5-11-04

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: D299111

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

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

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)
5/11/04

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

Applicant: Azko Nobel Functional Chemicals LLC

FORMULATION FROM LABEL:

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

BACKGROUND: Azko Nobel Functional Chemicals LLC has submitted an acute toxicity package in support of the registration of the technical grade active ingredient/manufacturing-use product of polyxylenol tetrasulfide (PXTS). The registrant has submitted a waiver for acute inhalation and studies that have been submitted to and identified by the Agency as MRID's 46062609, 46062610, 46062611, 46062612, and 46062613.

RECOMMENDATIONS: PSB findings are:

1. The waiver for acute inhalation is granted because the material has a tar-like consistency and a low vapor pressure of about 1.09×10^{-4} Pa. The registrant indicates that because of these parameters, a respirable environment of PXTS cannot be achieved and inhalation is not a viable route of human exposure.

2. The studies for acute oral, acute dermal, eye irritation, and dermal irritation are acceptable.

3. The study for skin sensitization is unacceptable for the following reasons:
   a. In the procedure, the lab report does not indicate the dosage of the positive control (in mL) that was used to challenge the animals.
   b. Control animal 506 died and a necropsy was not done on that animal. A necropsy must be performed on the decedent.
   c. The lab report doesn't indicate the irritation scores after the second and third indication. These scores must be indicated on the lab report.
   d. The lab report does not indicate the irritation scores for edema. These scores must be indicated on the lab report.

4. 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. No precautionary statements for dermal sensitization can be determined at this time.

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 ACUTE ORAL TOXICITY TESTING (§ 81-1, 870.1100)

Product Manager: Adam Heyward
MRID No.: 46062609

Reviewer: Chris Jiang
Study Completion Date: July 5, 2001
Report No.: 01-114

Testing Laboratory: Experimur
Author: John Findlay

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

Test Material: PXTS (50 % (w/v) in corn oil)), lot 1685-7-1, black solid material
Dosage: 5000 mg/kg formulated to a volume of 10 mL/kg

Species: Sprague-Dawley rats (Hsd strain) (5/sex/group)
Fasted Weight: ♂: 228 to 235 g; ♀: 163 to 177 g
Age: 10 weeks at dosing
Source: Harlan, Indianapolis, IN

Conclusions:

1. **LD_{50} (mg/kg):** **Males** > 5000 mg/kg
Females > 5000 mg/kg
Combined > 5000 mg/kg
2. **The estimated LD_{50} is greater than 5000 mg/kg.**
3. **Tox. Category**: IV **Classification**: Acceptable

Procedure (Deviations from §81-1): No deviations were noted.

Results:

Reported Mortality

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
5000	0/5	1/5	1/10

Observations: One female rat was found dead on day 4. All animals had the clinical symptoms of cyanosis, diarrhea, discolored paws, red material around the nose, discolored inguinal fur, and discoloration around the mouth. Other symptoms included hypoactivity which was noted in one female, wet inguinal fur which was observed in one male and four females, alopecia which was experienced by one male, ptosis which was demonstrated by one female, salivation which was noted in one male and one female, red material around the eyes which was noted in one male, irritability which was expressed in one male and two females, and noisy breathing which was shown by one male and one female.

Gross Necropsy Findings: Two males had unremarkable necropsies; two males had lungs that were red and patchy; and one male had kidneys that were red and mottled. All female necropsies were unremarkable with the exception of the decedent who had a gas-filled stomach and a dark liver.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2, 870.1200)

Product Manager: Adam Heyward
MRID No.: 46062610

Reviewer: Chris Jiang
Study Completion Date: July 5, 2001
Report No.: 01-113

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
Dosage: 5000 mg/kg

Species: New Zealand White rabbits (5/sex/group)
Weight: ♂: 2.41 kg to 2.61 kg; ♀: 2.65 to 2.75 kg on day 1
Age: 15 to 17 weeks at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Conclusions:

1. **LD_{50} (mg/kg):** **Males** > 5000 mg/kg; **Females** > 5000 mg/kg; **Combined** > 5000 mg/kg
2. **The estimated LD_{50} is greater than 5000 mg/kg.**
3. **Tox. Category**: IV — **Classification**: Acceptable

Procedure (Deviations from §81-2): No deviations were noted.

Results:

Reported Mortality

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
5000	0/5	0/5	0/10

Observations: Clinical observations included edema and/or erythema that persisted in the majority of rabbits through day 12, cracking of the treated skin on seven rabbits on day 7 and on six rabbits on day 8, followed by superficial skin flaking in all test animals.

Gross Necropsy Findings: Superficial skin flaking was observed on all rabbits. In addition, a red area on the apical lobe of the lung was revealed on one test subject.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (§81-4, 870.2400)

Product Manager: Adam Heyward
MRID No.: 46062611

Reviewer: Chris Jiang
Study Completion Date: June 27, 2001
Report No.: 01-111

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
Dosage: 0.1 g

Species: Three female New Zealand White rabbits
Weight: 2.15 kg to 2.64 kg on the day after arrival
Age: 16 weeks at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Summary:

1. **Toxicity Category**: III

2. **Classification**: Acceptable

Procedure (Deviations From §81-4): No deviations were reported; however, a delay in study initiation resulted from the rabbits being observed for health status and corneal lesions.

Results:

Observations	(number "positive"/number tested)			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	1/3	1/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae				
Redness	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: Adam Heyward
MRID No.: 46062612

Reviewer: Chris Jiang
Study Completion Date: June 27, 2001
Report No.: 01-112

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
Dosage: 0.5 g

Species: Three male New Zealand White rabbits
Weight: 2.15 kg to 2.64 kg on the day after arrival
Age: 16 weeks at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Summary:

1. **Toxicity Category**: IV

2. **Classification**: Acceptable

Procedure (Deviations From §81-5): No deviations were noted.

Results:

At the one-hour observation, all test animals had very slight erythema and rabbit 44 was observed to have very slight edema. At the one-day observation, rabbit 58 had very slight edema and rabbits 42 and 44 had very slight erythema but rabbit 58 was noted to have well-defined erythema. None of the rabbits had edema at the 48-hour and 72-hour observations, but rabbits 42 and 44 were observed with very slight erythema at these times. No edema or erythema was noted at the 7-day observation, but superficial skin flaking at the test sites was observed at this time.

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

Product Manager: Adam Heyward
MRID No.: 46062613

Reviewer: Chris Jiang
Study Completion Date: August 22, 2001
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**: Six to seven 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 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: In the procedure, the lab report does not indicate the dosage of the positive control (in mL) that was used to challenge the animals.

Control animal 506 died and a necropsy was not done on that animal. A necropsy must be performed on the decedent.

The lab report doesn't indicate the irritation scores after the second and third indication. It also does not indicate the scores for edema. These scores must be indicated on the lab report.