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.: 3008-OE
DP Barcode: D316777

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

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

CJ

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

7/28/05

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

Applicant: Osmose Inc.

FORMULATION FROM LABEL:

Active Ingredient(s):		% by wt.
Copper carbonate		57.6
Inert Ingredient(s):		42.4
	Total:	100.0%

1

BACKGROUND: Osmose Inc. has submitted an acute toxicity package for the registration of an end-use product to be used as a wood preservative. The studies have been submitted to and identified by the Agency as MRID 46533103 through 46533108. 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, which supersedes the primary review.

RECOMMENDATIONS: PSB findings are:

1. The current acute toxicity profile for 3008-OE is:

acute oral toxicity	III	Acceptable
acute dermal toxicity	III	Acceptable
acute inhalation toxicity	IV	Acceptable
primary eye irritation	IV	Acceptable
primary skin irritation	IV	Acceptable
dermal sensitization	Non-sensitizer	Acceptable

2. Below the ingredient statement, the label must declare the percentage of metallic copper per the Label Review Manual.

LABELING

The signal word is **CAUTION**.

The precautionary statements must read, "Harmful if swallowed or absorbed through skin. Avoid contact with skin, eyes, or clothing. Wash thoroughly with soap and water after handing and before eating, drinking, chewing gum, using tobacco, or using the toilet. Remove and wash contaminated clothing before reuse."

The statements of "Avoid breathing vapors." and "Wear goggles, face shield or safety glasses and rubber gloves when handling" are not required by the Agency; however, the registrant may retain these statements if the registrant feels that the statements are necessary.

The first aid statements must read:

IF SWALLOWED

-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to do so by a poison control center or doctor.
-Do not give anything by mouth to an unconscious person.

IF ON SKIN

-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

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

Product Manager: Adam Heyward
MRID No.: 46533103
Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16990
Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Dosage: 2000 mg/kg

Species: Thirteen female derived albino Sprague Dawley rats
Weight: 172 to 240 g
Age: Young adult (9 to 12 weeks)
Source: Ace Animals, Inc., Boyertown, PA

Conclusion:

1. **LD_{50} (mg/kg)**: **Females** > 2000 mg/kg
2. **The estimated LD_{50} is greater than 2000 mg/kg.**
3. **Tox. Category**: III **Classification**: Acceptable

Procedure (Deviations from §81-1): This study was done using the Up-and-Down method with only females because they are the more sensitive sex. These deviations had no impact on the integrity of the study.

Results:

Reported Mortality

Dosage (mg/kg)	(Number of deaths/Number tested)
430	0/1
1350	0/4
2000	3/8

Observations

430 mg/kg: This rat was active and healthy throughout the study.

1350 mg/kg: Clinical signs included diarrhea, ano-genital staining, reduced fecal volume, and soft feces.

2000 mg/kg: Clinical signs included diarrhea, ano-genital staining, hypoactivity, hunched posture, piloerection, reduced fecal volume, and soft feces

Gross Necropsy Findings: Gross necropsies were unremarkable for the euthanized animals. The decedents had intestines that had a black/red discoloration.

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

Product Manager: Adam Heyward
MRID No.: 46533104
Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16991
Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Dosage: 2000 mg/kg

Species: Two groups of five male and female Sprague Dawley derived albino rats
Weight: ♂: 347 to 366 g; ♀: 197 to 225 g **Age**: Young adult (10 to 11 weeks)
Source: Ace Animals, Inc., Boyertown, PA

Conclusion:

I. LD_{50} (mg/kg) **Males** > 2000 mg/kg
Females > 2000 mg/kg
Combined > 2000 mg/kg

II. **The estimated LD_{50} is greater than 2000 mg/kg.**

III. **Tox. Category**: III **Classification**: Acceptable

Procedure (Deviation from §81-2): No deviations occurred during the study.

Results:

Reported Results

DOSAGE (mg/kg)	(NUMBER DEATHS/NUMBER TESTED)		
	Males	Females	Combined
2000	0/5	0/5	0/10

Observations: All animals were active and healthy throughout the study.

Gross Necropsy Findings: Gross necropsies were unremarkable.

