.1 - 37.1 %
24 day(s) = 43.8 - 44.9 %
Control Subst.: Benzoic acid, sodium salt
Kinetic:
6 day(s) = 72.8 %
29 day(s) = 87.4 %

Method: OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: FACTORS AFFECTING TEST:

- Stability: stable below temperatures of 107°C
- Vapor pressure: < 9.78 x 10-5 Pa (7.34 x 10-7 torr)
- Water solubility: < 96 ng/mL
- Adsorption potential (log Pow): 6.2

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

Test condition: INOCULUM/TEST ORGANISM
- Type of sludge: Activated sludge
- Species/strain: Mixed liquor
- Source: Columbia Wastewater Treatment Plant, Columbia, MO
- Sampling site: Aeration basin #1
- Feeding: Aqueous mineral salts medium, pH = 7.47
- Method of cultivation: Each test system consisted of a 5-L glass flask containing a 3-L test solution volume comprised of mineral medium, microbial inoculum, reagent water, and the appropriate test or reference substance additions. To remove CO2, the incoming air was passed through a column containing Ascarite followed by a pre-trap containing 500 mL of ~5 N KOH. The air was then passed through 500 mL of reagent water to re-humidify the air, as well as to prevent contamination of the flasks from the KOH pre-trap. The CO2-free and humidified air was then passed through the reaction flasks.
- Preparation of inoculum: The activated sludge was homogenized in a blender at a medium speed for two minutes. The homogenized sludge was allowed to settle for 30 to 60 minutes, filtered through glass wool, and then aerated until use. Thirty milliliters of the prepared activated sludge was used as the inoculum for each reaction flask.
The suspended solids concentration in the prepared activated sludge was determined by filtering three 10-mL aliquots of sludge through pre-weighed glass-fiber filter pads, followed by drying on a Mettler HR73P halogen moisture analyzer. The increase in weight of the filter pads was used to determine the suspended solids level. The suspended solids concentration was 200 mg/L in the prepared mixed liquor suspended solids. Therefore, the total concentration of suspended solids in each reaction flask (30 mL of inoculum to 3,000 mL of test medium) was 2 mg/L.
- Pretreatment: Seven test systems were assembled. The seven reaction flasks were randomly designated for each test system utilizing a random number table. Each 5-L flask received 2,400 mL of mineral salts medium and 30 mL of the prepared activated sludge. Stirring and aeration with CO2-free air at 50-100 mL/minute were started for each flask. The flasks were allowed to aerate to purge the systems of CO2 before initiation of the test (dosing on day 0). The remaining mineral salts medium was also aerated with CO2-free air for this amount of time to prevent absorption of atmospheric carbon by the solution prior to dosing.
- Initial cell concentration: 9.5 x 10^6 CFU/mL

TEST SYSTEM
- Culturing apparatus: Each test system consisted of a 5-L glass flask containing a 3-L test solution volume comprised of mineral medium, microbial inoculum, reagent water, and the appropriate test or reference substance additions.

- Number of culture flasks per concentration:
Control - 2
Test Substance - 2
Abiotic Sterile Control - 1
Reference Substance - 1
Toxicity Control - 1
- Aeration device: To remove CO_2, the incoming air was passed through a column containing Ascarite followed by a pre-trap containing 500 mL of ~5 N KOH. The air was then passed through 500 mL of reagent water to re-humidify the air, as well as to prevent contamination of the flasks from the KOH pre-trap. The CO_2-free and humidified air was then passed through the reaction flasks.
- Measuring equipment: Air was introduced into each flask by positive pressure, and the flow rates (50-100 mL/minute) were measured and adjusted using flow meters. The outlet from each flask was connected to three CO_2 absorber gas-washing traps in series, each filled with 100 mL of 0.2 N KOH solution. These traps captured the CO_2 evolved from the reaction flasks. A magnetic stir bar was placed in each flask. The flasks were placed on insulated magnetic stir plates and stirred throughout the duration of the study. The test systems were kept in the dark (except for sampling and maintenance) in a temperature-controlled environmental chamber maintained at 22 ± 2°C. Temperature of the chamber was continuously measured using a bi-metallic (aluminum-constantan) thermocouple probe and MultiScan 1200 temperature monitoring system.
- Closed vessels used: Yes
INITIAL TEST SUBSTANCE CONCENTRATION: 21.8 mg C/L (replicate 1) and 21.9 mg C/L (replicate 2). These were the values derived after analysis.
METHOD OF PREPARATION OF TEST SOLUTION: Duplicate test substance systems were prepared by adding 570 mL of reagent water and a glass coverslip containing approximately 101.9 mg of TP-90B to 5-L carboys. The measured weights of test substance were 101.5 and 101.6 mg for replicates 1 and 2, respectively. The nominal concentration of carbon from the test substance in the final volume of 3,000 mL of solution was 19.9 mg C/L for each replicate.
DURATION OF THE TEST: 29 days
ANALYTICAL PARAMETER: Dissolved organic carbon, inorganic carbon (IC)
SAMPLING: The CO_2 produced in the test systems was trapped in the 0.2 N KOH solutions, which were then analyzed for inorganic carbon content. Samples of the KOH solutions were collected for CO_2 analysis on days 3, 6, 8, 10, 15, 20, 24, 28, and 29. For each sample day except day 29, triplicate aliquots of the KOH solution from the gas-washing bottle nearest each flask were placed into appropriately-labeled glass autosampler vials. The vials were filled leaving no headspace, capped using Teflon septa, and stored at room temperature until analysis. The first replicate of each set of triplicate samples was analyzed for IC content; and the other two were used as reserve samples. The remaining KOH

solution in this gas-washing bottle was discarded and replaced with 100 mL of a fresh 0.2 N KOH solution. The refilled gas-washing bottle was then rotated to the position farthest from the flask, and the other two gas-washing bottles were moved forward (nearer to the flask) one position.

TEST CONDITIONS
- Composition of medium:

Ingredients of the Mineral Salts Medium

Solution	Compound	Stock Solution Concentration (g/L) In Reagent Water
A1,3	KH_2PO_4	8.50
	K_2HPO_4	21.74
	$Na_2HPO_4 \times 7H_2O$	52.19
	NH_4Cl	0.50
B2	$CaCl_2 \times 2H_2O$	36.40
C2	$MgSO_4 \times 7H_2O$	22.50
D2	$FeCl_3 \times 6H_2O$	0.25
	Concentrated HCl	1 drop

1 - Each liter of mineral salts medium contained 10 mL of this solution.
2 - Each liter of mineral salts medium contained 1 mL of this solution.
3 - pH of solution A was 7.44.

- Test temperature: 21.9 ± 0.1°C
- pH value:

Test Solution pH Measurements

Treatment	Replicate	Initiation (Day 0)	Termination (Day 28)
Control	1	7.46	7.51
	2	7.46	7.51
Test Substance	1	7.47	7.44
	2	7.46	7.46
Abiotic Sterile Control	1	7.30	7.37
Reference Substance	1	7.45	7.66
Toxicity Control	1	7.46	7.65

- Concentration of suspended solids: 2 mg/L
CONTROLS: Negative controls, reference substance system, toxicity control system (test substance + reference substance), abiotic sterile control system (test substance + mercuric chloride)
REFERENCE SUBSTANCE: sodium benzoate

Conclusion: The percent theoretical CO_2 (% $ThCO_2$) produced by TP-90B was 51.3% and 55.5% by day 29 of the study. Therefore, TP-90B cannot be classified as readily biodegradable. The abiotic sterile control system indicated that CO_2 production in the test substance systems may be attributed to biodegradation since abiotic degradation was 6.0% $ThCO_2$ by day 29. The percent theoretical CO_2 produced by the reference substance, sodium benzoate, was 72.8% $ThCO_2$ by day 6 and 87.4% $ThCO_2$ by day 29, proving that the inoculum was viable. The percent

theoretical CO2 produced from the toxicity control system was 88.2% by day 29, indicating that TP-90B was not inhibitory to the microbial inoculum at the testing concentration.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
16-AUG-2004 (11)

3.6 BOD5, COD or BOD5/COD Ratio

-

3.7 Bioaccumulation

-

3.8 Additional Remarks

-

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:** yes
NOEC: = 43 - measured/nominal
LC50: = 491 - measured/nominal
Limit Test: no

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED
- Nominal/measured concentrations:
Nominal: 0, 25, 50, 100, 200, 400, 800 mg a.i./L
Measured: 0, 19.3, 43.0, 82.4, 168, 344, 701 mg a.i./L
- Effect data (Mortality):
24 hr LC50 = 491 mg/L; NOEC = 43.0 mg/L
48 hr LC50 = 491 mg/L; NOEC = 43.0 mg/L
72 hr LC50 = 491 mg/L; NOEC = 82.4 mg/L
96 hr LC50 = 491 mg/L; NOEC = 43.0 mg/L
- Concentration / response curve: The slope of the 96 hour concentration response line = 15
- Effect concentration vs. test substance solubility: The control and 19.3 mg a.i./L treatments were clear and colorless with no visible precipitate or surface film throughout the study. The 43.0, 82.4, and 168 mg a.i./L treatments had a visible surface film throughout the study. The 344 and 701 mg a.i./L treatments were cloudy with a surface film and test initiation and the surface film remained throughout the course of the study.
- Other effects: After 96 hours, mortality was 0, 0, 0, 0, 0, 0, and 100% in the 0 (control), 19.3, 43.0, 82.4, 168, 344, and 701 mg a.i./L, respectively. Two fish were observed on the bottom of the test chamber and three fish were observed breaking the surface of the test solution in the 82.4 mg a.i./L treatment. Four fish were observed on the bottom of the test chamber, one fish was discolored, one fish was discolored and laying on the bottom of the test chamber, and six fish were discolored and breaking the surface of the test solution in the 168 mg a.i./L treatment. All of the fish in the 344 mg a.i./L treatment were observed laying on the bottom of the test chamber, discolored, and with irregular respiration.

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: None
- Nature of adverse effects: None

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

Test condition: TEST ORGANISMS
- Strain: Rainbow Trout (Oncorhynchus mykiss)
- Supplier: Trout Lodge, Sumner, WA.
- Wild caught: No
- Age/size/weight/loading: The control fish were measured at test termination and ranged from 32 to 39 mm in standard length (mean = 36 ± 2.0 mm) and from 0.321 to 0.630 g in blotted wet weight (mean = 0.474 ± 0.0892 g).
- Feeding: Following hatch and swim-up, fish were fed salmon starter and/or brine shrimp nauplii daily.
- Pretreatment: No diseases were observed or treated during the 14-day period prior to use in the test. Two days prior to test initiation a sub-lot of individuals was removed and transferred to a separate tank for acclimation to the test temperature. Food was withheld and no mortality was observed.
- Feeding during test: No

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Not described
- Vehicle, solvent: None

STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not described
REFERENCE SUBSTANCE: TB-90B
DILUTION WATER
- Source: The dilution water was a moderately hard freshwater prepared by blending naturally hard well water with well water that was demineralized by reverse osmosis (RO). Prior to use, the dilution water was passed through a sediment filter and UV sterilizer.
- Aeration: Not described
- Alkalinity: 146 mg/L as $CaCO_3$
- Hardness: 144 mg/L as $CaCO_3$
- TOC: < 2.0 mg/L
- TSS: Not described
- pH: Not described
- Oxygen content: 9.6-10.3 mg/L
- Conductance: 308 µS
- Holding water: Not described

TEST SYSTEM
- Test type: Static
- Concentrations: 0, 25, 50, 100, 200, 400, 800 mg a.i./L nominal
- Exposure vessel type: Duplicate 20-L glass jars each containing approximately 15 L of test solution.
- Number of replicates, fish per replicate: Two replicates, 10 fish per replicate.
- Test temperature: 12.2-12.6°C
- Dissolved oxygen: 5.1-10.1 mg/L
- pH: 7.7-8.2
- Adjustment of pH: No
- Intensity of irradiation: 880 lux
- Photoperiod: 16 hr light:8 hr dark

DURATION OF THE TEST: 96 hrs
TEST PARAMETER: Observations of mortality, moribundity, and behavior were recorded and reported for all test concentrations. Observations were made at 24, 48, 72 and 96

hours. Upon termination of the study, all fish were euthanized according to appropriate procedures.
SAMPLING: One hundred-milliliter samples were collected from each treatment replicate at test initiation and again at 96 hours. Each replicate in each treatment was sampled. All samples were collected with a 100-mL volumetric pipet and placed into 250-mL separatory funnels.
MONITORING OF TEST SUBSTANCE CONCENTRATION: Based on the results of the range-finding test, nominal concentrations selected for the definitive exposure were 0 (control), 25, 50, 100, 200, 400, and 800 mg a.i./L. Analytical confirmation of TP-90B exposure concentrations was performed at 0 and 96 hours.

