1-6-05

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 75799-R
DP Barcode: D307937

To: Adam Heyward
Regulatory Management Branch II
Antimicrobials Division (7510C)

From: Chris Jiang, Chemist
Chemistry/Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

CJ

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

1/6/05

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

Applicant: Azko Nobel Functional Chemicals LLC

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s):	
PXTS	80.5 %
Other Ingredient(s):	19.5 %
Total:	100.0 %

BACKGROUND: Azko Nobel Functional Chemicals LLC has submitted an amended report for the sensitization data requirement which has been submitted in support of the registration of the technical grade active ingredient/manufacturing-use product of polyxylenol tetrasulfide (PXTS). This report has been submitted to and identified by the Agency as 46359301. The contractor has done the primary review of this submission and Product Science Branch of Antimicrobials Division has done a secondary review of this submission.

RECOMMENDATIONS: PSB findings are:

1. The acute toxicity studies with the exception of skin sensitization have been previously accepted by the Agency under D299111. Skin sensitization is the only outstanding data requirement.

2. The current acute toxicity profile of Reg. No. 75799-R is:

acute oral toxicity	IV	acceptable
acute dermal toxicity	IV	acceptable
acute inhalation toxicity	IV	waiver granted
primary eye irritation	III	acceptable
primary dermal irritation	IV	acceptable
dermal sensitization		unacceptable

LABELING:

1. The correct signal word is CAUTION.

2. The precautionary statements must read "Causes moderate eye irritation. Avoid contact with eyes or clothing. Wear goggles, face shield, or shielded safety glasses, long-sleeved shirt and long pants, socks, and shoes. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco, or using the toilet."

3. The label must include the following first aid statement for eye irritation:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

4. The study for skin sensitization is unacceptable because the for the lab report doesn't indicate the irritation scores after the second and third indication for either the positive control or the test statement. The company needs to conduct a new study and report the irritation (erythema and edema) scores after the first, second, and third inductions and after challenge. This procedure needs to be followed for both the test

material and positive control. This procedure needs to be followed for both the test material and positive control. The lab could also have challenged at a higher dose of test material and/or rechallenged.

5. The registrant must declare the sulfur as an active ingredient at 19.4%. This declaration must be made on both the CSF and label. Sulfur is known to be active at a concentration of 0.2%.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: Adam Heyward
MRID No.: 46359301

Reviewer: Chris Jiang
Study Completion Date: August 22, 2001
(Amended: July 7, 2004)
Report No.: 01-115

Testing Laboratory: Experimur
Author: John Findlay

Quality Assurance (40 CFR §160.12): A statement of GLP compliance was included.

Test Material: PXTS, lot 1685-7-1, black solid material
Positive Control Material: α-Hexylcinnamaldehyde (HCA) in acetone

Species: Male HsdPoc:Dunkin Hartley albino guinea pigs
Weight: 379 to 470 g on day 1 **Age**: Five to six weeks on day of dosing
Source: Harlan Sprague Dawley, Inc., Indianapolis, IN

Method: Modified Buehler method

Summary:

1. **This Product is not a dermal sensitizer.**

2. **Classification**: Unacceptable

Procedure (Deviation From §81-6): Minor excursions of relative humidity outside of the range specified by the protocol occurred during the study, but these deviations were considered to have no adverse effects on the outcome of the study.

Procedure: The animals used in the experiment were either induced with nothing, 0.3 g of neat test material, or 0.3 mL of undiluted HCA. All induction materials were dispensed onto the pad of a Hill Top Chamber which was applied to the upper left quadrant of the shaved back of each animal once per week for a period of three weeks. The midsection of each animal was wrapped with an elastic adhesive bandage to keep the Hill Top Chamber in place. After six hours, all wrapping materials were removed and the test sites of all treated animals were wiped with 95% ethanol moistened gauze. Two weeks after the third induction, the animals were either challenged with 0.3 g of neat test material or 0.3 mL of 50 % HCA/acetone solution that was dispensed onto the pad of a Hill Top Chamber which was applied to the lower left quadrant of the shaved back of each animal.
In all cases, the chambers were applied for six hours and then removed from the application sites which were subsequently wiped with ethanol-moistened gauze.
The test sites were evaluated at 24 and at 48 hours after the first induction and the challenge doses according to the Magnusson and Kligman Grading Scale.