DATA REVIEW FOR ACUTE INHALATION TOXICITY (§81-3, 870.1300)

Product Manager: Adam Heyward
MRID No.: 46533105

Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16992

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Dosage: 2.06 mg/L

Species: Two groups of five male and female derived, albino Sprague-Dawley rats
Age: Young adult (10 to 11 weeks)
Weight: ♀: 338 to 371 g; ♂: 216 to 256 g
Source: Ace Animals, Inc., Boyertown, PA

Summary:

1. **LC_{50} (mg/L):** **Males**: > 2.06 mg/L
   Females: > 2.06 mg/L
   Combined: > 2.06 mg/L
2. **The estimated LC_{50} is greater than 2.06 mg/L.**
3. **MMAD**: 3.5 µm
4. **Tox. Category**: IV **Classification**: Acceptable

Procedure (Deviation From §81-3): No deviations occurred during the study.

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER OF DEATHS/NUMBER TESTED)		
	Males	Females	Combined
2.06	0/5	0/5	0/10

Concentration

Nominal Chamber Concentration (mg/L)	Mean Gravimetric Chamber Concentration (mg/L)
639.54	2.06

Particle size distribution				
Exposure concentration (mg/L)	Average MMAD (µm)	Average GSD (µm)	% Particles*	
			< 0.7 µm	< 1.1 µm
2.06	3.5	2.07	1.6, 1.5	5.7. 5.8

*-percentage determined by two air samples

Chamber Environment	
Chamber Volume	6.7 L
Airflow	25.7 Lpm
Temperature	20 to 21 °C
Relative Humidity	40 to 46 %

Clinical Observations: The only clinical sign that was observed was hypoactivity.. Four males and all the females had to be removed from the cages because of this clinical sign.

Gross Necropsy Findings: Gross necropsies were unremarkable.

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

Product Manager: Adam Heyward
MRID No.: 46533106

Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16993

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Dosage: 0.1 mL

Species: Three male New Zealand albino rabbits
Weight: Not given **Age**: Young adult
Source: Robinson Services, Inc., Clemmons, NC

Summary:

1. **Toxicity Category**: IV

2. **Classification**: Acceptable

Procedure (Deviations From §81-4): No deviations occurred during the study.

Results:

Observations	Rabbit No.: 13925 (Male)				Rabbit No.: 13926 (Male)				Rabbit No.: 13927 (Male)			
	Hours				Hours				Hours			
	1	24	48	72	1	24	48	72	1	24	48	72
I. Corneal Opacity	0	0[1]	0	0	0	0[1]	0	0	0	0[1]	0	0
II. Iris	0	0	0	0	0	0	0	0	0	0	0	0
III. Conjunctivae:												
A. Redness	2	1	0	0	2	1	0	0	2	1	0	0
B. Chemosis	1	0	0	0	1	0	0	0	1	0	0	0
C. Discharge	1[2]	0	0	0	1[2]	0	0	0	1[2]	0	0	0

[1]-2% ophthalmic fluorescein sodium used to verify the absence of corneal opacity
[2]-light green staining around the eye

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

Product Manager: Adam Heyward
MRID No.: 46533107
Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16994
Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Dosage: 0.5 mL

Species: One female and two male New Zealand albino rabbits
Weight: Not given **Age**: Young adult
Source: Robinson Services, Inc., Clemmons, NC

Summary:

1. **Toxicity Category**: IV
2. **Classification**: Acceptable

Procedure (Deviations From §81-5): No deviations occurred during the study.

Results:

Animal Number	Draize score for erythema/edema after patch removal			
	1 hr	24 hr	48 hr	72 hr
13867	1/0	0/0	0/0	0/0
13868	1/0	0/0	0/0	0/0
13869	0/0	0/0	0/0	0/0

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

Product Manager: Adam Heyward
MRID No.: 46533108

Reviewer: Chris Jiang
Study Completion Date: April 15, 2005
Report No.: 16995

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel

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

Test Material: ORD-X370, lot FN1-25, light green liquid
Positive Control Material: α-Hexylcinnamaldehyde (HCA)

Species: Hartley albino guinea pigs
Age: Young adult
Weight: 333 to 467 grams
Source: Elm Hill Breeding Labs, Chelmsford, MA

Method: Buehler

Summary:

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

2. **Classification**: Acceptable

Procedure (Deviation From §81-6): No deviations occurred during the study.