Conclusion: The calculated 96-hour LC50 for rainbow trout exposed to TP-90B was estimated to be 491 mg a.i./L (95% confidence limits could not be estimated). The 96-hour no-observed-effect concentration (NOEC) was 43.0 mg a.i./L, based on the lack of mortality and sublethal effects at this and all lower concentrations. The slope of the 96-hour concentration-response line is 15.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

13-AUG-2004 (13)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: < 24 - measured/nominal
EC50: = 87 - measured/nominal
Limit Test: no

Method: OECD Guide-line 202
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED
- Nominal/measured concentrations:
Nominal: 0, 25, 50, 100, 200, 400, 800 mg a.i./L
Measured at 0 hrs: <MQL, 25.4, 86.7, 99.2, 196, 353, 729 mg a.i./L
Measured at 48 hrs: <MQL, 22.6, 44.5, 85.4, 184, 389, 675 mg a.i./L
Mean Measured: <MQL, 24.0, 65.6, 92.3, 190, 371, 702 mg a.i./L
- Effect data (Immobilisation): After 48 hours, immobility (mortality) in the control, 24.0, 65.7, 92.3, 190, 371, and 702 mg a.i./L treatments was 0, 20, 25, 0, 70, 100, and 100%. One daphnid was quiescent in the 24.0 and 92.3 mg a.i./L treatments along with the six surviving daphnids in the 190 mg

a.i./L treatment. The calculated 48-hour EC50 for Daphnia magna exposed to TP-90B is 87 mg a.i./L (95% confidence limits of 72 and 106 mg a.i./L). The 48-hour no-observed-effect concentration (NOEC) was <24.0 mg a.i./L.
- Concentration / response curve: The slope of the 48-hour concentration-response line is estimated to be 2.7.
- Cumulative immobilisation:
Control - 0/20
24 mg/L - 4/20
65.6 mg/L - 5/20
92.3 mg/L - 0/20
190 mg/L - 14/20
371 mg/L - 20/20
702 mg/L - 20/20
- Effect concentration vs. test substance solubility: All test solutions = 92.3 mg a.i./L appeared clear and colorless with no visible precipitate or surface film throughout the test. The 190 mg a.i./L test solution appeared cloudy throughout the test. The 371 mg a.i./L test solution appeared cloudy throughout the test with a surface film present at 24- and 48-hours. The 702 mg a.i./L test solution appeared cloudy with a surface film throughout the test.
RESULTS CONTROL: No immobilization

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

Test condition: TEST ORGANISMS
- Strain: Daphnia magna
- Source/supplier: In-house culture
- Breeding method: Not described
- Age: < 24 hours old
- Feeding: A suspension of Selenastrum capricornutum and Ankistrodesmus falcatus at least once a day, supplemented by an artificial diet prepared according to ABC SOP's
- Pretreatment: None
- Feeding during test: No
- Control group: 0 mg a.i./L
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Not described
- Vehicle, solvent: None
STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not described
REFERENCE SUBSTANCE: TP-90B
DILUTION WATER
- Source: The dilution water was a moderately hard freshwater prepared by blending naturally hard well water with well water that was demineralized by reverse osmosis.
- Aeration: No
- Alkalinity: 150 mg/L, as $CaCO_3$
- Hardness: 156 mg/L, as $CaCO_3$
- TOC: < 2.0 mg/L
- TSS: Not reported
- pH: 8.2-8.3
- Oxygen content: 8.0-8.5 mg/L
- Conductance: 344 µS
TEST SYSTEM
- Test type: static

- Concentrations: 0 (control), 25, 50, 100, 200, 400, 800 mg a.i./L nominal
- Renewal of test solution: Not described
- Exposure vessel type: Test chambers consisted of duplicate 250-mL glass beakers each containing approximately 200 mL of test solution.
- Number of replicates, individuals per replicate: 2 replicates per test concentration, with 10 fleas per replicate
- Test temperature: 19.5 ± 0.1°C
- Dissolved oxygen: 8.0-8.6 mg/L
- pH: 8.2-8.5
- Adjustment of pH: Not described
- Intensity of irradiation: 527 lux
- Photoperiod: 16:8 (light:dark)

DURATION OF THE TEST: 48 hours
TEST PARAMETER: biological observations were made at test initiation and at each 24 hour interval
SAMPLING: One hundred-milliliter samples were collected from each treatment with a 100-mL volumetric pipet at test initiation and again at 48 hours. At test initiation, samples were collected from the parent solutions. At 48 hours, samples were collected from both replicates in each treatment. All replicate samples were composited into separatory funnels.

MONITORING OF TEST SUBSTANCE CONCENTRATION: Based on the results of the range-finding test, nominal concentrations selected for the definitive exposure were 00 (control), 25, 50, 100, 200, 400, 800 mg a.i./L. Analytical confirmation of TP-90B exposure concentrations was performed at 0 and 48 hours.

Conclusion: The calculated 48-hour EC50 for Daphnia magna exposed to TP-90B is 87 mg a.i./L (95% confidence limits of 72 and 106 mg a.i./L). The 48-hour NOEC was <24.0 mg a.i./L. The slope of the 48-hour concentration-response line is estimated to be 2.7.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

13-AUG-2004 (12)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: = 11.4 - measured/nominal
LOEC: = 22.9 - measured/nominal
EC10: - measured/nominal
EC50: = 53 -
Limit Test: no

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS: EXPOSED
- Nominal/measured concentrations:
Nominal: 0, 1.6, 3.1, 6.3, 13, 25, 50, and 100 mg a.i./L
Measured 0-hour: <MQL, 1.52, 3.18, 5.45, 12.9, 22.4, 48.1, 90.8 mg a.i./L
Measured 72 hours: <MQL, 1.26, 3.02, 5.73, 10.9, 23.7, 48.0, 93.7 mg a.i./L
Measured 96 hours: <MQL, 1.27, 2.68, 5.37, 10.4, 22.7, 46.5, 105 mg a.i./L
Mean: <MQL, 1.35, 2.96, 5.52, 11.4, 22.9, 47.5, 96.5 mg a.i./L

- Effect data/Element values:

Hour	ECType	EC Value (mg a.i./L)	95% Confidence Limits (mg a.i./L)	NOEC (mg a.i./L)
24	EC50	59	36 - 83	22.9
	EbC50	13	6.0 - 19	11.4
	ErC50	15	---	5.52
48	EC50	27	24 - 31	22.9
	EbC50	20	15 - 24	5.52
	ErC50	>22.9(a)	---	22.9
72	EC50	22	19 - 24	5.52
	EbC50	21	19 - 23	5.52
	ErC50	48	46 - 50	11.4
96	EC50	26	25 - 28	11.4
	EbC50	24	22 - 26	11.4
	ErC50	53	50 - 55	11.4

a) Model does not fit. Estimate based on visual check of the data.
"---" Indicates an estimate could not be made.

- Cell density data:

Mean Measured Concentration (mg a.i./L)	Rep	Cell Density (x 104 cells/mL) 24-Hr	48-Hr	72-Hr	96-Hr	% Difference(a)
Control	A	1.8	8.8	45	110	NA

	B	3.6	7.7	42	125	
	C	2.3	11	51	161	
	Mean	2.6	9.2	46	132	
1.35	A	3.2	14	48	156	+6.1
	B	2.4	8.2	41	144	
	C	2.4	7.2	43	121	
	Mean	2.7	9.8	44	140	
2.96	A	2.1	9.9	58	175	+17
	B	2.6	4.1	45	139	
	C	2.7	6.9	56	149	
	Mean	2.5	7.0	53	154	
5.52	A	2.8	6.8	47	135	+0.76
	B	2.7	7.3	48	139	
	C	2.6	8.9	46	125	
	Mean	2.7	7.7	47	133	
11.4	A	2.0	7.0	42	134	-14
	B	1.7	6.0	29	85	
	C	1.6	6.9	30	119	
	Mean	1.8	6.6	34*	113	
22.9	A	1.8	5.9	22	80	-39
	B	2.0	6.2	21	86	
	C	1.2	4.7	23	73	
	Mean	1.7	5.6	22*	80*	
47.5	A	1.3	3.1	11	27	-85
	B	1.9	2.8	8.7	21	
	C	0.89	2.3	6.0	12	
	Mean	1.4	2.7	8.6*	20*	
96.5	A	0.89	0.89	1.7	2.1	-98
	B	1.4	0.67	1.4	2.4	
	C	1.0	1.1	1.2	2.4	
	Mean	1.1	0.89	1.4*	2.3*	

Initial inoculation at 0-hour was 1.0 x 10^4 cells/mL.
a) Percent inhibition (-) or stimulation (+) as compared to the control at 96 hours.
*Statistically significant reduction (P=0.0000 to 0.0270) when compared to the control at 72 and 96 hours.

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

Test condition: TEST ORGANISMS
- Strain: Selenastrum capricornutum UTEX 1648
- Source/supplier: Department of Botany, Culture Collection of Algae, University of Texas at Austin
- Laboratory culture: Received January 22, 2003. Periodically, new Selenastrum cultures were cloned from an existing culture derived from the parent stock. The algal culture used for this test was three days old at test initiation.
- Method of cultivation: The parent stock was identified as Selenastrum capricornutum. The prepared cultures were maintained in a temperature-controlled environmental chamber under continuous light.
- Pretreatment: All cultures were maintained under the same conditions as those used for testing.
- Controls: 0 mg a.i./L nominal

- Initial cell concentration: 10,000 cells/mL
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: For the definitive test, a 0.10 mg/mL primary standard was prepared by adding 0.2063 g of TP-90B to 2,000 mL of freshwater algal nutrient media (FWAM). Test substance treatments were prepared by a 50% serial dilution of the primary standard with algal media. One hundred milliliter aliquots of the resulting solutions were transferred to the exposure flasks.
- Vehicle, solvent: None
STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not described
REFERENCE SUBSTANCE: TP-90B
DILUTION WATER
- Source: ABC reagent water
- Aeration: Not described
GROWTH/TEST MEDIUM CHEMISTRY
- Alkalinity: Not described
- Hardness: Not described
- Salinity: Not described
- TOC: Not described
- EDTA: Not described
- TSS: Not described
- pH: 7.5 ± 1
- Dissolved oxygen: Not described
TEST SYSTEM
- Test type: static
- Concentrations: 0 (control), 1.6, 3.1, 6.3, 13, 25, 50, and 100 mg a.i./L, nominal
- Renewal of test solution: none
- Exposure vessel type: 250-mL Erlenmeyer flask
- Number of replicates: 3 replicates per test concentration
- Test temperature: 23.5 ± 0.2°C
- pH: 7.4-9.0
- Intensity of irradiation: 4456 ± 80 lux
- Photoperiod: continuous
TEST PARAMETER: 50% algal growth inhibition (EC50)
MONITORING OF TEST SUBSTANCE CONCENTRATION: Analytical confirmation of TP-90B exposure concentrations was performed at 0, 72, and 96 hours.

Conclusion: The 24-, 48-, and 72-hour EC50's, based on cell density, were estimated to be 59 mg a.i./L (95% CL = 36 - 83 mg a.i./L), 27 mg a.i./L (95% CL = 24 - 31 mg a.i./L), and 22 mg a.i./L (19 - 24 mg a.i./L), respectively. The 96-hour EC50, based on cell density, was estimated to be 26 mg a.i./L (95% CL = 25 - 28 mg a.i./L). The 24-, 48-, and 72-hour EC50's, based on area under the growth curve (EbC50), were estimated to be 13 mg a.i./L (95% CL = 6.0 - 19 mg a.i./L), 20 mg a.i./L (95% CL = 15 - 24 mg a.i./L), and 21 mg a.i./L (19 - 23 mg a.i./L). The 96-hour EC50, based on area under the growth curve, was estimated to be 24 mg a.i./L (95% CL = 22 - 26 mg a.i./L). The 24-, 48-, and 72-hour EC50's, based on growth rate (ErC50), were estimated to be 15 mg a.i./L (95% CL = could not be calculated), >22.9 mg a.i./L (95% CL = could not be calculated), and 48 mg a.i./L (46 - 50 mg a.i./L). The

48-hour ErC50 did not fit the model. The estimate is based on a visual check of the data. The 96-hour ErC50, based on growth rate, was estimated to be 53 mg a.i./L (95% CL = 50 - 55 mg a.i./L). The 96-hour no-observed-effect concentration (NOEC) for cell density, area under the growth curve, and growth rate was 11.4 mg a.i./L.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
13-AUG-2004 (14)

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

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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

-

5.0 Toxicokinetics, Metabolism and Distribution

-

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: female
No. of Animals: 6
Vehicle: other: none
Doses: 550, 2000 mg/kg
Value: > 2000 mg/kg bw

Method: OECD Guide-line 425
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY:
- Time of death: The second rat dosed at 2000 mg/kg died within approximately one hour of dosing. The next rat was then dosed at 550 mg/kg. As this rat did not die, three other rats were dosed at 2000 mg/kg, none of which died.
- Number of deaths at each dose: 1 death at 2000 mg/kg
CLINICAL SIGNS: At 2000 mg/kg: Animal 1 exhibited convulsions approximately 5 minutes following dosing. A degree of recovery soon occurred although the animal was lethargic 30 minutes after dosing and remained so throughout the first day. In addition, lachrymation was noted approximately 4 hours after administration of the test item. Recovery had occurred within 24 hours.

Animal 2 exhibited convulsions, lachrymation, and salivation approximately 30 minutes after dosing. Death had occurred within approximately one hour. Animal 3 exhibited lethargy on Day 1. Reduced activity and hunched posture were then noted on days 2 and 3. Recovery occurred by day 4. Animal 4 was unconscious within approximately 30 minutes of dosing. Some recovery was apparent within 24 hours of dosing, when piloerection was noted. Full recovery had occurred within 48 hours. Animal 5 appeared moribund within approximately 30 minutes of dosing, remaining so for the remainder of the day. It was cold to the touch and exhibited a hunched posture on days 2 and 3. Recovery had occurred within 72 hours.

At 550 mg/kg: Convulsions were apparent within approximately 6 minutes of dosing. A degree of recovery soon occurred with the animal remaining lethargic from approximately 11 minutes after dosing and continuing for the remainder of the day.

Recovery had occurred within 24 hours.

NECROPSY FINDINGS: No abnormalities were observed in any animal at the necropsy examination performed at the end of the observation period or in the early decedent animal.

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

Test condition: TEST ORGANISMS: Hsd: Sprague Dawley SD rats
- Source: Harlan Italy S.r.l., 33049 San Pietro al Natisone (UD), Italy
- Age: 6-8 weeks
- Weight at study initiation: 176-200 grams
- Controls: None

ADMINISTRATION:
- Doses: 550, 2000 mg/kg (A single animal was erroneously dosed at 550
 mg/kg. This was a deviation from protocol which indicated to sequentially dose 5 animals at 2000 mg/kg.)
- Doses per time period: 1
- Volume administered or concentration: 10 mL/kg
- Post dose observation period: Immediately following dosing, 30 minutes, 2 hours, 4 hours, and daily thereafter for a total of 14 days.

