



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, DC 20460

FEB 8 2005

OFFICE OF  
PREVENTION,  
PESTICIDES AND TOXIC  
SUBSTANCES

**MEMORANDUM:**

**Subject:** Review of PXTS Hydrolysis Study, Wood Preservative Product Registration

**To:** Adam Heyward, Product Manager, Team 34  
Regulatory Management Branch II  
Antimicrobials Division (7510C)

**From:** Talia Milano, Chemist *Talia Milano 2/4/05*  
Risk Assessment and Science Support Branch (RASSB)  
Antimicrobials Division (7510C)

**Thru:** Nader Elkassabany, Team Leader, Team Two *Nader Elkassabany 2/4/05*  
Risk Assessment and Science Support Branch (RASSB)  
Antimicrobials Division (7510C)

Norm Cook, Branch Chief *Norm Cook 2/8/05*  
Risk Assessment and Science Support Branch (RASSB)  
Antimicrobials Division (7510C)

**Data Submitter:**  
Akzo Nobel Functional Chemicals LLC

**Chemical Name:**  
Polyxylenol tetrasulfide (80.5%)

EPA Reg. No.: 75799-R  
DP #: 311159  
PC Code: 006929  
Decision #: 331327  
MRID #: 464091-01

1

**Action Requested:**

A review of the study, PXTS: An Evaluation of Hydrolysis as a Function of pH (MRID # 464091-01). This study has been submitted in response to the data evaluation review completed by Siroos Mostaghimi, Ph.D, subject titled, Data Evaluation Report [DER] for the Hydrolysis of PTXS (as a function of pH) (DP Barcode 299968). Per Siroos' findings as stated in his DER, the requirements of a preliminary hydrolysis study were fulfilled in the previously submitted study titled, PXTS: An Evaluation of Hydrolysis as a Function of pH (MRID # 460626-23). However, there was a request for additional data to fulfill compliance with OPPTS Fate, Transport, and Transformation Test Guidelines titled, Hydrolysis as a Function of pH (835.2100).

**Background:**

The oligomer, polyxylenol tetrasulfide (80.5%), is under consideration for a new registration. This chemical consists of substituted phenols bound together via sulfide linkages. It is anticipated to be used as a wood preservative and will be present in the environment, and as a result it is important to be aware of its persistence. This is a chemical behavior that is conclusive from hydrolytical analyses. Per Agency request, Akzo Nobel has submitted a hydrolysis study to supplement the preliminary submission in order to fulfill the requirements for the registration of this chemical.

**Documentation Provided:**

1. PXTS: An Evaluation of Hydrolysis as a Function of pH. (MRID # 464091-01)
2. Correspondence between Adam Heyward and Margery M. Exton dated 11/11/04.

**Documentation obtained for reference:**

1. PXTS: An Evaluation of Hydrolysis as a Function of pH. (MRID # 460626-23)
2. Data Evaluation Report on MRID # 460626-23 by Siroos Mostaghimi, Ph.D.

**Overview of the two hydrolysis studies:**

*MRID # 460626-23, reviewed in DP Barcode 299968*

The hydrolysis test was conducted in sterile buffer solutions of pH 4, 7, and 9 at 50°C over a five day period. The samples were analyzed by means of reverse phase, gradient elution using HPLC with UV detection. The pH buffered samples were extracted with ethyl acetate, evaporated to dryness, and then reconstituted with methanol. Through analytical determination, which was acceptable per DP Barcode 299968, it was concluded that the percent recoveries exhibited rapid hydrolytic degradation of PXTS, with a half-life of considerably less than a year. As stated in the study, a determination of the potential degradants was not feasible due to the adverse influence of extracted buffer components on gas chromatographic conditions. There were no additional tests conducted or supplementary experiments.

MRID # 464091-01, reviewed in current DP Barcode 311159

The hydrolysis test was conducted in sterile aqueous buffer solutions at pH of 5, 7, and 9 at 25°C over a thirty day period. The same decrease of the PXTS concentrations was observed as it was in the preliminary study. An analysis was carried out for the presence of monomeric phenolics, which are the anticipated hydrolytical degradate of this chemical. The technician carried several investigations to determine the cause of the PXTS decrease because the degradates were not detected. It was concluded that there was a decrease in extraction efficiency when using the ethyl acetate extraction solvent. There are two behaviors of PXTS which are believed to be the reason for the decrease exhibited in the data. The two factors are, a conformational shift of PXTS in response to the aqueous environment, and the strong adsorbing behavior of this chemical to the vessel walls.

#### Summary of Data in MRID # 464091-01:

PXTS was evaluated for any potential hydrolytic degradation in sterilized aqueous media at pH of 5, 7, and 9 at 25°C. The concentration of PXTS that was used was 125 µg/L, which is ten times the determined water solubility value. The technician analyzed each pH value in duplicate for each of the eight extraction intervals (day 0, 3, 7, 10, 14, 17, 21, 30), which resulted in sixteen separate Teflon vessels that were sampled. There were also vessels set aside for complete extractions to be carried out after the solution analysis. This strategy was incorporated into the laboratory technique, as stated on page 12, because of the, "very hydrophobic nature of PXTS, it was expected that the test material might partition out of the water to the sides and bottom of the container and therefore be unavailable in the water for quantification."