Procedure: After a preliminary range-finding study, the definitive study was undertaken. Once each week for three weeks, 0.4 mL of the undiluted test material was applied to the clipped left side of each test animal using occlusive Hilltop chambers. After chamber application, the trunks of the animals were wrapped with non-allergic Durapore tape. After the exposure period, the chambers were removed and the test sites were cleansed of residual test substance. The guinea pigs were scored for erythema at 24 and at 48 hours after each induction.
Twenty-seven days after the first induction, the animals were challenged with 0.4 mL of a 50% dilution of the test substance in distilled water at a virgin site on the clipped right side. The guinea pigs were scored for erythema at 24 and at 48 hours after challenge. Ten additional animals (naive control) were dosed at challenge only with 0.4 mL of a 50% dilution of the test substance in distilled water.
A historical positive control study using 0.4 mL of undiluted HCA for induction and using 0.4 mL of a 75% HCA in mineral oil in acetone for challenge was done using similar induction and challenge procedures as described above.

Results: Twenty-four hours after the first induction, 5/20 test animals were observed to have no erythema and 15/20 guinea pigs displayed very faint usually non-confluent. By 48 hours, four animals experienced very faint usually non-confluent erythema and sixteen guinea pigs exhibited faint erythema that was usually confluent. Eleven test subjects had no erythema and 9/20 guinea pigs showed very faint usually non-confluent erythema at 24 hours and at 48 hours after the second induction. Twenty-four hours after the third induction, sixteen animals showed no erythema and four test subjects had very faint usually non-confluent erythema. By 48 hours after the third induction, no dermal irritation was observed. Twenty-four hours after each of the inductions, green staining was observed at all dose sites.

The historical positive control showed appropriate results.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (OPPTS 870.1100)
(UP AND DOWN PROCEDURE)

Product Manager: Adam Heyward
MRID No.: 465331-03

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16990

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance Statement was included. A statement of Good Laboratory Practice (GLP) compliance also was included stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications, except that specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study Sponsor.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion

Dosage:	Main Test: 430, 1,350, 2,000 mg/kg (The test substance was thoroughly shaken prior to application per the Sponsor's instructions.)
Species:	Sprague-Dawley derived, albino rats
Sex:	13 Female - nulliparous and nonpregnant
Age:	Young adult (9 - 12 weeks)
Weight:	172 - 240 grams at experimental start
Source:	Ace Animals, Inc., Boyertown, PA
Housing:	Temperature Range: 20 - 23 °C Relative Humidity: Information not provided Photoperiod: 12-hour light/dark cycle
Acclimation:	7 - 27 days

Conclusion:

1. **LD_{50} (mg/kg)**: Females > 2,000 mg/kg

2. **Tox. Category**: III **Classification**:

12

Procedure (Deviations from 870.1100):

- No deviations were reported by the laboratory.
- The relative humidity of animal housing was not provided.
- Body weight changes were recorded but not calculated.
- The day, but not time of death was listed for those animals that died during the study.

Results:

Main Test - Reported Mortality

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	943	430	S	S
2	1048	1,350	S	S
3	1124	2,000	D	D
4	1234	1,350	S	S
5	1250	2,000	S	S
6	1294	2,000	D	D
7	1337	1,350	S	S
8	1372	2,000	S	S
9	1419	2,000	D	D
10	1434	1,350	S	S
11	1446	2,000	S	S
12	1470	2,000	S	S
13	1541	2,000	S	S

S - Survival D - Death

Note: For the Main Test, the test substance was administered in the sequence as presented above. The decision to proceed with the next animal was based on the survival of the previous animal following dosing. Dose progressions and stopping criteria were determined using a statistical program.

13

Observations:
430 mg/kg Dose Level (1 animal): This animal survived, gained body weight, and appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior.

1,350 mg/kg Dose Level (4 animals): All animals survived exposure to the test substance and gained body weight. Clinical signs observed included diarrhea, ano-genital staining, reduced fecal volume, and soft feces. However, all animals recovered by Day 4 and appeared active and healthy for the remainder of the 14-day observation period.

2,000 mg/kg Dose Level (8 animals): Three animals died within three days of test substance administration. Toxic signs noted prior to death included ano-genital staining, diarrhea, hypoactivity, and hunched posture. Surviving animals exhibited similar clinical signs as well as piloerection, soft feces, and reduced fecal volume. However, the survivors recovered by Day 7 and appeared active and healthy for the remainder of the 14-day observation period.

Gross Necropsy Findings: No gross abnormalities were noted for any of the euthanized animals dosed at the 430, 1,350, and 2,000 mg/kg levels. Gross necropsy of the decedents dosed at the 2,000 mg/kg level revealed discoloration of the intestines.