EXAMINATIONS: Clinical signs and body weight, as well as the following: all surviving animals were killed on day 15 by carbon dioxide narcosis. All animals were subjected to a gross necropsy examination for both external and internal abnormalities. The cranial, thoracic and abdominal cavities were opened to allow examination of their contents. Larger organs were sectioned. Both the stomach and representative sections of the gastro-intestinal tract were opened for examination of the mucosal surfaces.

Conclusion: These results indicate that the test item, TP-90B Rubber Chemical, has some toxic effect in the rat following oral administration of a single dose at a level of 2000 mg/kg. The mortality pattern indicates the median lethal dose (LD50) to be in excess of 2000 mg/kg body weight.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

21-SEP-2004 (23)

Type: LD50
Species: rat
Strain: other: Sherman Wistar
Sex: no data
No. of Animals: 100
Vehicle: other: none
Doses: 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 ml/kg bw
Value: = 3.41 ml/kg bw

Method: other: not specified
Year: 1958
GLP: no
Test substance: other TS

Result: MORTALITY: 1.0 ml/kg - 1/10
2.0 ml/kg - 2/10
3.0 ml/kg - 3/10
4.0 ml/kg - 6/10
5.0 ml/kg - 7/10
6.0 ml/kg - 9/10
7.0 ml/kg - 10/10
8.0 ml/kg - 10/10
9.0 ml/kg - 10/10
10.0 ml/kg - 10/10

- Time of death:1.0 ml/kg - day 4
2.0 ml/kg - days 3 and 4
3.0 ml/kg - days 2 and 3
4.0 ml/kg - days 1 and 2
5.0 ml/kg - days 1 and 2
6.0 ml/kg - days 1 and 4
7.0 ml/kg - days 1 and 4
8.0 ml/kg - days 1 and 2
9.0 ml/kg - day 1
10.0 ml/kg - day 1

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

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

Test condition: TEST ORGANISMS: Rats - Sherman Wistar
- Source: not described
- Age: not described
- Weight at study initiation: not described
- Controls: none

ADMINISTRATION: syringe and stomach tube
- Doses: 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 ml/kg
- Doses per time period: one
- Volume administered or concentration: dependent on rat weight
- Post dose observation period: 14 days

EXAMINATIONS: No observations besides mortality

Test substance: Thiokol Chemical Corporation - Platicizer Type TP90B
Conclusion: The results obtained were evaluated according to the Thompson Moving Average Method, as described by Carrol S. Weil in his publication entitled "Tables for Convenient Calculation of Median-Effective Dose (LD50 or ED50) and Instructions in their Use", which appeared in Biometrics, Vol. 8, No. 3, p. 249-263, September 1952.

LD50 and 95% confidence limits: 3.41 (2.36-4.92) ml/kg
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
20-AUG-2004 (27)

5.1.2 Acute Inhalation Toxicity

Type: other: Acute Inhalation Screening Study
Species: rat
Strain: Wistar
Sex: male/female
No. of Animals: 10
Vehicle: other: undiluted
Doses: 65 grams
Exposure time: 1 hour(s)

Method: other: not given
Year: 1977
GLP: no
Test substance: other TS

Remark: Effects and death may have been enhanced or precipitated by the degree of temperature and humidity during exposure. The temperature inside the chamber varied from 72 to 96 degrees F during the exposure. The humidity varied from 47% to 68% during the exposure.
Result: MORTALITY:
- Time of death:
6 animals within 24 hours of exposure
2 animals 24-48 hours after exposure
1 animal 48-72 hours after exposure
1 animal 72-96 hours after exposure
- Number of deaths at each dose: 10
CLINICAL SIGNS: During exposure the animals pawed at their oculo-nasal areas. Labored breathing was evident. Swelling of the eyelids and irritation surrounding the nasal area was noted. The animals which were alive after 24 hours of observation exhibited nasal hemorrhage, lethargy and ruffled yellow coats. Food and water intake was practically nil.
NECROPSY FINDINGS: Revealed white areas around the perimeter of the lungs. No histopathology was performed.
SEX-SPECIFIC DIFFERENCES: Equally toxic to males and females.
Source: Rohm and Haas Company, Spring House, PA, USA
Test substance: TP-90B decomposition volatiles. Sixty-five grams of the test

material was placed into the distillation flask, and heated in a heating mantle to obtain vapors.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Adult
- Weight at study initiation: Between 212 and 270 g
- Number of animals: 10
- Controls: Not described

ADMINISTRATION:
- Type of exposure: Vapor
- Concentrations: 65 g

EXAMINATIONS: The animals were examined until death. Gross necropsies were performed on all animals that died.

Reliability: (3) invalid
20-AUG-2004 (9)

Type: other: Acute Inhalation Screening Study
Species: rat
Strain: Wistar
Sex: male/female
No. of Animals: 10
Vehicle: no data
Doses: 200 mg/l
Exposure time: 1 hour(s)

Method: other: Federal Hazardous Substances Labeling Act
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: A group of ten young adult male and female rats, equally divided as to sex were exposed to an aerosol of TP-90B/6213 in an inhalation chamber for a period of 1 hour. The spray was directed away from the nasal and ocular areas and circulated throughout the chamber for the duration of the exposure. Maximum aerosolization of 200 mg/l was achieved prior to the test period. At the conclusion of the observation period, the survivors were sacrificed and gross necropsies were performed.

Result: MORTALITY:
- Time of death: No deaths observed.
- Number of deaths at each dose: None

CLINICAL SIGNS: During exposure the animals pawed at their nasal areas. After 35-40 minutes they became languid. Normalcy prevailed upon removal from chamber. Eating habits and behavior patterns remained normal throughout the observation period.
NECROPSY FINDINGS: Since there were no abnormalities, histologic sections were not performed.
POTENTIAL TARGET ORGANS: Not described
SEX-SPECIFIC DIFFERENCES: Equally non-toxic to males and females

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

Conclusion: There were no deaths when ten rats were exposed to an atmosphere of 200 ppm for a period of one hour. It was concluded that TP-90B/6213 would not require labeling under the Federal Hazardous Substances Labeling Act.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Young Adult
- Weight at study initiation:
Males: Between 259 and 274 g
Females: Between 237 and 253 g
- Number of animals: 10 (5/sex)
- Controls: Not described
ADMINISTRATION:
- Type of exposure: 1 Hr Aerosol
- Concentrations: 200 mg/l
EXAMINATIONS: The animals were observed for a fourteen day period following the exposure. At the conclusions of the observation period the animals were sacrificed and gross necropsies were performed. Since there were no abnormalties observed, histologic sections were not performed.

Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
13-AUG-2004 (7)

Type: other: Acute Inhalation Screening Study
Species: mouse
Strain: Swiss Webster
Sex: male/female
No. of Animals: 10
Vehicle: other: none
Doses: 65 g
Exposure time: 1 hour(s)

Method: other: Not described
Year: 1977
GLP: no
Test substance: other TS

Remark: Effects and death may have been enhanced or precipitated by the degree of temperature and humidity during exposure. The temperature inside the chamber varied from 72 to 96 degrees F during the exposure. The humidity varied from 47% to 68% during the exposure.

Result: MORTALITY:
- Time of death:
7 deaths within 24 hours of exposure
1 death within 24-48 hours of exposure
2 deaths within 48-72 hours after exposure
- Number of deaths at each dose: 10
CLINICAL SIGNS: During exposure the animals pawed at their oculo-nasal areas. Lethargy and labored breathing increased in severity as the exposure progressed. Following removal from the chamber the animals remained lethargic. Several animals lapsed into comas. Food and water intake was

practically nil.
NECROPSY FINDINGS: Revealed white areas around the perimeter of the lungs. No histopathology was performed.
POTENTIAL TARGET ORGANS: Not described.
SEX-SPECIFIC DIFFERENCES: Equally toxic to males and females

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

Test substance: TP-90B decomposition volatiles. Sixty-five grams of the test material was placed into the distillation flask, and heated in a heating mantle to obtain vapors.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Adult
- Weight at study initiation: Between 21.5 and 26.5 g
- Number of animals: 10
- Controls: Not described

ADMINISTRATION:
- Type of exposure: Vapor
- Concentrations: 65 g

EXAMINATIONS: The animals were examined until death. Gross necropsies were performed on all animals that died.

Reliability: (3) invalid
20-AUG-2004 (8)

Type: other: Acute Inhalation Screening Study
Species: mouse
Strain: Swiss Webster
Sex: male/female
No. of Animals: 10
Vehicle: no data
Doses: 200 mg/l
Exposure time: 1 hour(s)

Method: other: Federal Hazardous Substances Labeling Act
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: A group of ten young adult male and female mice, equally divided as to sex were exposed to an aerosol of TP-90B/6213 in an inhalation chamber for a period of 1 hour. The spray was directed away from the nasal and ocular areas and circulated throughout the chamber for the duration of the exposure. Maximum aerosolization of 200 mg/l was achieved prior to the test period.

Result: MORTALITY:
- Time of death: No deaths observed.
- Number of deaths at each dose: None

CLINICAL SIGNS: During exposure the animals pawed at their nasal areas. After 35-40 minutes they became languid. Normalcy prevailed upon removal from chamber. Eating habits and behavior patterns remained normal throughout the observation period.
NECROPSY FINDINGS: Since there were no abnormalities, histologic sections were not performed.

POTENTIAL TARGET ORGANS: Not described
SEX-SPECIFIC DIFFERENCES: Equally non-toxic to males and females.

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

Conclusion: There were no deaths when ten mice were exposed to an atmosphere of 200 ppm for a period of one hour. It was concluded that TP-90B/6213 would not require labeling under the Federal Hazardous Substances Labeling Act.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Young Adult
- Weight at study initiation:
Males: Between 24 and 26 g
Females: Between 21 and 24 g
- Number of animals: 10 (5/sex)
- Controls: Not described
ADMINISTRATION:
- Type of exposure: 1 Hr Aerosol
- Concentrations: 200 mg/l
EXAMINATIONS: The animals were observed for a fourteen day period following the exposure. At the conclusions of the observation period the animals were sacrificed and gross necropsies were performed. Since there were no abnormalities observed, histologic sections were not performed.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

13-AUG-2004 (6)

Type: other: Acute Inhalation Screening Study
Species: guinea pig
Strain: other: Ace Hartley
Sex: male/female
No. of Animals: 10
Vehicle: other: None
Doses: 65 g
Exposure time: 1 hour(s)

Method: other: Not described
Year: 1977
GLP: no
Test substance: other TS

Remark: Effects and death may have been enhanced or precipitated by the degree of temperature and humidity during exposure. The temperature inside the chamber varied from 72 to 96 degrees F during the exposure. The humidity varied from 47% to 68% during the exposure.

Result: MORTALITY:
- Time of death:
1 animal within 24 hours of exposure
- Number of deaths at each dose: 1
CLINICAL SIGNS: During exposure the animals pawed at their oculo-nasal regions. Lethargy increased in severity as the exposure progressed. Shortness of breath was evident.

Following removal from the chamber the animals remained lethargic through the day. Eating habits, water intake and behavior patterns returned to normalcy within 72 hours in the survivors and remained constant throughout the observation period.
NECROPSY FINDINGS: Revealed white areas around the perimeter of the lungs. No histopathology was performed.
POTENTIAL TARGET ORGANS: Not described
SEX-SPECIFIC DIFFERENCES: Equally toxic to males and females

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

Test substance: TP-90B decomposition volatiles. Sixty-five grams of the test material was placed into the distillation flask, and heated in a heating mantle to obtain vapors.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Adult
- Weight at study initiation: Between 318 and 401 g
- Number of animals: 10
- Controls: Not described

ADMINISTRATION:
- Type of exposure: Vapor
- Concentrations: 65 g

EXAMINATIONS: The animals were examined for a 14 day observation period. Gross necropsies were performed on all animals that died. At the conclusion of the observation period, the survivors were sacrificed and gross autopsies performed.

Reliability: (3) invalid
20-AUG-2004 (4)

Type: other: Acute Inhalation Screening Study
Species: guinea pig
Strain: other: Ace Hartley
Sex: male/female
No. of Animals: 10
Vehicle: no data
Doses: 200 mg/l
Exposure time: 1 hour(s)

Method: other: Federal Hazardous Substances Labeling Act
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: A group of ten young adult male and female guinea pigs, equally divided as to sex were exposed to an aerosol of TP-90B/6213 in an inhalation chamber for a period of 1 hour. The spray was directed away from the nasal and ocular areas and circulated throughout the chamber for the duration of the exposure. Maximum aerosolization of 200 mg/l was achieved prior to the test period.

Result: MORTALITY:
- Time of death: No deaths observed.
- Number of deaths at each dose: None

CLINICAL SIGNS: During exposure the animals huddled together in the chamber, pawing at their nasal areas. Normalcy prevailed upon removal from chamber. Eating habits and behavior patterns remained normal throughout the observation period.
NECROPSY FINDINGS: Since there were no abnormalities, histologic sections were not performed.
POTENTIAL TARGET ORGANS: Not described
SEX-SPECIFIC DIFFERENCES: Equally non-toxic to males and females.

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

Conclusion: There were no deaths when ten guinea pigs were exposed to an atmosphere of 200 ppm for a period of one hour. It was concluded that TP-90B/6213 would not require labeling under the Federal Hazardous Substances Labeling Act.