Reference materials of the degradates that were anticipated were obtained so that a HPLC (with UV detection) based analytical method could be developed specifically to detect any possible presence of these degradates. After the analysis was conducted, it was found that the PXTS concentration had decreased, but there was no detection of the proposed degradates. As a result, the vessels were re-extracted with a different solution, dichloromethane (DCM). This supplementary extraction yielded additional PXTS which indicated that ethyl acetate was not effective enough for a full recovery of the compound. Figures 3-41 provided in the study include the representative chromatograms of the reference samples and extractions.

#### Discussion of the analytical method in MRID # 464091-01:

The test substance that was used was received and documented to have a purity of 100% PXTS, and an expiration date of 3/28/05.

It is indicated in the protocol, included as Appendix 1, that the samples were kept in an incubator at 25°C and maintained at ±1°C (mean temperature determined to be 25.9°C) and that the experiment directed for the samples to be stored in the dark. The actual temperature readings were not supplied in the report. The study also suggested that the

vessels were protected from air, which corresponds to the statement in the study that nitrogen was used to fill the empty head space of each sample.

The study report does not indicate what the corresponding temperature is for the calculation of the water solubility, which is  $<12.5 \mu\text{g/L}$ . This factor was also addressed in the DER in response to DP 299968.

The different phenolic compounds that were chosen to represent the potential degradates of PXTS were: Phenol, 3-Methylcatechol, 4-Methylcatechol, 2-Methylresorcinol, Methylhydroquinone, 4-Mercaptophenol, and 4-Methylmercaptophenol. The retention times for each of these potential degradates was obtained to be used as a reference in the experimental runs. The study does not indicate the basis for choosing these specific compounds to be representative of the potential degradates of PXTS.

Even though the registrant did not use all acetate buffers for the analysis (acetate, pH5, phosphate, pH7, and borate, pH9), the pH was verified for all of the test solutions to be within  $\pm 0.01$  pH unit of the desired value. It is not indicated as to whether or not the pH reading was consistently obtained throughout the 30 day analysis or if it was just collected on the initial and 30<sup>th</sup> day.

The experiment employed Teflon vessels in an attempt to minimize the adherence of PXTS to glass surfaces. This decision to use Teflon vessels is justified on page 16 of the current study, through stating that, "repeated extraction[s] of the vessels showed that [the] PXTS oligomer strongly adheres to the glass surface." There is no raw data supporting this claim about glass vessels adversely affecting the extractability of PXTS. Data in reference to the proposed adsorption behavior of this chemical would be useful.

The registrant presents in the conclusion of the study report, on page 21, that there are three probable reasons for the decrease of PXTS that was noted, which are: (1) hydrolytic degradation, (2) incomplete recovery when using ethyl acetate, or (3) a decrease in molar absorptivity associated with a conformational shift to a tighter molecular cluster. It is indicated that the first two hypotheses were experimentally evaluated.

The original extracts that had been stored after 30 days were analyzed for potential degradates. Before analyzing the originals, a storage stability analysis was run to verify the usefulness of the original extracts. It was found that the chemical was stable so that the original extracts could be used for analysis and that none of the proposed degradates were present.

After the degrade analysis of the original extracts, the containers were further extracted with DCM. The purpose of this additional extraction was to examine whether or not it would be legitimate to conclude that ethyl acetate was ineffective as an extraction solvent for PXTS. DCM was originally used as an extract in an earlier study, but it was found that it was not as effective as ethyl acetate for extracting the hypothesized degradates. The presence of degradates are the heart of the study because they are the indicators of

hydrolytical degradation. There were measurable PXTS concentrations detected from the DCM extract, supporting ethyl acetate's ineffectiveness for extraction.

There was no further examination of the potential conformational shift which was anticipated due to the hydrophobic nature of PXTS. The study does state in the conclusion on page 23 that, "the nature of the concentration decrease suggest[s] that while a conformational shift in response to the aqueous environment may play a role, a greater role is suggested by the increased strong binding of PXTS to the vessel walls with incubation time, resulting in a decreased extraction efficiency with an ethyl acetate extraction solvent." It appears to be because of the adsorption behavior of PXTS prevailing as the reason for a decrease in chemical detection over time, the registrant decided not to further examine the conformational shift.

**Conclusion:**

The chemical, PXTS, exhibits a hydrophobic nature, which results in an extremely difficult hydrolytical analysis. PXTS exhibited hydrophobic behavior by adsorbing to the vessel walls when placed in the presence of water. This adsorption was recognized in the second submission, MRID # 464091-01. The claim that was made in the initial hydrolysis study, MRID # 460626-23, was that PXTS is hydrolytically unstable. Through altering the analytical extraction method in the second submission, MRID # 464091-01, the registrant has supported that PXTS is continually present throughout the hydrolysis test. Because of the presence of PXTS in the second study, RASSB assumes that the first claim of hydrolytical instability was based on a lack of experimental method.

While there is no direct explanation of the mechanism of adsorption; it is conclusive that PXTS did not hydrolyze over the course of 30 days. As a result, this study is classified as supplemental and can be used to support the registration. The agency will be able to use these data in risk assessments, and another hydrolysis study is not required at this time.