Statistical Analysis: The *Acute Oral Toxicity (Guideline 425) Statistical Program* (Weststat, version 1.0, May 2001) was used for dose progression selections and stopping criteria determinations. The LD_{50} was determined to be greater than 2,000 mg/kg based on the fact that three animals dosed consecutively at 2,000 mg/kg survived.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (OPPTS 870.1200)
(LIMIT TEST)

Product Manager: Adam Heyward
MRID No.: 465331-04

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16991

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance statement was provided. A statement of Good Laboratory Practice (GLP) compliance also was included stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications, except that the specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study sponsor.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion

Species:	10 Sprague-Dawley derived, albino rats
Sex:	5 / sex; Females were nulliparous and nonpregnant
Age:	Young adult (10 - 11 weeks)
Weight :	Males: 347 - 366 grams at experimental start
	Females: 197 - 225 grams at experimental start
Source:	Ace Animals, Inc. Boyertown, PA
Housing:	Temperature Range: 19 - 22 °C
	Relative Humidity: Information not provided
	Photoperiod: 12-hour light / dark cycle
Acclimation:	21 days

Summary:

1. **LD_{50} (mg/kg):** Males > 2,000 mg/kg
   Females > 2,000 mg/kg
   Combined > 2,000 mg/kg

2. **The estimated LD_{50} is** > 2,000 mg/kg

3. **Tox. Category**: III **Classification:**

15

Procedure (Deviations From 870.1200):

- No deviations were reported by the laboratory.
- The relative humidity of animal housing was not provided.
- Changes in animal body weights were recorded, but not calculated.

Results:

Reported Mortality

DOSAGE (mg/kg)	DEATHS / number tested		
	Males	Females	Total
2,000	0 / 5	0 / 5	0 / 10

Observations: All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse pharmacologic effects, or abnormal behavior.

Gross necropsy findings: No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

16

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (OPPTS 870.1300)
(LIMIT TEST)

Product Manager: Adam Heyward
MRID No.: 465331-05

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16992

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance Statement was provided. A statement of Good Laboratory Practice (GLP) compliance also was included stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications except that specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study Sponsor.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion (prior to aerosolization, the test substance was thoroughly shaken per the Sponsor's instructions)

Species: 10 Sprague-Dawley derived, albino rats
Sex: 5 Males and 5 Females
Age: Young adult (10 - 11 weeks)
Weight: Males: 338 - 371 grams at experimental start
Females: 216 - 256 grams at experimental start (nulliparous and nonpregnant)
Housing: Temperature Range: 19 - 22 °C
Relative Humidity: Information not provided
Photoperiod: 12-hour light/dark cycle
Acclimation: 21 days
Source: Ace Animals, Inc., Boyertown, PA

Concentration:

Group	Gravimetric Exposure Concentration (mg/L)	Nominal Concentration (mg/L)
I	2.06	639.54

17

Summary:

1. **The single exposure acute inhalation LC_{50} of ORD-X370 is greater than 2.06 mg/L in male and female rats.**

2. **MMAD: 3.5 µm**

3. **Tox. Category: IV** **Classification:**

Procedure (Deviation From 870.1300):

- No deviations were reported by the laboratory.
- The relative humidity of caging conditions was not provided.
- Dimensions of the chamber were not provided.
- The oxygen content of chamber was not provided.
- Changes in weights of animals were recorded but not calculated.

Results:

Reported Mortality

Exposure Concentration (mg/L)	Number of deaths / number tested		
	Males	Females	Combined
2.06	0 / 5	0 / 5	0 / 10

Chamber Atmosphere

Exposure conc. (mg/L)	Sample	MMAD (µm)	GSD (µm)	% Particles at Effective Cutoff Diameter (Cumulative)							
				0.4 µm	0.7 µm	1.1 µm	2.1 µm	3.3 µm	4.7 µm	5.8 µm	9.0 µm
2.06	1	3.4	2.00	0.4	1.6	5.7	18.7	44.3	69.3	79.9	91.9
	2	3.6	2.14	0.0	1.5	5.8	17.5	43.1	67.8	78.9	91.3

18

Chamber Environment During Exposure

Exposure Level (mg/L)	2.06
Chamber Volume (L)	6.7
Airflow (Lpm)	25.7
Temperature (°C)	20 - 21
Relative Humidity (%)	40 - 46

Clinical Observations: All animals survived exposure to the test atmosphere and gained body weight over the 14-day observation period. Following exposure, most animals were hypoactive but recovered by Day 1. There were no other signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior.