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Young Adult
- Weight at study initiation:
Males: Between 315 and 342 g
Females: Between 308 and 323 g
- Number of animals: 10 (5/sex)
- Controls: Not described
ADMINISTRATION:
- Type of exposure: 1 Hr Aerosol
- Concentrations: 200 mg/l
EXAMINATIONS: The animals were observed for a fourteen day period following the exposure. At the conclusions of the observation period the animals were sacrificed and gross necropsies were performed. Since there were no abnormalities observed, histologic sections were not performed.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

13-AUG-2004 (5)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 10
Vehicle: other: undiluted
Doses: 2000 mg/kg
Value: > 2000 mg/kg bw

Method: OECD Guide-line 402 "Acute dermal Toxicity"
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY: No mortality occurred following dosing in male or

female animals.
CLINICAL SIGNS: No signs of toxicity were observed. Changes in body weight observed during the period of the study were within the range expected for this strain and age of animal in the males. The only exception was a single male, which showed a body weight loss during the first week of the observation period. A reduced body weight gain was also observed in the females at the end of the study.
NECROPSY FINDINGS: No abnormalities were found on necropsy of animals on termination of the study.
SEX-SPECIFIC DIFFERENCES: None.

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

Test condition: TEST ORGANISMS: Sprague Dawley rats
- Source: Harlan Italy S.r.l., 33049 San Pietro al Natisone (UD), Italy
- Age: 6-8 weeks
- Weight at study initiation: 201-257 g
- Controls: historical data

ADMINISTRATION:
- Area covered: 10% of the total body surface of each animal
- Occlusion: A strip of aluminum foil was placed over the treated site, and the whole assembly held in place by encircling the trunk of the animal with a length of elastic bandage.
- Vehicle: none
- Concentration in vehicle: undiluted
- Total volume applied: not described
- Doses: 2000 mg/kg
- Removal of test substance: After a period of 24 hours, the adhesive bandage and gauze dressings were removed. The treated skin was washed gently with warm water to remove residual test item.

EXAMINATIONS: Animals were checked twice daily for mortality and morbidity. Clinical signs were observed immediately upon dosing, approximately 1, 2 and 4 hours after dosing and daily thereafter for a total of 14 days. Body weights were measured on Day -1, immediately prior to dosing (Day 1), and at weekly intervals thereafter (Days 8 and 15). All animals were killed on Day 15 by carbon dioxide narcosis. They were subjected to a gross necropsy examination for both external and internal abnormalities. The cranial, thoracic and abdominal cavities were opened to allow examination of their contents. Larger organs were sectioned. Particular attention was paid to the treated site.

Conclusion: These results indicate that the test item, TP-90B Rubber Chemical has no systemic toxic effect in the rat following dermal exposure over a 24-hour period at a level of 2000 mg/kg.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

13-AUG-2004 (24)

Type: other: Acute Dermal Toxicity Study
Species: rabbit
Strain: no data
Sex: male/female
No. of Animals: 6
Vehicle: other: None
Doses: 2 g/kg of body weight

Method: other: Federal Hazardous Substances Labeling Act
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Prior to exposure, the animals were prepared by clipping the skin of the trunk, which is approximately 10% of the body surface, free of hair. One-half of the group of 6 rabbits was further prepared by making epidermal abrasions every two or three centimeters longitudinally over the areas of future exposure. The abrasions were sufficiently deep to penetrate the stratum corneum but not to disturb the derma and cause bleeding.

The trunks of the animals were then enclosed in a clear polyethylene sleeve with the ends tucked under and taped in order to eliminate leakage of the TP-90B/6213.

The TP-90B/6213 was then applied to the assigned animals at the indicated dosage level by means of a syringe and needle; the needle being used to penetrate the sleeve and deposit the material on the animals skin.

Following dosing the rabbits were immobilized in stocks for 24 hours after which the sleeve and excess TP-90B/6213 was removed and the skin was cleaned and examined for a two week period.

Result: MORTALITY:
- Time of death: No deaths
- Number of deaths at each dose: No deaths

CLINICAL SIGNS: Other than slight erythema at the test site area, no symptoms of toxicity were noted.
NECROPSY FINDINGS: Not described
POTENTIAL TARGET ORGANS: Not described
SEX-SPECIFIC DIFFERENCES: No specific differences reported.

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

Test condition: TEST ORGANISMS:
- Source: Not described
- Age: Not described
- Weight at study initiation: Between 2.39 and 2.67 kg
- Controls: Not described

ADMINISTRATION:
- Area covered: The trunk of animals
- Occlusion: Enclosed in a clear polyethylene sleeve with the ends tucked under and taped in order to eliminate leakage of the experimental material.

- Vehicle: none
- Concentration in vehicle: undiluted
- Total volume applied: sufficient to make dose per animal equal
- Doses: 2 g/kg
- Removal of test substance: After 24 hours and the skin was cleaned

EXAMINATIONS: The animals were examined for a 2 week period.

Conclusion: There were no deaths from TP-90B/6213 when dermally applied to the backs of six albino rabbits at a level of 2.0 g/kg. It would not require labeling under the Federal Hazardous Substances Labeling Act.

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

13-AUG-2004 (3)

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
Vehicle: other: none
PDII: 0
Result: not irritating
EC classificat.: not irritating

Method: other: EPA/OECD
Year: 1991
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE
- Erythema: At 4.5, 24, 48 and 72 hours was 0
- Edema: At 4.5, 24, 48 and 72 hours was 0

REVERSIBILITY: No alterations in the skin were observed at the application site of any animal.
OTHER EFFECTS: None were observed.

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

Test condition: TEST ANIMALS:
- Strain: New Zealand Albino
- Sex: Male
- Source: Oak Hill Rabbitry, Holland, Michigan
- Age: 8-10 weeks
- Weight at study initiation:

Between 2.10 and 2.50 kg
- Number of animals: 6
- Controls: untreated site
ADMINISTRATION/EXPOSURE
- Preparation of test substance: none
- Area of exposure: shaved 8 x 8 cm area on left flank
- Occlusion: Yes
- Vehicle: No
- Concentration in vehicle: Undiluted material
- Total volume applied: 0.5 ml
- Postexposure period: 4 days
- Removal of test substance: The covering material was removed after a four hour contact period, and excess test material was wiped from the site.
EXAMINATIONS
- Scoring system: Draize
- Examination time points: Dermal irritation readings were performed approximately 30 minutes after patches were removed (4.5 hours) as well as 24, 48 and 72 hours after treatment.

Conclusion: Based on the results of this study, the test material TP-90B Plasticizer, Lot #1142-10M would be considered to be non-irritating to the skin of rabbits.

Reliability: (2) valid with restrictions

13-AUG-2004 (20)

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 72 hour(s)
No. of Animals: 3
Vehicle: other: none
PDII: 0
Result: not irritating
EC classificat.: not irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE
- Erythema: 0.0
- Edema: 0.0
OTHER EFFECTS: None

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

Test condition: TEST ANIMALS: Rabbits
- Strain: New Zealand White
- Sex: female
- Source: Francucci Enzo, Rieti, Italy
- Age: 9-11 weeks
- Weight at study initiation: 2.8-3.3 kg
- Number of animals: 3
- Controls: Untreated areas of test animal

ADMINISTRATION/EXPOSURE
- Preparation of test substance: The test substance was spread evenly over a gauze square
- Area of exposure: 2.5 x 2.5 cm
- Occlusion: A strip of aluminum foil was placed over the treated site and the whole assembly held in place by encircling the trunk of the animal with a length of elastic adhesive bandage, this forming a semi-occlusive barrier.
- Vehicle: None
- Concentration in vehicle: Undiluted
- Total volume applied: 0.5 mL
- Postexposure period: 72 hours
- Removal of test substance: 4 hours
EXAMINATIONS
- Scoring system: Draize

Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4

Oedema formation	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and Extending beyond area of exposure)	4

- Examination time points: 1, 24, 48, and 72 hours

Conclusion: These results indicate that TP-90B Rubber Chemical has no irritant effect on the skin of the rabbit.

Reliability: (1) valid without restriction

13-AUG-2004 (21)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time: 72 hour(s)
Comment: not rinsed
No. of Animals: 6
Vehicle: none
Result: not irritating

Method: other: EPA/OECD
Year: 1991
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE
- Cornea: 0.83
- Iris: 0.0
- Conjuntivae (Redness): 3.0
- Conjuntivae (Chemosis): 0.0
- Overall irritation score: 5.0

OTHER EFFECTS: None

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

Test condition: TEST ANIMALS:
- Strain: New Zealand Albino
- Sex: Male
- Source: Oak Hill Rabbitry, Holland, Michigan
- Age: Not described.
- Weight at study initiation: Between 2.03 and 2.60 kg
- Number of animals: 6
- Controls: The contralateral eye served as the untreated control for each rabbit

ADMINISTRATION/EXPOSURE
- Preparation of test substance: Administered undiluted
- Amount of substance instilled: 0.1 ml
- Vehicle: None
- Postexposure period: 72 hours

EXAMINATIONS
- Ophtalmoscopic examination: Yes
- Scoring system: Draize
- Observation period: 1, 24, 48 and 72 hours after treatment
- Tool used to assess score: A solution of 2% sodium fluorescein and ultraviolet light were employed to reveal possible corneal injury.

Conclusion: TP-90B Plasticizer, Lot #1142-10M (undiluted) was instilled into the conjunctival sac of the right eye of six rabbits at a dose of 0.1 ml. The eyes were observed and scored at 1, 24, 48 and 72 hours after treatment.
The maximum group mean score was 5.00 at the 24 hour observation. This mean score decreased to 0 at the 72 hour observation. Therefore, TP-90B Plasticizer, Lot #1142-10M (undiluted) would be classified as not irritating to the eye of the rabbit.

Reliability: (2) valid with restrictions
21-SEP-2004 (19)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time: 72 hour(s)
Comment: not rinsed
No. of Animals: 3
Vehicle: none
Result: slightly irritating
EC classificat.: not irritating

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE (average of scores at 24, 48 and 72 hours)
- Cornea: 0.0
- Iris: 0.0
- Conjuntivae (Redness): 0.0
- Conjuntivae (Chemosis): 0.0
- Overall irritation score: 0.0

REVERSIBILITY: The test substance had a slight irritant effect in the eye at 1 hour post-dose only, this being quickly reversible.

OTHER EFFECTS: None

Source: Rohm and Haas Company, Spring House, PA USA
Test condition: TEST ANIMALS: Rabbits
- Strain: New Zealand White
- Sex: female
- Source: Francucci Enzo, Rieti, Italy
- Age: 9-11 weeks
- Weight at study initiation: 2.9-3.5 kg
- Number of animals: 3
- Controls: Untreated eye

ADMINISTRATION/EXPOSURE
- Preparation of test substance: None
- Amount of substance instilled: 0.1 mL
- Vehicle: Undiluted
- Postexposure period: 72 hours

EXAMINATIONS
- Ophthalmoscopic examination: "under standard conditions"
- Scoring system: Draize et al., 1944
- Observation period: 1, 24, 48, and 72 hours
- Tool used to assess score: No details

Conclusion: The results of this study indicated that the test item, TP-90B Rubber Chemical, has no significant irritant effects in the eye.
Reliability: (1) valid without restriction
16-AUG-2004 (22)

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Exposure Time: 72 hour(s)
Comment: not rinsed
No. of Animals: 6
Vehicle: none
Result: not irritating
EC classificat.: not irritating

Method: other: not specified
Year: 1966
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: AVERAGE SCORE
- Cornea: no effects
- Iris: no effects
- Conjuntivae (Redness): no effects
- Conjuntivae (Chemosis): no effects
- Overall irritation score: not specified

Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ANIMALS: Rabbit
- Strain: not specified
- Sex: not specified
- Source: not specified
- Age: not specified
- Weight at study initiation: not specified
- Number of animals: 6
- Controls: Left, untreated eye

ADMINISTRATION/EXPOSURE
- Preparation of test substance: undiluted
- Amount of substance instilled: 0.1 mL
- Vehicle: none
- Postexposure period: 72 hours

EXAMINATIONS
- Ophtalmoscopic examination: not specified
- Scoring system: Draize scoring system
- Observation period: 3 days, at 24 hour intervals
- Tool used to assess score: not specified

Conclusion: Thikol Chemical Corporation - Sample No. TP-90B, Lot No. 4153, as tested, is not an ocular irritant.
Reliability: (2) valid with restrictions
16-AUG-2004 (2)

5.3 Sensitization

Type: Buehler Test
Species: guinea pig
Concentration 1st: Induction 100 % occlusive epicutaneous
2nd: Challenge 75 % occlusive epicutaneous
No. of Animals: 20
Vehicle: water
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide-line 406 "Skin Sensitization"
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: The results of the study were negative. TP-90B did not elicit a sensitization response in the guinea pig. The test would have been considered positive if 15% or more animals in the test group exhibited erythema or dermal swelling following challenge with a non-irritant concentration of the test item.
Main study - Induction:
No response was seen to either the test item or the vehicle alone in animals of the test and control groups following 6 hours topical exposure.

Main study - Challenge:
No response was observed to the test item in either test or control group animals 24 and 48 hours following 6 hours topical exposure. No reaction was observed to the vehicle alone.

No changes in body weight occurred throughout the course of the study.

Source: Rohm and Haas Company, Spring House, PA USA
Test condition:
- Species: Guinea Pig
- Strain: Dunkin-Hartley
- Sex: female
- Number of animals per sex per dose:

Preliminary screen: 5 females, each dosed with 4 concentrations of test item, for a total of 10 concentrations (100, 75, 50, 20, 10, 5, 2, 1, 0.5, 0.1%) in duplicate.
Main study: Test group of 20 females, and a control group of 10 females.
- Route of administration

Main study - Induction: On the day of dosing (days 1, 8, 15), the hair was clipped from the left flank of each animal. Animals of the test group were treated with the undiluted test item. A gauze patch measuring 20 x 20 mm was covered with 0.4 mL of the test item and was placed onto the selected skin site. This was secured in position by encircling the trunk of the animal with a length of adhesive strapping. All animals of the test group were treated with the test item in this manner and animals of the control group were similarly treated

with the selected vehicle (sterile water).

