

201-15627A

**HIGH PRODUCTION VOLUME (HPV) CHALLENGE
PROGRAM**

**Test Plan
For
Hexaoxatricosane
CAS Number 143-29-3**

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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 WP2uvrA. 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 CO₂ 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 @ 20° 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/EC₅₀ 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 EC₅₀ = 26 mg/L). The 96-hour LC₅₀ for trout (491 mg/L) and the 48-hour EC₅₀ (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 LD₅₀ 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 LC₅₀ 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 LD₅₀ 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:

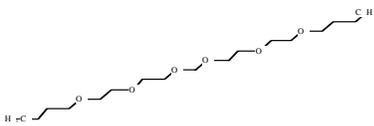
- (1) **Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.
- (2) **Reliable with Restrictions:** 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. Pharmacol.* 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:

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SIDS INITIAL ASSESSMENT Profile

Hexaoxatricosane (CAS No. 143-29-3)

and/or necropsy. Necropsy examination of four of these pups confirmed the diagnoses of agenesis and/or microdactyly. 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.