9-1-04

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-E
DP Barcode: D299114

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)

9/1/04

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		53.9 %
Other Ingredient(s):		46.1 %
	Total:	100.0 %

BACKGROUND: Azko Nobel Functional Chemicals LLC has submitted an acute toxicity package in support of the registration of a wood preservative. The registrant has submitted a waiver for acute inhalation and studies that have been submitted to and identified by the Agency as MRID's 46033403, 46033404, 46033405, 46033406, 46033407, and 46072501.

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. The depilatory didn't remove hair cleanly enough to score the test sites of the animals so the depilatory had to be reapplied (causing moderate to severe skin irritation). This skin irritation could be interpreted as a sensitization response.
   b. The lab report said that all the animals were rechallenged; however, no rechallenge scores can be found in the report.
   c. In the procedure, the lab report does not indicate the dosage of the positive control (in mL) that was used to challenge the animals.
   d. Control animal 66 and test animal 83 died and necropsies were not done on those animals. Necropsy must be performed on the decedents.
   e. 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.

4. The current acute toxicity profile of Reg. No. 75799-E 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. 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.: 46033403

Reviewer: Chris Jiang
Study Completion Date: April 8, 2003
Report No.: 03-227

Testing Laboratory: Experimur
Author: John Findlay

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

Test Material: PXTS Formulation-D (50 % (w/v) in corn oil)), lot 1685-30-1, black solid
Dosage: 5000 mg/kg formulated to a volume of 2 mL/kg

Species: Sprague-Dawley derived [Crl:CD (SD)IGS BR] rats (5/sex/group)
Fasted Weight: ♂: 231 to 246 g; ♀: 156 to 172 g
Age: 8 weeks at dosing
Source: Charles River Laboratories, Inc., Portage, MI

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): Excursions in the relative humidity of the animal room outside of the range specified in the protocol occurred; however, these deviations did not have an impact on the integrity of the study.

Results:

Reported Mortality

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

Observations: One female rat died on day 2 of the study. Clinical symptoms included salivation, discolored and/or wet paws, discoloration around the mouth, inguinal fur that was discolored and/or wet, hypoactivity, diarrhea, hunched posture, labored breathing, and alopecia.

Gross Necropsy Findings: Gross necropsies were unremarkable with the exception of the decedent who had mottled lungs that were pigmented and a stomach that was filled with air and black mucosa.

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

Product Manager: Adam Heyward
MRID No.: 46033404

Reviewer: Chris Jiang
Study Completion Date: April 22, 2003
Report No.: 03-228

Testing Laboratory: Experimur
Author: John Findlay

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

Test Material: PXTS Formulation-D, lot 1685-30-1, black solid
Dosage: 5000 mg/kg

Species: New Zealand White rabbits (5/sex/group)
Weight: ♂: 3.18 to 3.39 kg; ♀: 3.10 to 4.12 kg on day 1
Age: 4 *months 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): Excursions in the relative humidity of the animal room outside of the range specified in the protocol occurred; however, these deviations did not have an impact on the integrity of the study.

Results:

Reported Mortality

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

Observations: Clinical observations included erythema and superficial scaling of the skin in each of the test subjects. Edema was observed in 4/5 of each of the sexes. *Cracking skin, thickened skin, and eschar formation were noted in 1/5 of each of the* sexes.

Gross Necropsy Findings: Gross necropsies were unremarkable except for the scaly skin at the application site noted in all animals.

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

Product Manager: Adam Heyward
MRID No.: 46033405

Reviewer: Chris Jiang
Study Completion Date: April 15, 2003
Report No.: 03-229

Testing Laboratory: Experimur
Author: John Findlay

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

Test Material: PXTS Formulation-D, lot 1685-30-1, black solid
Dosage: 0.1 g

Species: Three female New Zealand White rabbits
Weight: 2.94 kg to 4.14 kg on the day after arrival
Age: 4 months at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Summary:

1. **Toxicity Category**: III

2. **Classification**: Acceptable

Procedure (Deviations From §81-4): Excursions in the relative humidity of the animal room outside of the range specified in the protocol occurred; however, these deviations did not have an impact on the integrity of the study.

Results:

Observations	(number "positive"/number tested)			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	1/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae				
Redness	0/3	1/3	1/3	0/3
Chemosis	2/3	0/3	0/3	0/3

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

Product Manager: Adam Heyward
MRID No.: 46072501

Reviewer: Chris Jiang
Study Completion Date: July 10, 2003
Report No.: 03-247

Testing Laboratory: Experimur
Author: John Findlay

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

Test Material: PXTS Formulation-D, lot 1685-30-1, black solid
Dosage: 0.1 g

Species: Three male New Zealand White rabbits
Weight: 1.98 kg to 2.08 kg on the day after arrival
Age: 12 weeks at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Summary:

1. **Toxicity Category**: IV

2. **Classification**: Acceptable

Procedure (Deviations From §81-4): An excursion in the animal room temperature outside of the range specified in the protocol occurred; however, this deviation did not have an impact on the integrity of the study.

Results:

Observations	(number "positive"/number tested)			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	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.: 46033406

Reviewer: Chris Jiang
Study Completion Date: April 9, 2003
Report No.: 03-230

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

Test Material: PXTS Formulation-D, lot 1685-30-1, black solid
Dosage: 0.5 g

Species: One female and two male New Zealand White rabbits
Weight: 2.94 kg to 4.14 kg on the day after arrival
Age: 4 months at dosing
Source: Kuipar Rabbit Ranch, Gary, IN

Summary:

1. **Toxicity Category**: IV

2. **Classification**: Acceptable

Procedure (Deviations From §81-5): Excursions in the relative humidity of the animal room outside of the range specified in the protocol occurred; however, these deviations did not have an impact on the integrity of the study.

Results:

There was no dermal irritation in any of the males, but the female recovered from the very slight erythema that was observed at the one-hour observation.

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

Product Manager: Adam Heyward
MRID No.: 46033407

Reviewer: Chris Jiang
Study Completion Date: April 22, 2003
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 1685-30-1, black solid
Positive Control Material: 1-chloro-2,4-nitrobenzene (DNCB)
Vehicles: Ethanol and acetone

Species: Male Hartley albino guinea pigs (CRL:(HA) BR)
Weight: 371 to 431 g on day 1 **Age**: Six weeks on day of dosing
Source: Charles River Laboratories, Wilmington, MA

Method: Modified Buehler method

Summary:

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

2. **Classification**: Unacceptable

Procedure (Deviation From §81-6): 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.

The depilatory didn't remove hair cleanly enough to score the test sites of the animals so the depilatory had to be reapplied (causing moderate to severe skin irritation). With the Sponsor's approval, all guinea pigs were rechallenged.

Procedure: The animals used in the experiment were either induced with nothing, 0.3 g of neat test material, or 0.3 mL of 0.3% DNCB in ethanol. 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 Tricaprylin-moistened gauze. Two weeks after the third induction, the animals were either challenged with 0.3 g of neat test material or 0.05 % (w/v) DNCB/acetone solution that was dispensed onto the pad of a Hill Top Chamber which was applied to the right 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 Tricaprylin-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: None of the test animals showed erythema after any of the inductions or after challenge.

The positive control showed appropriate results.

Special Comments: The depilatory didn't remove hair cleanly enough to score the test sites of the animals so the depilatory had to be reapplied (causing moderate to severe skin irritation). This skin irritation could be interpreted as a sensitization response.

The lab report said that all the animals were rechallenged; however, no rechallenge scores can be found in the report.

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 66 and test animal 83 died and necropsies were not done on those animals. Necropsy must be performed on the decedents.

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.