Results: Animals 513 and 514 showed discrete or patchy erythema at the 24-hour observation after the first induction. Erythema was not present on any animal after the 48-hour observation after the first induction. Discrete or patchy erythema was noted on guinea pigs 512, 518, and 522 after the 24-hour observation after challenge. After the 48-hour observation after challenge, only animal 518 showed discrete or patchy erythema.

The positive control showed appropriate results.

Special Comments: Control animal 506 died and a necropsy was performed. The necropsy revealed diarrhea, dilatation of the gallbladder, and dark red pigmentation of the cecum.

The lab report doesn't indicate the irritation scores after the second and third indications for either the positive control or the test substance; therefore, a new study must be conducted indicating the irritation scores (erythema and edema) after the first, second, and third inductions and after challenge. This procedure needs to be followed for both the test material and positive control. The lab could also have challenged at a higher dose of test material and/or rechallenged.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: Adam Heyward
MRID No.: 463593-01

Reviewer: Veronica Middleton
Study Completion Date: August 22, 2001
(Amended: July 7, 2004)
Report No.: 01-115

Testing Laboratory: Experimur, Chicago, IL
Author: John Findlay, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance Statement and a statement of GLP compliance were included.

Test Material: PXTS, Lot No. 1685-7-1, black solid
Positive Control Material: α-Hexylcinnamaldehyde (HCA)

Species: Male albino HsdPoc:Dunkin Hartley guinea pigs
Weight: 379 to 470 grams **Age:** 5-6 weeks
Source: Harlan Sprague Dawley, Inc.

Method: Modified Buehler method

Summary:

1. **The test material was not a dermal sensitizer.**

2. **Classification:**

Procedure (Deviation From §81-6): No deviations or circumstances were known to have occurred during the conduct of this study that would affect the quality or integrity of the data generated. Minor excursions of relative humidity outside the protocol-specified range occurred during the study, but did not adversely impact the outcome of the study. Although the protocol stated that dead animals will be discarded without necropsy, a gross necropsy was performed on the control guinea pig that died during the study in an attempt to determine the cause of death.

Procedure: Since the neat test material proved to be non-irritating during the first induction dose, a range-finding study was not performed. PXTS was applied neat once per week to the shaved backs of twenty male guinea pigs (treated group) during an induction period of three consecutive weeks. Another group of ten male negative control guinea pigs was handled in the same manner, but was not treated with the test material during the induction phase. A third group of ten male guinea pigs was treated with undiluted Hexylcinnamaldehyde (HCA) during the induction phase and served as a positive control. Two weeks following the third induction dose, the treated and negative control guinea pigs

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received a challenge dose of the neat test material. Positive control guinea pigs were similarly dosed with 50% (w/v) HCA in acetone. Following the first induction and challenge doses, guinea pigs were scored for erythema and edema approximately 24 and 48 hours after removal of wrappings.

Results: During the third week of the induction phase, one guinea pig in the negative control group died of unknown causes. Five of then (50%) animals in the positive control group exhibited a positive reaction. Three of twenty (15%) and four of nine (44%) animals in the treated and negative control groups, respectively, exhibited minimal erythema reactions (i.e., erythema score of 1) following the challenge dose. These responses in the treated and negative control groups were considered to be dermal irritation rather than an induced sensitization response. None of the animals in the negative control, treated or positive control groups exhibited any edema reactions at any of the observation and scoring intervals. All surviving animals gained weight during the study.

According to the findings under the conditions of this study, the test material was not classified as a dermal sensitizer.