Gross Necropsy Findings: No gross abnormalities were noted for the animals when necropsied at the conclusion of the 14-day observation period.

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (OPPTS 870.2400)

Product Manager: Adam Heyward
MRID No.: 465331-06

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16993

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance statement was provided. A statement of Good Laboratory Practice (GLP) compliance also was included stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications except that specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study sponsor.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion

Dosage:	0.1 mL
Species:	3 New Zealand albino rabbits
Sex:	Male
Age:	Young adult
Source:	Robinson Services, Inc., Clemmons, NC
Housing:	Temperature Range: 20 - 22 °C
	Relative Humidity: Information not provided
	Photoperiod: 12-hour light/dark cycle
Acclimation:	14 days

Summary:

1. **Toxicity Category**: IV

2. **Classification**:

Procedure (Deviations From 870.2400):

- No deviations were reported by the laboratory.
- Young adult rabbits were used for the experiment instead of adult rabbits as recommended in the guidelines.
- Relative humidity of animal housing was not provided.

20

Results: All animals appeared active and healthy. Apart from the eye irritation noted below, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behavior. There was no corneal opacity or iritis observed in any treated eye during this study. One hour after test substance instillation, all three treated eyes exhibited conjunctivitis. The overall incidence and severity of irritation decreased thereafter. All animals were free of ocular irritation by 48 hours.

Incidence of Irritation

Time Post Instillation	Corneal Opacity	Iritis	Conjuctivitis
1 hour	0 / 3	0 / 3	3 / 3
48 hours	0 / 3	0 / 3	3 / 3
Day 7	0 / 3	0 / 3	0 / 3
Day 21	0 / 3	0 / 3	0 / 3

Individual Scores for Ocular Irritation

Observations	Rabbit No.: 13925 (Male)				Rabbit No.: 13926 (Male)				Rabbit No.: 13927 (Male)			
	Hours				Hours				Hours			
	1	24	48	72	1	24	48	72	1	24	48	72
I. Corneal Opacity	0	0[1]	0	0	0	0[1]	0	0	0	0[1]	0	0
II. Iris	0	0	0	0	0	0	0	0	0	0	0	0
III. Conjunctivae:												
A. Redness	2	1	0	0	2	1	0	0	2	1	0	0
B. Chemosis	1	0	0	0	1	0	0	0	1	0	0	0
C. Discharge	1[2]	0	0	0	1[2]	0	0	0	1[2]	0	0	0

[1] 2 % ophthalmic fluorescein sodium used to verify the absence of corneal opacity

[2] Light green staining around the eye

21

DATA REVIEW FOR ACUTE DERMAL IRRITATION TESTING (OPPTS 870.2500)

Product Manager: Adam Heyward
MRID No.: 465331-07

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16994

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance statement was provided. A statement of Good Laboratory Practice (GLP) compliance also was included, stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications, except that specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study sponsor.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion

Dosage: 0.5 mL
Species: 3 New Zealand albino rabbits
Sex: 2 Males and 1 Female - the female was nulliparous and nonpregnant
Age: Young adult
Source: Robinson Services, Inc., Clemmons, NC
Housing: Temperature: 19 - 21 °C
Humidity: Information not provided
Photoperiod: 12-hour light/dark cycle
Acclimation: 7 days

Summary:

1. **Toxicity Category**: IV

2. **Classification**:

Procedure (Deviations From 870.2500):
- No protocol deviations were reported by the laboratory.
- Young adult rabbits were used for the study although the guidelines recommend testing adult animals.
- The humidity range of animal housing was not provided.

22

Results:
All animals appeared active and healthy. Apart from the dermal irritation noted in the table below, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behavior.

One hour after patch removal, two treated sites exhibited very slight erythema. All animals were free of dermal irritation by 24 hours.

Incidence of Irritation

Time after Patch Removal	Erythema	Edema
1 hour	2 / 3	0 / 3
24 hours	0 / 3	3 / 3
48 hours	0 / 3	0 / 3
72 hours	0 / 3	0 / 3

23

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (OPPTS 870.2600)
(BUEHLER METHOD)

Product Manager: Adam Heyward
MRID No.: 465331-08

Reviewer: Karen Hicks
Study Completion Date: April 15, 2005
Report No.: 16995

Testing Laboratory: Product Safety Laboratories
Author: Daniel J. Merkel, B.S.