Main study - Challenge: On day 29, 0.4 mL aliquot of the test item at 75% concentration in sterile water was spread evenly over an absorbent patch measuring approximately 20 x 20 mm. This was placed onto the skin of the posterior region of the prepared site on the right flank. A similar patch, this containing 0.4 mL of the vehicle selected for the challenge (sterile water) was placed onto the anterior region of the prepared site. The patches were secured in position by encircling the trunk of the animal with a length of adhesive strapping. All animals of both the test and control groups were treated with both the test item and vehicle in this manner.

After an exposure period of 6 hours (induction and challenge) the dressings were removed, and the treated sites cleaned of remaining test item by washing with warm water.
- Induction concentration: 0.4 mL undiluted TP-90B
- Induction vehicle: None
- Challenge concentration: 0.4 mL of TP-90B at 75% concentration
- Challenge vehicle: sterile water
- Grading system used: Approximately 24 and 48 hours after removal of the patches, the treated sites were examined for signs of reaction to treatment. Each site was assessed and scored using the following scale:
No reaction - 0
Slight, patchy erythema (barely perceptible or questionable) +/-
Slight, but confluent or moderate but patchy erythema 1
Moderate erythema - 2
Severe erythema with or without edema - 3
- Age of animal at study initiation: 4-5 weeks
- Positive controls: a-hexylcinnamaldehyde
- Results of range-finding or screening studies: A slight, patchy erythema was observed in 1 animal at the site treated with the undiluted test item. No reaction was apparent in the remaining animals at any of the 10 concentrations investigated, suggesting that the test item at a concentration of 100% was reasonably tolerated. This concentration was selected for use during the induction phases of the main study. A concentration of 75% in sterile water was selected for use at challenge, being judged non-irritant.
- Justification for vehicles: not detailed
- Length of rest period between induction and challenge: 2 weeks
- Protocol deviations: During the challenge phase, the clipping procedure to be undertaken approximately 3 hours prior to evaluation of skin reaction was not performed due to oversight.

Conclusion: The results of this study indicate that the test item, TP-90B Rubber Chemical, does not elicit a sensitization response in the guinea pig, there being no evidence of response at

challenge following a period of induction exposure to the test item.

Reliability: (1) valid without restriction
16-AUG-2004 (25)

Type: other: Modified Buehler Test
Species: guinea pig
Concentration 1st: Induction 100 % active substance occlusive epicutaneous
2nd: Challenge 100 % active substance occlusive epicutaneous
No. of Animals: 18
Vehicle: other: none
Result: not sensitizing
Classification: not sensitizing

Method: other: EPA/OECD
Year: 1991
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS OF PILOT STUDY: The initial dose of TP-90B Plasticizer, Lot #1142-10M, or 1-chloro 2,4-dinitrobenzene produced no positive irritation scores in any of the guinea pigs.
RESULTS OF TEST
- Sensitization reaction: Average scores for the challenge dose were 0 for TP-90B Plasticizer, Lot #1142-10M and the challenged negative controls. The average challenge dose score of 1-chloro 2,4-dinitrobenzene was 0.54.
- Clinical signs: All guinea pigs survived the study in apparent good health and gained weight during the course of the study.
- Rechallenge: The challenge dose of TP-90B Plasticizer, Lot #1142-10M did not elicit a positive response in any of the ten guinea pigs. Two negative control animals challenged with TP-90B Plasticizer, Lot #1142-10M also did not elicit a positive response. The challenge dose of 1-chloro 2,4-dinitrobenzene resulted in a positive response in 6/6 guinea pigs, characterized by a grade 1 for erythema and/or edema.
Source: Rohm and Haas Company, Spring House, PA, USA
Test condition: TEST ANIMALS:
- Strain: Hartley albino guinea pigs
- Sex: Male
- Source: Harlan Sprague Dawley
- Age: Young adult
- Weight at study initiation: Between 182 and 247 g
- Number of animals: 18
- Controls:
2 negative controls
6 positive controls
ADMINISTRATION/EXPOSURE
- Study type: Non-adjuvant
- Preparation of test substance for induction: Undiluted material

- Induction schedule: The animals were unwrapped after a 24 hour exposure period (initial dose). Nine succeeding induction doses were unwrapped after a 6 hour exposure period. This procedure was repeated three times weekly (with at least one day intervening between treatments) for a total of ten applications.
- Concentrations used for induction: Undiluted
- Challenge schedule: Two weeks after the final application the animals received a topical challenge dose (24-hour contact) at a naive site located on the right flank.
- Concentrations used for challenge: Undiluted
- Rechallenge: No
- Positive control: 6 guinea pigs received a 0.1% solution of 1-chloro 2,4 dinitrobenzene in (5% DMSO in H2O)
EXAMINATIONS
- Grading system: Buehler Method
- Pilot study: Yes

Conclusion: Based on comparisons of the initial test dose response to the challenge test dose and to the reactions elicited by the positive and negative controls, TP-90B Plasticizer would not be considered a dermal sensitizing agent.

Reliability: (2) valid with restrictions
16-AUG-2004 (18)

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 9 weeks
Frequency of treatment: once per day, 7 days per week
Doses: 10, 100, 800 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL: = 100 mg/kg bw

Method: OECD combined study TG422
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL: 100 mg/kg/day
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: One mid-dose female was sacrificed, on day 0 post-partum, for humane reasons, since signs of difficult delivery were noted. No other animals died prior to study termination.
- Clinical signs: Weekly physical examinations including detailed clinical signs with neurotoxicity assessment did not show any signs which could be correlated to the treatment with the test item in males or females in any group during the treatment period.
- Body weight gain: Body weight and body weight gain were

unaffected by treatment in the males throughout the study and in females before pairing. Slight decreases, not statistically significant, in body weight and body weight gain were observed in the high dose females during the gestation period when compared to controls. No differences were noted in females of any treatment group during the post-partum period when compared to controls.
- Food/water consumption: Food consumption remained comparable between control and treated groups in both sexes before pairing. A statistically significant reduction in food consumption was noted in high dose females on day 7 post-coitum. A similar reduction (not statistically significant) was noted on day 14 post-coitum in the same group.
- Clinical chemistry: No toxicologically significant change in any clinical chemistry parameter occurred at any dose level.

A statistically significant decrease in alkaline phosphatase level was observed in the high dose male group. Since this change was minimal, was decreased compared to the control group and occurred in only one sex, it is not considered toxicologically significant. A statistically significant decrease in alanine aminotransferase level was noted in the low dose male group when compared to controls. This decrease is considered incidental to treatment since no dose response was evident.
Statistically significant decreases in urea were seen in the low and high dose males compared to controls. These changes are not considered treatment-related since the changes are decreased relative to controls and there is no evident dose response. Statistically significant changes in creatinine and inorganic phosphorus levels were observed in the high dose male group. These changes are not considered treatment-related since the values are decreased compared to controls, the magnitude of the change is small and they occurred only in one sex.

Urea level was also statistically significantly decreased in the low dose male group. This change is not considered treatment-related since the effect was decreased, there was no obvious graded dose response at the mid- and high dose groups and the effect occurred in only one sex.

No differences in clinical chemistry parameters were noted between control and treated females.
- Hematology: No toxicologically significant changes in hematology occurred in this study. Statistically significant decreases in prothrombin time were observed in the high dose male group. This change is considered incidental and not treatment-related since it was seen in only one sex, and the magnitude of the effect was low.

Statistically significant decreases in neutrophil percentage were observed in the high dose females. This change is

considered incidental and not treatment-related since it was seen in one sex only and no other changes were seen in the white blood cell differential counts.
- Organ weights: Treatment-related organ weight changes occurred in the liver of high dose males and females. Statistically significant increases in absolute and relative liver weights were observed in the high dose males when compared to controls. Increases in absolute (not statistically significant) and relative (statistically significant) liver weights were also noted in only the high dose females.

Statistically significant increases in absolute and relative kidney weights were noted in the mid-dose male group only. Since the absolute and relative kidney weights of the high dose males were not affected (i.e., no apparent dose response), there was no corresponding increase in females, and no corresponding microscopic change in this tissue, the kidney weight changes were considered not related to treatment with the test item. Slight, but statistically significant increases in absolute and relative adrenal weights were observed in the high dose female group. This change is considered incidental and not treatment-related since there was no corresponding microscopic histopathologic change in this tissue and similar effects were not seen in the high dose male group.
- Gross pathology: No macroscopic change was reported at necropsy in the examined organs/tissues of the animals killed at termination that could be considered related to the administration of the test substance. The recorded changes were considered to be incidental or spontaneous in origin.
- Histopathology: No microscopic changes clearly related to test substance administration were observed in male or female rats given 10 or 100 mg/kg/day of the test article.

Diffuse hepatocellular hypertrophy (enlarged hepatocytes in all areas of the lobules) occurred in male and female rats of the high dosage group and was considered to be treatment-related.

Focal germ-cell depletion and degeneration occurred in one testis (unilateral) of each of four different male rats of the high dosage group. Exfoliated spermatogenic cells were observed in the epididymis in three of these high dose rats and in one additional high dose rat without testicular changes. The significance of this finding is uncertain. Systemic toxicity usually does not affect only one of a paired organ.

All other microscopic changes were considered to have occurred spontaneously and to be unrelated to test substance administration. These changes generally occurred at single, low, or similar frequencies among the groups and their type, incidence or severity was not influenced by compound

administration.
- Other:
- Pre- and post-dose observations: Treatment-related signs of intoxication were observed in high dose males and females at the post-dose observations. Ataxia, semi-closed eyes and hunched posture were the principal signs observed at 2 hours post-dose in some high dose males on day 7 of the study. Thereafter, the above signs were noted occasionally until day 10 of the study. Starting from day 30 until day 35 of the study, ataxia, reduced activity and salivation were also noted within 15 minutes of dosing in the same male group.

Starting from the first day of treatment, post-dose observations in high-dose females included pronation, ataxia, semi-closed eyes, reduced activity, hunched posture and lethargy 2 and 3 hours after treatment. In addition, twitches, piloerection and salivation were also noted 15 minutes (starting from day 15 of the study) and 1 hour after dosing in a few high dose females throughout the study.
- Motor activity and sensory reaction to stimuli: No treatment-related effects on motor activity and sensory reaction to stimuli were seen in either sex at any dose.

An increased incidence, with statistical significance, in motor activity measurements of males was noted in the low and mid-dose groups. No increase was observed in the high dose group and there was no increased magnitude of the response of the mid-dose compared to the low dose rats. The increased activity in the low and mid-dose groups is considered incidental to treatment with the test item. No differences were noted in treated females when compared to controls.

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

Test condition: TEST ORGANISMS: Hsd Sprague Dawley SD Rats
- Age: ~ 12 weeks
- Weight at study initiation: Male: 361.23-362.49 Female: 262.20-262.98
- Number of animals: 10 male and 10 female per group
ADMINISTRATION / EXPOSURE
- Duration of test/exposure: For males, treatment commenced when the males were approximately 12 weeks old and continued for two weeks prior to pairing, during pairing until mating was confirmed, and up to and including the day before sacrifice. For females, treatment commenced when they were approximately 12 weeks old and continued for two weeks prior to pairing through the mating and gestation periods, up to day 3 of lactation. Dams and offspring were sacrificed on Day 4 post-partum.
- Type of exposure: oral gavage
- Post exposure period: none
- Vehicle: 0.5% aqueous carboxymethylcellulose
- Concentration in vehicle: appropriate to keep dosing volume constant
- Total volume applied: 10 ml/kg
- Doses: 0, 10, 100, 800 mg/kg/day

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: Once before the commencement of treatment, and at least once per week thereafter, each animal was given a detailed clinical examination. Each animal was removed from the home cage and observed in an open arena. The tests included observation of changes in gait and posture, reactivity to handling, presence of clonic or tonic movements, stereotypies or bizarre behavior and effects on the autonomic nervous system (e.g., lachrymation, piloerection, pupil size, unusual respiratory pattern). During the gestation periods, the observations were carried out on Days 1, 7, 14, and 20.
- Mortality: twice per day
- Body weight: Males were weighed weekly from allocation to termination. Females were weighed weekly from allocation to pairing, and on gestation days 0, 7, 14, and 20. Dams were also weighed on days 1 and 4 post-partum, with the exception of one mid-dose female, which was weighed on days 2 and 5 post-partum.
- Food consumption: The weight of food consumed by each cage of males and females was recorded weekly during the pre-mating period starting from allocation. Individual food consumption for the females was measured on gestation days 0, 7, 14 and 20, and on days 1 and 4 post-partum, with the exception of one mid-dose female where food consumption was measured on days 2 and 5 post-partum.
- Water consumption: not reported
- Hematology: Measurements performed on blood samples are as follows: hematocrit; hemoglobin; red blood cell (RBC) count; mean RBC volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; white blood cell count; differential leukocyte count (neutrophils, lymphocytes, eosinopils, basophils, monocytes, large unstained cells); abnormalities of the blood film; platelets; prothrombin time; partial thromboplastine time
- Biochemistry: Clinical chemistry parameters investigated included: alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase; urea; creatinine; gamma glutamyl transferase; globulin and A/G ratio; fasting glucose; total bilirubin; total cholesterol; total protein; albumin; sodium; phosporus; potassium; calcium; chloride; total glycerides.
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: The following organs from all adult animals in all groups were dissected free of fat and weighed: adrenals, brain, epididymides, heart, kidneys, liver, spleen, thymus, testes.
- Microscopic: The tissues listed, as follows, were examined in all adult animals: corpora lutea, abnormalities (gross lesions), adrenals (paired), bone marrow (from the sternum), brain, caecum, coagulating glands (paired), colon, duodenum, epididymides (paired), esophagus, heart, ileum, jejunum, kidneys (paired), liver, lymph nodes (cervical), lymph nodes (mesenteric), lungs, ovaries with oviduct (paired), prostate, pituitary, rectum, sciatic nerve, seminal vescicles, spinal column with spinal cord, spleen, stomach, thymus, thyroid,

trachea, testes (paired), urinary bladder, uterus with cervix, vagina.
OTHER EXAMINATIONS:
- Pre- and post-dose observations: Examination of individual animals for signs of reaction to treatment was carried out daily. Starting on day 1 until day 14 of dosing, all animals were observed prior to dosing, immediately after dosing, and at 1, 2 and 3 hours after dosing. From day 15 until study termination, observations were made prior to dosing, immediately after dosing, and 15 minutes and 1 hour after dosing.
- Sensory reactivity and grip strength: Once during the study, in week 5 of treatment, 5 males were randomly selected from each group for evaluation of sensory reactivity to stimuli of different modalities (e.g., auditory, visual and propioceptive stimuli), and an assessment of grip strength was also performed. Once during the study, on day 20 post-coitum, 5 females were selected for the same tests.
- Motor activity: Once during the study, on week 4 of treatment, 5 males were randomly selected from each group and the motor activity was measured by an automated activity recording device. Measurements were performed using a computer-generate random order. On day 20 post-coitum, 5 females were selected for the same activity.
STATISTICAL METHODS: For continuous variables, the significance of the difference amongst group means was assessed by analysis of variance. Differences between the treated group and the control group were assessed by Dunnett's test using a pooled error of variance. The homogeneity of the data was assessed by Bartlett's Test before Dunnett's Test was performed. If the data were found to be inhomogeneous, a modified t-test (Cochran and Cox) was applied. Statistical analysis of histopathological findings was not carried out by means of the non-parametric Kolmogorov-Smirnov test.

