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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 4, 2005

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 81073-R
DP Barcode: D313280
Case No:

To: Marshall Swindell PM 33 / Tony Kish, Team Reviewer
Regulatory Management Branch
Antimicrobials Division (7510C)

From: Robert A. Turpin, Jr., Scientist
Chemistry/Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

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

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

Applicant: Clean Earth Technologies, LLC

FORMULATION FROM LABEL:

| Active Ingredient(s): | % by wt. |
|---|---|
| Hydrogen peroxide ..... | 24.0 |
| Peroxyacetic acid ..... | 1.2 |
| Other Ingredient(s): ..... | _ |

74.8

Total: 100%

BACKGROUND: The applicant has submitted an application for registration of its product, Peridox, as a disinfectant and sporicide. In support of the application, the applicant has submitted studies of the acute toxicity of the product, a draft label and a Confidential Statement of Formula (CSF).

RECOMMENDATIONS (PSB findings):

The primary eye irritation test was not performed because it is exempt as provided in 40 CFR Part 158.340. The product is corrosive to skin and the pH is less than 2.

The acute toxicity profile for Reg. No. 81073-R is currently:

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

LABELING:

Date: August 2, 2005
ID #81073-R / Peridox
Signal Word: DANGER

Note 1: The Precautionary Statement for a product with the Signal Word "DANGER" for eye and skin irritation is properly stated as Corrosive, causing irreversible damage. The statement is acceptable.

Note 2: The First Aid statement is acceptable.

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

**Product Manager**: Marshall Swindell
**Reviewer**: Robert Turpin
**MRID No.**: 464707-01
**Study Completion Date**: June 7, 2004
**Report No.**: 15108
**Testing Laboratory** : Product Safety Laboratories
**Author(s)** : 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**: PS1 'B Photosensitizer Formulation (4X1-Liter) / Lot # **030904FG004** / clear, colorless liquid

**Species**: Rat
**Age**: Young adult (9-12 weeks)
**Weight**: 189 - 238 grams
**Source**: Ace Animals, Inc.

**Conclusion**:

1. $LD_{50}$ (mg/kg): **Males = NA**
   **Females** = 3,129 mg/kg
   **Combined** = NA
2. **The estimated $LD_{50}$ is** 95% C.I. 1,750 to 5,000 mg/kg
3. **Tox. Category**: III **Classification**: Acceptable

**Procedure (Deviations from §81-1)**:

1. No deviations were reported by the laboratory.
2. The lower value of the temperature of animal housing was slightly below the limit recommended by the guidelines.
3. The relative humidity of animal housing was not provided.
4. Body weight changes were recorded but not calculated.

**Results**:

| Dosage (mg/kg) | (Number Deaths/Number Tested) | | |
|---|---|---|---|
| | Males | Females | Combined |

| | | | |
|---|---|---|---|
| 5,000 | NA | 4/9 | 4/9 |
| | | | |

**Observations:** 175 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.

550 mg/kg Dose Level (1 animal): This animal survived exposure to the test substance and gained body weight. Following administration, this animal exhibited facial and ano-genital staining and rales (dry). However, the animal recovered by Day 5 and appeared active and healthy for the remainder of the 14-day observation period.

1,750 mg/kg Dose Level (3 animals): All animals survived exposure to the test substance and gained body weight. Following administration, clinical signs noted included hypoactivity, reduced fecal volume, and a distended abdomen. However, the animals recovered by Day 5 and appeared active and healthy for the remainder of the 14-day observation period.

5,000 mg/kg Dose Level (4 animals): All animals died within one day of test substance administration. Toxic signs noted prior to death included hypoactivity, piloerection, and abnormal posture.

**Gross Necropsy:** No gross abnormalities were noted for any of the euthanized animals dosed at 175, 550, 1,750 and 5,000 mg/kg dose levels when necropsied at the conclusion of the 14-day observation period. Gross necropsy of the decedents at the 5,000 mg/kg dose level revealed discoloration of the lungs and/or intestines, and slight gaseous distention of the intestines.