Quality Assurance (40 CFR §160.12): A Quality Assurance statement was included. A statement of Good Laboratory Practice (GLP) compliance also was included stating that the study meets the requirements of 40 CFR Part 160 and OECD specifications, with the following exceptions, which the laboratory states are not believed to have any impact on the conduct or interpretation of this study:

- Specific information related to the stability, characterization, identity and verification of the test substance concentration as received and tested is the responsibility of the study sponsor.
- The stability, uniformity of mixture and verification of concentration of alpha-Hexylcinnamaldehyde Technical (HCA) in its carriers during the historical positive control study were not determined.

Test Material: ORD-X370 / Lot # FN1-25 / light green liquid dispersion
Positive Control Material: alpha-Hexylcinnamaldehyde Technical (HCA)
(Historical data - completed March 4, 2005)

Species: 34 Hartley albino guinea pigs
Sex: 30 Male and 4 Female; females were nulliparous and nonpregnant
Age: Young adult
Weight: Test and naive control groups: Males: 333 to 467 grams
Source: Elm Hill Breeding Labs, Chelmsford, MA
Housing: Temperature Range: 19 - 23 °C
Relative Humidity: Information not provided
Photoperiod: 12-hour light/dark cycle
Acclimation: 10 - 26 days

Method: Buehler method

Summary:

1. **Based on these findings and on the evaluation system used, ORD-X370 is not considered to be a contact sensitizer.** (Note: Study evaluated erythema only)

2. **Classification:**

Procedure (Deviation From 870.2600):

- No protocol deviations were reported by the laboratory.
- Relative humidity information of animal housing was not provided.
- Body weights recorded are the initial weight and the weight on the day after challenge, not the weight at study termination.
- Only erythema was graded, and not edema.

Procedure:

Preliminary Irritation: The fur was removed by clipping (Oster model #A5-small) the dorsal area and flanks of each guinea pig. This area was divided into four test sites (two sites on each side of the midline) on each animal. The test substance was applied neat (100%) and also diluted with water to yield w/w concentrations of 75 %, 50 %, and 25 %. Each concentration was applied (0.4 mL each) to a test site using an occlusive 25 mm Hill Top Chamber. The sites were wrapped with non-allergenic Durapore adhesive tape. After 6 hours of exposure, the chambers were removed and the test sites were gently cleansed of any residual test substance. Approximately 24 hours after application, each site was evaluated for local reactions (erythema only) according to the scoring system provided.
From these results, the HNIC (the highest concentration that produced responses in 4 guinea pigs no more severe than two scores of 0.5 and two scores of zero) was established and used for challenge. The HNIC selected for the challenge phase was a 50 % w/w mixture in distilled water.

Induction Phase: Once each week for three weeks, four-tenths of a milliliter of the undiluted test substance (100 %) was applied to the left side of each test animal using an occlusive 25-mm Hill Top Chamber. The chambers were secured in place and wrapped with non-allergenic Durapore adhesive tape to avoid dislocation of the chambers and to minimize loss of the test substance. After the 6-hour exposure period, the chambers were removed and the test sites gently wiped with water and a clean towel to remove any residual test substance. Approximately 24 hours and 48 hours after each induction application, readings were made of local reactions (erythema).

25

Challenge Phase: 27 days after the first induction dose, 0.4 mL of a 50 % w/w mixture of the test substance in distilled water (HNIC) was applied to a naive site on the right side of each animal as a challenge dose, using the procedures described above. These sites were evaluated for a sensitization response (erythema) approximately 24 hours and 48 hours after the challenge application.
In addition to the test animals, 10 guinea pigs from the same shipment were maintained under identical environmental conditions and were treated with the HNIC of the test substance at challenge only. These animals constituted the "naive control" group.

Results:
Based on the results of this study, the laboratory states that the test substance is not considered to be a contact sensitizer.

	Sensitization Response Indices (Erythema)			
	Incidence of Positive Response[1]		Severity[2]	
	Hours		Hours	
	24	48	24	48
Test Animals	0 / 20	0 / 20	0.20	0.08
Naive Control Animals	0 / 10	0 / 10	0.35	0.10

[1] Animals with scores greater than 0.5
[2] Sum of the erythema scores divided by the number of animals evaluated.