The mean values, standard deviations and statistical analysis were calculated from actual values in the computer without rounding off.

The non-parametric Kruskal-Wallis analysis of variance was used for all other parameters. Intergroup differences between the control and the treated group were assessed by the non-parametric version of the Williams' test.

Conclusion: Gavage treatment of rats with TP-90B RUBBER CHEMICAL for at least 43 consecutive days in males and females at doses of 0 (control), 10, 100, or 800 mg/kg/day resulted in a No-Observed-Adverse-Effect Level (NOAEL) of 100 mg/kg/day.

At the high dose (800 mg/kg/day) the following treatment-related effects were seen:
Post-dose clinical signs indicating effects on the central nervous system in males and females
Decreased body weight and body weight gain in females

during gestation
Reduced food consumption in females on days 7 and 14 post-coitum
Increased liver weights
Microscopic changes in the liver

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
21-SEP-2004 (28)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100, and Escherichia coli strain WP2 uvrA
Concentration: See test condition section
Cytotoxic Concentration: See test condition section
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 2003
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: Not described.
CYTOTOXIC CONCENTRATION:
- With metabolic activation: In Main Assay II, toxicity was observed at all dose levels for all strains except TA1535.
- Without metabolic activation: In Main Assay I, slight toxicity was observed in TA1537 at "higher dose levels". In Main Assay II, toxicity was observed at all dose levels for all strains except TA1535.
TEST-SPECIFIC CONFOUNDING FACTORS: Excessive toxicity was initially observed during the independent repeat assay. However, this was corrected by using lower dose levels in a separate repeat assay.
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 TA98, TA100, TA1535, TA1537; E. coli WP2uvrA
- Metabolic activation system: liver S9 fraction from rats pre-treated with phenobarbitone and betanaphthoflavone
ADMINISTRATION:
- Dosing: In Main Assay I, using the plate incorporation method, the test item was assayed at a maximum dose-level of

5000 µg/plate and at four lower dose-levels, seprated by two-fold dilutions: 2500, 1250, 625 and 313 µg/plate.

As no increases in revertant numbers were observed, all treatments of Main Assay II included a pre-incubation step and used the same dose-range employed in Main Assay I. This dose range proved to be too toxic with all tester strains, in the absence and presence of S9 metabolism, with the exception of TA1535. Moreover, moderate microbial contamination was observed on the plates relative to the treatment with TA98 in the absence of S9 metabolism.

Therefore, in order to assay the test item at adequate less-toxic concentrations, a Main Assay III was performed using the following dose-levels:

Tester Strain	S9	Dose Levels (µg/plate)
TA1537	+/-	400, 200, 100, 50.0, 25.0
TA98	+	400, 200, 100, 50.0, 25.0
TA98	-	400, 200, 100, 50.0, 25.0, 12.5, 6.25, 3.13
TA100 & WP2uvrA	+/-	800, 400, 200, 100, 50.0

- Number of replicates: 3 replicate plates were used at each test point
- Application: The first experiment was performed using a plate-incorporation method. The components of the assay (the tester strain bacteria, the test item and S9 mix or phosphate buffer) were added to molten overlay agar and vortexed. The mixture was then poured onto the surface of a minimal medium agar plate, and allowed to solidify prior to incubation.

The overlay mixture was composed as follows:

(i) Overlay agar (held at 45°C)	2 mL
(ii) Test or control item solution	0.1 mL
(iii)S9 mix or phosphate buffer (pH 7.4, 0.1M)	0.5 mL
(iv) Bacterial suspension	0.1 mL

The second and third experiment were performed using a pre-incubation method. The components were added in turn to an empty test tube:

(i) Bacterial suspension	0.1 mL
(ii) Test or control item solution	0.05 mL
(iii)S9 mix or phosphate buffer (pH 7.4, 0.1M)	0.5 mL

The incubate was vortexed and placed at 37°C for 30 minutes. Two mL of overlay agar was then added and the mixture vortexed again and poured onto the surface of a minimal medium agar plate and allowed to solidify.

- Positive and negative control groups and treatment (parenthesis denotes pre-incubation method):

Tester Strain	Absence of S9	Presence of S9
TA1535	sodium azide 1 µg/plate	2-aminoanthracene 1 µg/plate
TA100	sodium azide 1 µg/plate	2-aminoanthracene 1 µg/plate (2 µg/plate)
TA1537	9-amino-acridine 50 µg/plate	2-aminoanthracene 1 µg/plate
TA98	2-nitrofluorene 2 µg/plate	2-aminoanthracene 1 µg/plate (2 µg/plate)
WP2uvrA	methylmethanesulphonate 500 µg/plate	2-aminoanthracene 10 µg/plate (20 µg/plate)

- Pre-incubation time: 30 minutes at 37°C
DESCRIPTION OF FOLLOW UP REPEAT STUDY: Results were confirmed in an independent pre-incubation assay.
CRITERIA FOR EVALUATING RESULTS: For the test item to be considered mutagenic, two-fold (or more) increases in mean revertant numbers must be observed at two consecutive dose levels or at the highest practicable dose level only. In addition, there must be evidence of a dose-response relationship showing increasing numbers of mutant colonies with increasing dose levels.

Conclusion: It is concluded that the test item, TP-90B rubber chemical, does not induce reverse mutation in Salmonella typhimurium and Escherichia coli under the reported experimental conditions.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

16-AUG-2004 (26)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: other: Hsd:ICR (CD-1)
Route of admin.: gavage
Exposure period: 1 exposure; sacrificed at 24 and 48 hours
Doses: 0, 375, 750, 1500 mg/kg
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: MORTALITY: One female at the low dose was found dead 24 hours after treatment.
CLINICAL SIGNS: Animals from the high treatment group showed ataxia, hunched posture, ungroomed appearance, reduced activity and three female animals were found moribund approximately 20 minutes after treatment. Animals from the intermediate group showed reduced activity and hunched posture, and one male animal was found moribund approximately 25 minutes after treatment. A full recovery was observed for

all animals, the day after treatment. A female animal was found dead at the low dose level 24 hours after treatment. Reduced activity and hunched posture were also observed in a female animal from the vehicle control group, 24 hours and 48 hours after treatment.
EFFECT ON MITOTIC INDEX OR PCE/NCE RATIO: No increases in the numbers of micronucleated PCE's were observed in any TP-90B treatment group at any sampling time.
STATISTICAL RESULTS: Following treatment with TP-90B, no statistically significant increase in the incidence of micronucleated PCE's over the control value was observed at any sampling time for male and female animals combined, or considered separately at each sampling time. Statistically significant increases in the incidence of micronucleated PCE's over the control values were seen in the positive control group, indicating the correct functioning of the test system.

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

Test condition: TEST ORGANISMS: CD-1 Mouse
- Age: 5 weeks
- Weight at study initiation: 21-23 g (F); 23-24 g (M)
- No. of animals per dose: 5 females, 5 males

ADMINISTRATION:
- Vehicle: corn oil
- Duration of test: 48 hours
- Frequency of treatment: Once
- Sampling times and number of samples: 24 hours (5 males and 5 females, each from positive control, vehicle, low, mid, and high dose); 48 hours (5 males and 5 females, each from positive control, and high dose)
- Control groups and treatment: corn oil and Mytomicin C (3 mg/kg)

EXAMINATIONS:
- Clinical observations: ca. 0.5, 5, 24 and 48 hours after treatment
- Organs examined at necropsy: bone marrow from femurs (mature and immature erythrocytes)
- Criteria for evaluating results: The test item is considered to induce micronuclei if a statistically significant increase in the micronucleus incidence in polychromatic erythrocytes (PCE) (at $P<0.05$) is observed in any treatment group, in the pooled data for both sexes, or for either considered separately. Where increases in the incidence of micronucleated PCE's are observed which are statistically significant, but fall within the range of negative control values within this laboratory, then concurrent and historical control data are used to demonstrate that these increases do not have biological significance.
- Criteria for selection of M.T.D.: preliminary toxicity test

Conclusion: It is concluded that, under the reported experimental conditions, TP-90B administered by oral gavage at the selected dose levels to male and female mice, does not induce micronuclei in the polychromatic erythrocytes.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

16-AUG-2004 (1)

5.7 Carcinogenicity

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5.8.1 Toxicity to Fertility

Type: other: Combined Repeated Gavage Dose Toxicity Study
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: 9 weeks
Frequency of treatment: once per day, 7 days per week
Premating Exposure Period
male: 2 weeks
female: 2 weeks
Duration of test: 9 weeks
Doses: 10, 100, 800 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL Parental: = 100 mg/kg bw
NOAEL F1 Offspring: = 100 mg/kg bw

Method: OECD Guide-line 422
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL: 100 mg/kg/day
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Parental data:
- Body weight: Body weight and body weight gain were unaffected by treatment in the males throughout the study and in females before pairing. Slight decreases, not statistically significant, in body weight and body weight gain were observed in the high dose females during the gestation period when compared to controls. No differences were noted in females of any treatment group during the post-partum period when compared to controls.
- Food/water consumption: Food consumption remained comparable between control and treated groups in both sexes before pairing. A statistically significant reduction in food consumption was noted in high dose females on day 7 post-coitum. A similar reduction (not statistically significant) was noted on day 14 post-coitum in the same group.
- Description, severity, time of onset and duration of clinical signs: Weekly physical examinations including detailed clinical signs with neurotoxicity assessment did not show any signs which could be correlated to the treatment with the test item in males or females in any group during the treatment period.

- Fertility index: Fertility index in the high-dose group was decreased compared to controls. A treatment-related effect on fertility is apparent in the high dose group. A total of fifteen females proved not to be pregnant at necropsy; three in the control group and in the mid-dose group, two in the low-dose group and seven in the high-dose group.
- Pre-coital interval: Pre-coital interval in tested rats was comparable to controls.
- Duration of gestation: Gestation periods in tested rats were comparable to controls.
- Gestation index: An increased incidence, not statistically significant, in the number and percentage of pre-birth loss was noted in high dose females when compared to controls.
- Changes in lactation: not characterized
- Changes in estrus cycles: The estrus cycles of tested animals were comparable to controls.
- Effects on sperm: not characterized
- Hematological findings incidence and severity: No toxicologically significant changes in hematology occurred in this study. Statistically significant decreases in prothrombin time were observed in the high dose male group. This change is considered incidental and not treatment-related since it was seen in only one sex, and the magnitude of the effect was low.

Statistically significant decreases in neutrophil percentage were observed in the high dose females. This change is considered incidental and not treatment-related since it was seen in one sex only and no other changes were seen in the white blood cell differential counts.
- Clinical biochemistry findings incidence and severity: No toxicologically significant change in any clinical chemistry parameter occurred at any dose level.

A statistically significant decrease in alkaline phosphatase level was observed in the high dose male group. Since this change was minimal, was decreased compared to the control group and occurred in only one sex, it is not considered toxicologically significant. A statistically significant decrease in alanine aminotransferase level was noted in the low dose male group when compared to controls. This decrease is considered incidental to treatment since no dose response was evident.
Statistically significant decreases in urea were seen in the low and high dose males compared to controls. These changes are not considered treatment-related since the changes are decreased relative to controls and there is no evident dose response. Statistically significant changes in creatinine and inorganic phosphorus levels were observed in the high dose male group. These changes are not considered treatment-related since the values are decreased compared to controls, the magnitude of the change is small and they occurred only in one sex.

Urea level was also statistically significantly decreased in the low dose male group. This change is not considered treatment-related since the effect was decreased, there was no obvious graded dose response at the mid- and high dose groups and the effect occurred in only one sex.

No differences in clinical chemistry parameters were noted between control and treated females.
- Mortality: One mid-dose female was sacrificed, on day 0 post-partum, for humane reasons, since signs of difficult delivery were noted. No other animals died prior to study termination.
- Gross pathology incidence and severity: No macroscopic change was reported at necropsy in the examined organs/tissues of the animals killed at termination that could be considered related to the administration of the test item. The recorded changes were considered to be incidental or spontaneous in origin.
- Number of implantations: There were no effects on the mean number of implantation sites at any dose level.
- Number of corpora lutea: not reported
- Organ weight changes: Treatment-related organ weight changes occurred in the liver of high dose males and females. Statistically significant increases in absolute and relative liver weights were observed in the high dose males when compared to controls. Increases in absolute (not statistically significant) and relative (statistically significant) liver weights were also noted in only the high dose females.

Statistically significant increases in absolute and relative kidney weights were noted in the mid-dose male group only. Since the absolute and relative kidney weights of the high dose males were not affected (i.e., no apparent dose response), there was no corresponding increase in females, and no corresponding microscopic change in this tissue, the kidney weight changes were considered not related to treatment with the test item. Slight, but statistically significant increases in absolute and relative adrenal weights were observed in the high dose female group. This change is considered incidental and not treatment-related since there was no corresponding microscopic histopathologic change in this tissue and similar effects were not seen in the high dose male group.
- Histopathology incidence and severity: No microscopic changes clearly related to test substance administration were observed in male or female rats given 10 or 100 mg/kg/day of the test article.

Diffuse hepatocellular hypertrophy (enlarged hepatocytes in all areas of the lobules) occurred in male and female rats of the high dosage group and was considered to be treatment-related.

Focal germ-cell depletion and degeneration occurred in one testis (unilateral) of each of four different male rats of the high dosage group. Exfoliated spermatogenic cells were observed in the epididymis in three of these high dose rats and in one additional high dose rat without testicular changes. The significance of this finding is uncertain. Systemic toxicity usually does not affect only one of a paired organ.

All other microscopic changes were considered to have occurred spontaneously and to be unrelated to test article administration. These changes generally occurred at single, low, or similar frequencies among the groups and their type, incidence or severity was not influenced by compound administration.
- Litter size and weights: A decrease in the average number of pups per litter was observed at birth, and on day 4 post-partum in the high-dose group. Decreased litter weight and mean pup weight in the high-dose group (not statistically significant) were noted at birth and on day 4 post-partum.
- Sex and sex ratios: Sex ratios at birth and on day 4 post-partum did not show any differences between control and treated groups when calculated as the percentage of males.
- Viability index: Pup survival to day 4 was decreased in the high-dose group. The number of females with live pups on day 4 post-partum was 6, 8, 6, and 3 in the control, low-, mid- and high-dose groups, respectively. A statistically significant increase in pup mortality (females and total) from day 0 to day 4 was noted in the high dose group. Similar results were also seen in male pups but the difference was not statistically significant.

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

Test condition: TEST ORGANISMS: Hsd Sprague Dawley SD Rats
ADMINISTRATION / EXPOSURE
- Type of exposure: oral gavage
- Duration of test/exposure: For males, treatment commenced when the males were approximately 12 weeks old and continued for two weeks prior to pairing, during pairing until mating was confirmed, and up to and including the day before sacrifice. For females, treatment commenced when they were approximately 12 weeks old and continued for two weeks prior to pairing through the mating and gestation periods, up to day 3 of lactation. Dams and offspring were sacrificed on Day 4 post-partum.
- Treatment: TP-90B was administered to rats daily
- Control group and treatment: Vehicle alone at same dose volume
- Vehicle: 0.5% aqueous carboxymethylcellulose
- Concentration in vehicle: appropriate to keep dosing volume constant
- Total volume applied: 10 ml/kg
- Doses: 0, 10, 100, 800 mg/kg/day
MATING PROCEDURES: Pairings were monogamous. Vaginal smears were taken during pairing up to the day of positive

identification of mating. Each cage was checked each morning for the presence of copulation plugs. The pairing combinations of animals which had not had positive identification of mating after 14 days of pairing were changed within each treatment group. Animals that did not have signs of mating during the initial pairing were placed with a second male that previously had positive signs of mating. The subsequent pairing was monitored for mating as described above for the first pairing. No more than 28 days was allowed for pairing.
PARAMETERS ASSESSED DURING STUDY P AND F1:
- Clinical signs: Once before the commencement of treatment, and at least once per week thereafter, each animal was given a detailed clinical examination. Each animal was removed from the home cage and observed in an open arena. The tests included observation of changes in gait and posture, reactivity to handling, presence of clonic or tonic movements, stereotypies or bizarre behavior and effects on the autonomic nervous system (e.g., lachrymation, piloerection, pupil size, unusual respiratory pattern). During the gestation periods, the observations were carried out on Days 1, 7, 14, and 20.
- Mortality: twice per day
- Body weight: Males were weighed weekly from allocation to termination. Females were weighed weekly from allocation to pairing, and on gestation days 0, 7, 14, and 20. Dams were also weighed on days 1 and 4 post-partum, with the exception of one mid-dose female, which was weighed on days 2 and 5 post-partum.
- Food consumption: The weight of food consumed by each cage of males and females was recorded weekly during the pre-mating period starting from allocation. Individual food consumption for the females was measured on gestation days 0, 7, 14 and 20, and on days 1 and 4 post-partum, with the exception of one mid-dose female where food consumption was measured on days 2 and 5 post-partum.
- Water consumption: not reported
- Hematology: Measurements performed on blood samples are as follows: hematocrit; hemoglobin; red blood cell (RBC) count; mean RBC volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; white blood cell count; differential leukocyte count (neutrophils, lymphocytes, eosinopils, basophils, monocytes, large unstained cells); abnormalities of the blood film; platelets; prothrombin time; partial thromboplastine time
- Biochemistry: Clinical chemistry parameters investigated included: alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase; urea; creatinine; gamma glutamyl transferase; globulin and A/G ratio; fasting glucose; total bilirubin; total cholesterol; total protein; albumin; sodium; phosporus; potassium; calcium; chloride; total glycerides.
- Estrous cycle: Vaginal smears were taken daily in the morning, starting two weeks before pairing (first day of dosing) until a positive identification of mating was made. The vaginal smear data were examined to determine anomalies of

the estrous cycle, and the pre-coital interval (i.e., the number of nights paired prior to the detection of mating.
- Sperm examination: Each cage was checked each morning for the presence of copulation plugs.
OFFSPRING: The total litter size was (live and dead) was counted as soon as possible after parturition. Live pups were identified individually within the litter by toe amputation, sexed and examined for external abnormalities. Live and dead pups were counted and weighed on days 1 and 4 post-partum, with the exception of one mid-dose female, where pups were weighed on days 2 and 5 post-partum. All litters were observed daily. All pups found dead were given a post-partum examination.
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: The following organs from all adult animals in all groups were dissected free of fat and weighed: adrenals, brain, epididymides, heart, kidneys, liver, spleen, thymus, testes.
- Histopathology P and F1: The tissues listed, as follows, were examined in all adult animals: corpora lutea, abnormalities (gross lesions), adrenals (paired), bone marrow (from the sternum), brain, caecum, coagulating glands (paired), colon, duodenum, epididymides (paired), esophagus, heart, ileum, jejunum, kidneys (paired), liver, lymph nodes (cervical), lymph nodes (mesenteric), lungs, ovaries with oviduct (paired), prostate, pituitary, rectum, sciatic nerve, seminal vescicles, spinal column with spinal cord, spleen, stomach, thymus, thyroid, trachea, testes (paired), urinary bladder, uterus with cervix, vagina.
OTHER EXAMINATIONS:
- Pre- and post-dose observations: Examination of individual animals for signs of reaction to treatment was carried out daily. Starting on day 1 until day 14 of dosing, all animals were observed prior to dosing, immediately after dosing, and at 1, 2 and 3 hours after dosing. From day 15 until study termination, observations were made prior to dosing, immediately after dosing, and 15 minutes and 1 hour after dosing.
- Sensory reactivity and grip strength: Once during the study, in week 5 of treatment, 5 males were randomly selected from each group for evaluation of sensory reactivity to stimuli of different modalities (e.g., auditory, visual and propioceptive stimuli), and an assessment of grip strength was also performed. Once during the study, on day 20 post-coitum, 5 females were selected for the same tests.
- Motor activity: Once during the study, on week 4 of treatment, 5 males were randomly selected from each group and the motor activity was measured by an automated activity recording device. Measurements were performed using a computer-generate random order. On day 20 post-coitum, 5 females were selected for the same activity.
STATISTICAL METHODS: For continuous variables, the significance of the difference amongst group means was assessed by analysis of variance. Differences between the

treated group and the control group were assessed by Dunnett's test using a pooled error of variance. The homogeneity of the data was assessed by Bartlett's Test before Dunnett's Test was performed. If the data were found to be inhomogeneous, a modified t-test (Cochran and Cox) was applied. Statistical analysis of histopathological findings was not carried out by means of the non-parametric Kolmogorov-Smirnov test.

The mean values, standard deviations and statistical analysis were calculated from actual values in the computer without rounding off.

The non-parametric Kruskal-Wallis analysis of variance was used for all other parameters. Intergroup differences between the control and the treated group were assessed by the non-parametric version of the Williams' test.

Conclusion: Gavage treatment of rats with TP-90B RUBBER CHEMICAL for at least 43 consecutive days in males and females at doses of 0 (control), 10, 100, or 800 mg/kg/day resulted in a No-Observed-Adverse-Effect Level (NOAEL) of 100 mg/kg/day.

At the high dose (800 mg/kg/day) the following treatment-related effects were seen:
Post-dose clinical signs indicating effects on the central nervous system in males and females
Decreased body weight and body weight gain in females during gestation
Reduced food consumption in females on days 7 and 14 post-coitum
Decreased fertility indices and increased pre-birth pup losses
Embryo-foetal toxicity
Increased liver weights
Microscopic changes in the liver

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
21-SEP-2004 (28)

5.8.2 Developmental Toxicity/Teratogenicity

Species: other: Combined Repeated Gavage Dose Toxicity Study **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 9 weeks
Frequency of treatment: once per day, 7 days per week
Duration of test: 9 weeks
Doses: 10, 100, 800 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 100 mg/kg bw
NOAEL Teratogenicity: = 100 mg/kg bw

Method: other: OECD Guideline 422
Year: 2004
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOAEL: 100 mg/kg/day
MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: One mid-dose female was sacrificed, on day 0 post-partum, for humane reasons, since signs of difficult delivery were noted. No other animals died prior to study termination.
- Number pregnant per dose level: A treatment-related effect on fertility is apparent in the high dose group. A total of fifteen females proved not to be pregnant at necropsy; three in the control group and in the mid-dose group, two in the low-dose group and seven in the high-dose group.
- Number aborting: A decrease in the average number of pups per litter was observed at birth in the high-dose group.
- Number of resorptions: An increased incidence, not statistically significant, in the number and percentage of pre-birth loss was noted in high dose females when compared to controls.
- Number of implantations: There were no effects on the mean number of implantation sites at any dose level.
- Number of corpora lutea: not reported
- Duration of Pregnancy: Gestation periods were similar between controls and tested groups.
- Body weight: Body weight and body weight gain were unaffected by treatment in the males throughout the study and in females before pairing. Slight decreases, not statistically significant, in body weight and body weight gain were observed in the high dose females during the gestation period when compared to controls. No differences were noted in females of any treatment group during the post-partum period when compared to controls.
- Food/water consumption: Food consumption remained comparable between control and treated groups in both sexes before pairing. A statistically significant reduction in food consumption was noted in high dose females on day 7 post-coitum. A similar reduction (not statistically

significant) was noted on day 14 post-coitum in the same group.
- Description, severity, time of onset and duration of clinical signs: Weekly physical examinations including detailed clinical signs with neurotoxicity assessment did not show any signs which could be correlated to the treatment with the test item in males or females in any group during the treatment period.
- Hematological findings incidence and severity: No toxicologically significant changes in hematology occurred in this study. Statistically significant decreases in prothrombin time were observed in the high dose male group. This change is considered incidental and not treatment-related since it was seen in only one sex, and the magnitude of the effect was low.

Statistically significant decreases in neutrophil percentage were observed in the high dose females. This change is considered incidental and not treatment-related since it was seen in one sex only and no other changes were seen in the white blood cell differential counts.
- Clinical biochemistry findings incidence and severity: No toxicologically significant change in any clinical chemistry parameter occurred at any dose level.

A statistically significant decrease in alkaline phosphatase level was observed in the high dose male group. Since this change was minimal, was decreased compared to the control group and occurred in only one sex, it is not considered toxicologically significant. A statistically significant decrease in alanine aminotransferase level was noted in the low dose male group when compared to controls. This decrease is considered incidental to treatment since no dose response was evident.

Statistically significant decreases in urea were seen in the low and high dose males compared to controls. These changes are not considered treatment-related since the changes are decreased relative to controls and there is no evident dose response. Statistically significant changes in creatinine and inorganic phosphorus levels were observed in the high dose male group. These changes are not considered treatment-related since the values are decreased compared to controls, the magnitude of the change is small and they occurred only in one sex.

Urea level was also statistically significantly decreased in the low dose male group. This change is not considered treatment-related since the effect was decreased, there was no obvious graded dose response at the mid- and high dose groups and the effect occurred in only one sex.

No differences in clinical chemistry parameters were noted between control and treated females.

- Gross pathology incidence and severity: No macroscopic change was reported at necropsy in the examined organs/tissues of the animals killed at termination that could be considered related to the administration of the test item. The recorded changes were considered to be incidental or spontaneous in origin.
- Organ weight changes: Treatment-related organ weight changes occurred in the liver of high dose males and females. Statistically significant increases in absolute and relative liver weights were observed in the high dose males when compared to controls. Increases in absolute (not statistically significant) and relative (statistically significant) liver weights were also noted in only the high dose females.

Statistically significant increases in absolute and relative kidney weights were noted in the mid-dose male group only. Since the absolute and relative kidney weights of the high dose males were not affected (i.e., no apparent dose response), there was no corresponding increase in females, and no corresponding microscopic change in this tissue, the kidney weight changes were considered not related to treatment with the test item. Slight, but statistically significant increases in absolute and relative adrenal weights were observed in the high dose female group. This change is considered incidental and not treatment-related since there was no corresponding microscopic histopathologic change in this tissue and similar effects were not seen in the high dose male group.
- Histopathology incidence and severity: No microscopic changes clearly related to test substance administration were observed in male or female rats given 10 or 100 mg/kg/day of the test article.

Diffuse hepatocellular hypertrophy (enlarged hepatocytes in all areas of the lobules) occurred in male and female rats of the high dosage group and was considered to be treatment-related.

Focal germ-cell depletion and degeneration occurred in one testis (unilateral) of each of four different male rats of the high dosage group. Exfoliated spermatogenic cells were observed in the epididymis in three of these high dose rats and in one additional high dose rat without testicular changes. The significance of this finding is uncertain. Systemic toxicity usually does not affect only one of a paired organ.

All other microscopic changes were considered to have occurred spontaneously and to be unrelated to test substance administration. These changes generally occurred at single, low, or similar frequencies among the groups and their type, incidence or severity was not influenced by compound administration.

FETAL DATA:
- Litter size and weights: : A decrease in the average number of pups per litter was observed at birth, and on day 4 post-partum in the high-dose group. Decreased litter weight and mean pup weight in the high-dose group (not statistically significant) were noted at birth and on day 4 post-partum.
- Number viable: Pup survival to day 4 was decreased in the high-dose group. The number of females with live pups on day 4 post-partum was 6, 8, 6, and 3 in the control, low-, mid- and high-dose groups, respectively. A statistically significant increase in pup mortality (females and total) from day 0 to day 4 was noted in the high dose group. Similar results were also seen in male pups but the difference was not statistically significant.
- Sex ratio: Sex ratios at birth and on day 4 post-partum did not show any differences between control and treated groups when calculated as the percentage of males.
- Abnormalities: Six pups in one litter of the high-dose group showed fore/hindlimb digits missing or not defined during pre-weaning observations and/or necropsy. Necropsy examination of four of these pups confirmed the diagnoses of agenesis and/or microdactily. The other two pups were not available for necropsy. One pup from a different litter had flexure of the hindlimbs. These findings are considered treatment-related since they are rare findings in this species.

Alterations of bent tail and malrotated limbs are not considered to be treatment-related findings. Bent tail was noted at necropsy in three pups (1 litter) in the control group, in three pups (1 litter) of mid-dose, and 1 pup (1 litter) of the high dose groups on Day 4 post-partum. Malrotated hindlimbs were noted in 1 pup each in the control, low and mid-dose groups only. These alterations were observed in both the control and treated groups and there was no obvious dose response.

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

Test condition: TEST ORGANISMS: Hsd Sprague Dawley SD Rats
ADMINISTRATION / EXPOSURE
- Type of exposure: oral gavage
- Duration of test/exposure: For males, treatment commenced when the males were approximately 12 weeks old and continued for two weeks prior to pairing, during pairing until mating was confirmed, and up to and including the day before sacrifice. For females, treatment commenced when they were approximately 12 weeks old and continued for two weeks prior to pairing through the mating and gestation periods, up to day 3 of lactation. Dams and offspring were sacrificed on Day 4 post-partum.
- Treatment: TP-90B was administered to rats daily
- Control group and treatment: Vehicle alone at same dose volume
- Vehicle: 0.5% aqueous carboxymethylcellulose
- Concentration in vehicle: appropriate to keep dosing volume

constant
- Total volume applied: 10 ml/kg
- Doses: 0, 10, 100, 800 mg/kg/day
MATING PROCEDURES: Pairings were monogamous. Vaginal smears were taken during pairing up to the day of positive identification of mating. Each cage was checked each morning for the presence of copulation plugs. The pairing combinations of animals which had not had positive identification of mating after 14 days of pairing were changed within each treatment group. Animals that did not have signs of mating during the initial pairing were placed with a second male that previously had positive signs of mating. The subsequent pairing was monitored for mating as described above for the first pairing. No more than 28 days was allowed for pairing.
PARAMETERS ASSESSED DURING STUDY:
- Body weight gain: Males were weighed weekly from allocation to termination. Females were weighed weekly from allocation to pairing, and on gestation days 0, 7, 14, and 20. Dams were also weighed on days 1 and 4 post-partum, with the exception of one mid-dose female, which was weighed on days 2 and 5 post-partum.
- Food consumption: The weight of food consumed by each cage of males and females was recorded weekly during the pre-mating period starting from allocation. Individual food consumption for the females was measured on gestation days 0, 7, 14 and 20, and on days 1 and 4 post-partum, with the exception of one mid-dose female where food consumption was measured on days 2 and 5 post-partum.
- Clinical observations: Once before the commencement of treatment, and at least once per week thereafter, each animal was given a detailed clinical examination. Each animal was removed from the home cage and observed in an open arena. The tests included observation of changes in gait and posture, reactivity to handling, presence of clonic or tonic movements, stereotypies or bizarre behavior and effects on the autonomic nervous system (e.g., lachrymation, piloerection, pupil size, unusual respiratory pattern). During the gestation periods, the observations were carried out on Days 1, 7, 14, and 20.
- Examination of fetuses: The total litter size was (live and dead) was counted as soon as possible after parturition. Live pups were identified individually within the litter by toe amputation, sexed and examined for external abnormalities. Live and dead pups were counted and weighed on days 1 and 4 post-partum, with the exception of one mid-dose female, where pups were weighed on days 2 and 5 post-partum. All litters were observed daily. All pups found dead were given a post-partum examination.
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights P and F1: The following organs from all adult animals in all groups were dissected free of fat and weighed: adrenals, brain, epididymides, heart, kidneys, liver, spleen, thymus, testes.
- Histopathology P and F1: The tissues listed, as follows,

were examined in all adult animals: corpora lutea, abnormalities (gross lesions), adrenals (paired), bone marrow (from the sternum), brain, caecum, coagulating glands (paired), colon, duodenum, epididymides (paired), esophagus, heart, ileum, jejunum, kidneys (paired), liver, lymph nodes (cervical), lymph nodes (mesenteric), lungs, ovaries with oviduct (paired), prostate, pituitary, rectum, sciatic nerve, seminal vescicles, spinal column with spinal cord, spleen, stomach, thymus, thyroid, trachea, testes (paired), urinary bladder, uterus with cervix, vagina.
OTHER EXAMINATIONS:
- Hematology: Measurements performed on blood samples are as follows: hematocrit; hemoglobin; red blood cell (RBC) count; mean RBC volume; mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; white blood cell count; differential leukocyte count (neutrophils, lymphocytes, eosinopils, basophils, monocytes, large unstained cells); abnormalities of the blood film; platelets; prothrombin time; partial thromboplastine time
- Biochemistry: Clinical chemistry parameters investigated included: alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase; urea; creatinine; gamma glutamyl transferase; globulin and A/G ratio; fasting glucose; total bilirubin; total cholesterol; total protein; albumin; sodium; phosporus; potassium; calcium; chloride; total glycerides.
- Estrous cycle: Vaginal smears were taken daily in the morning, starting two weeks before pairing (first day of dosing) until a positive identification of mating was made. The vaginal smear data were examined to determine anomalies of the estrous cycle, and the pre-coital interval (i.e., the number of nights paired prior to the detection of mating.
- Sperm examination: Each cage was checked each morning for the presence of copulation plugs.
- Pre- and post-dose observations: Examination of individual animals for signs of reaction to treatment was carried out daily. Starting on day 1 until day 14 of dosing, all animals were observed prior to dosing, immediately after dosing, and at 1, 2 and 3 hours after dosing. From day 15 until study termination, observations were made prior to dosing, immediately after dosing, and 15 minutes and 1 hour after dosing.
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Decreased fertility indices and increased pre-birth pup losses
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Developmental effects of microdactily and/or agenesis of digits and flexure of hindlimbs
Increased liver weights
Microscopic changes in the liver

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
21-SEP-2004 (28)

5.8.3 Toxicity to Reproduction, Other Studies

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5.9 Specific Investigations

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5.10 Exposure Experience

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5.11 Additional Remarks

16-MAY-2003

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

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8.2 Fire Guidance

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8.3 Emergency Measures

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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

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8.8 Reactivity Towards Container Material

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(1) Getuli, C. 2003. TP-90B Micronucleus test. Research Toxicology Centre, Rome, Italy. Report Number 02RC-0079.

(2) Gittes, Hyman. Eye Irritation Study of TP-90B. Marcus Sittenfield & Associates Industrial Biology Laboratories, Inc. 66RM-1008.

(3) Green, L.A. Acute Dermal Toxicity Study: Federal Hazardous Substances Labeling Act in Albino Rabbits with TP-90B/6213. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Co. Report No. 77RM-1075, February 8, 1977.

(4) Green, L.A. Acute Inhalation Screening Inhalation Study in Ace Hartley Guinea Pigs with TP-90B Decomposition Volatiles. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1074, May 10, 1977.

(5) Green, L.A. Acute Inhalation Screening Inhalation Study in Albino Guinea Pigs with TP-90B/6213. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1075, May 10, 1977.

(6) Green, L.A. Acute Inhalation Screening Inhalation Study in Albino Mice with TP-90B/6213. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1075, May 10, 1977.

(7) Green, L.A. Acute Inhalation Screening Inhalation Study in Albino Rats with TP-90B/6213. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1075, May 10, 1977.

(8) Green, L.A. Acute Inhalation Screening Inhalation Study in Swiss Webster Mice with TP-90B Decomposition Volatiles. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1074, May 10, 1977.

(9) Green, L.A. Acute Inhalation Screening Inhalation Study in Wistar Rats with TP-90B Decomposition Volatiles. Study conducted at Bio-Toxicology Laboratories, Inc., Moorestown, NJ. Rohm and Haas Report No. 77RM-1074, May 10, 1977.

(10) Hahn, J. 2003. TP-90B: Vapor pressure determination by the gas saturation method. ABC Laboratories, Columbia, MO. Report Number 02RC-0083

(11) Heim, D. 2003. TP-90B: Determination of ready biodegradability using the CO2 evolution method. ABC Laboratories, Columbia, MO. Report Number 02RC-087.

(12) Hughes, C. 2003. TB-90B: Acute toxicity to the water flea, Daphnia magna, determined under static test conditions. ABC Laboratories, Columbia, MO. Report Number 02RC-0090.

(13) Hughes, C. 2003. TP-90B: Acute toxicity to the rainbow trout, Oncorhynchus mykiss, determined under static conditions. ABC Laboratories, Columbia, MO. Report Number 02RC-0089.

(14) Hughes, C. 2003. TP-90B: Toxicity to the unicellular green alga, Selenastrum capricornutum. ABC Laboratories, Columbia, MO. Report Number 02RC-0091.

(15) Huntley, K, and Locke, J. 2003. Determination of water solubility by the column elution method for TP-90B. ABC Laboratories, Columbia, MO. Report Number 02RC-0085.

(16) Huntley, K, and Lowe, S. 2003. TP-90B: Estimation of n-Octanol/Water Partition Coefficient by High Performance Liquid Chromatography (HPLC). Report No. 02RC-0084.

(17) Huntley, K. 2003. TP-90B: Determination of boiling point and density. ABC Laboratories, Columbia, MO. Report Number 02RC-0080.

(18) Kuklinski, M. Dermal Sensitization Study in Albino Guinea Pigs - EPA/OECD With Test Article TP-90B Plasticizer, Lot #1142-10M. Study conducted at Biologic Safety Research, Inc., Muskegon, MI (BSR #029-003). Rohm and Has Co. Report No. 91RM-1033, July 28, 1991.

(19) Kuklinski, M. Primary Eye Irritation in the Albino Rabbit - EPA/OECD: Test Article TP-90B Plasticizer, Lot #1142-10M. Study conducted by Biologic Safety Research, Inc., Muskegon, Michigan (BSR Study #029-002). Rohm and Haas Co. Report No. 91RM-1035, May 13, 1991.

(20) Kuklinski, M. Primary Skin Irritation in the Albino Rabbit - EPA/OECD: Test Article TP-90B Plasticizer, Lot #1142-10M. Study conducted by Biologic Safety Research, Inc. (BSR Study #029-001), Muskegon, Michigan. Rohm and Haas Co. Report No. 91RM-1034, May 13, 1991.

(21) Longobardi, C. 2003. TP-90B Rubber Chemical: Acute dermal irritation study in the rabbit. Report No. 02RC-0073.

(22) Longobardi, C. 2003. TP-90B Rubber Chemical: Acute eye irritation study in rabbits. Report No. 02RC-0074.

(23) Longobardi, C. 2003. TP-90B Rubber Chemical: Acute oral toxicity study in rats. Report No. 02RC-0071.

(24) Longobardi, C. 2004. TP-90B Rubber Chemical: Acute dermal toxicity study in rats. Report No. 02RC-0072.

(25) Longobardi, C. 2004. TP-90B Rubber Chemical: Delayed dermal sensitization study in guinea pig (Buehler test). Report No. 02RC-0076.

(26) Scarcella, O. 2003. TP-90B Rubber Chemical bacterial mutation assay. Research Toxicology Centre, Rome, Italy. Report Number 02RC-078.

(27) Shelanski, Morris. Acute oral toxicity study with Thiokol Chemical Corporation - Plasticizer Type TP90B. Industrial Biology Research ad Testing Laboratories, Inc. 58RM-1002.

(28) Sisti, R. 2004. TP-90B Rubber Chemical: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening in the Rat. Report No. 02RC-0203.

10.1 End Point Summary

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10.2 Hazard Summary

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10.3 Risk Assessment

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