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

**Product Manager:** Marshall Swindell **Reviewer:** Robert Turpin
**MRID No.:** 464561-04 **Study Completion Date:** June 7, 2004

**Report No.:** 15109
**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:** PS1 'B Photosensitizer Formulation (4X1-Liter) / Lot # 030904FG004 / clear, colorless liquid

**Species:** Rat
**Weight:** Males - 282 to 305 grams; Females - 192 to 220 grams **Age:**
**Source:**

**Summary:**

1. $LD_{50}$ (mg/kg): **Males** = >5,000 mg/kg
   **Females** = >5,000 mg/kg
   **Combined** = >5,000 mg/kg

2. **The estimated $LD_{50}$ is** >5,000 mg/kg

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

**Procedure (Deviation From §81-2):**

1. No deviations were recorded by the laboratory.
2. The relative humidity of animal housing was not provided.

**Results:**

Reported Mortality

| DOSAGE (mg/kg) | (NUMBER DEATHS/NUMBER TESTED) | | |
|---|---|---|---|
| | Males | Females | Combined |
| 5,000 | 0/5 | 0/5 | 0/10 |

| | | | |
|---|---|---|---|
| | | | |

**Observations**: All animals survived, gained body weight, and appeared active and healthy. Apart from the dermal irritation (blanching, hyperkeratosis, or eschar) noted at the dose site of all animals between Days 1 and 14, there were no other signs of gross toxicity, 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.

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

**Product Manager:** Marshall Swindell **Reviewer:** Robert Turpin
**MRID No.:** 464561-05 **Study Completion Date:** June 10, 2004

**Report No.:** 15110
**Testing Laboratory:** Product Safety Laboratory
**Author:** Daniel . 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:** PS1 'B Photosensitizer Formulation (4X1-Liter) / Lot # 030904FG005 and Lot # 030904FG007 / clear, colorless liquid
**Concentration:** 0.51 mg/L to 2.07 mg/L

**Species:** Rat
**Weight:** Males - 266-311 grams; Females - 189-235 grams
**Age:** Young adults (8 to 10 weels)
**Source:** Ace Animals, Inc.

**Summary:**

1. $LC_{50}$ (mg/L): **Males** = 2.08 mg/L
   **Females** = <2.08 mg/L
   **Combined** = >0.51<2.08 mg/L
2. **The estimated $LC_{50}$ is** <2.08 mg/L
3. **MMAD:** 3.0 µm (Sample 1) and 3.1 µm (Sample 2) at the 0.51 mg/L exposure level
   3.6 µm (Sample 1) and 3.5 µm (Sample 2) at the 2.08 mg/L exposure level
4. **Tox. Category:** III **Classification:** Acceptable

**Procedure (Deviation From §81-3):**

1. No deviations were reported by the laboratory.
2. The laboratory does not state whether females were nulliparous and nonpregnant.
3. The relative humidity of caging conditions was not provided.
4. Dimensions of the chamber were not provided.
5. The oxygen content of chamber was not provided.
6. Only two exposure levels were used, instead of three.
7. Changes in weights of animals were recorded but not calculated.

**Results:**

Reported Mortality

| Exposure Concentration (mg/L) | (NUMBER DEATHS/NUMBER TESTED) | | |
|---|---|---|---|
| | Males | Females | Combined |
| 0.51 | 0/5 | 0/5 | 0/10 |
| 2.08 | 2/5 | 4/5 | 6/10 |
| | | | |
| | | | |

| Chamber Atmosphere | | | |
|---|---|---|---|
| Dose Level | MMAD | GSD | particles < |
| 0.51 | 3.0 µm | 2.58 µm | 15.7 |
| 2.08 | 3.6 µm | 2.75 µm | 15.2 |

| Chamber Environment | |
|---|---|
| Chamber Volume | 6.7L |
| Airflow | 25.7 Lpm |
| Temperature | 19-20 ° C |
| Relative Humidity | 31-33% |

**Clinical Observations:** 0.51 mg/L Exposure Level: All animals survived exposure to the test atmosphere and gained body weight during the study. Following exposure, adverse clinical signs observed included abnormal respiration, hunched posture, and hypoactivity. However, all animals recovered by Day 4 and appeared active and healthy for the remainder of the 14-day observation period.

2.08 mg/L Exposure Level: Two males and three females were found dead at the end of the exposure period. The fourth female decedent was found dead within 24 hours of exposure.

Toxic signs noted prior to death were abnormal respiration, hunched posture, hypoactivity, corneal opacity, and reduced fecal volume. With the exception of corneal opacity, clinical signs noted for the four surviving animals were similar to those described above. However, the surviving animals recovered from these symptoms by Day 13 and appeared active and healthy for the remainder of the study. Although several survivors lost body weight through Day 7, all survivors gained body weight over the entire 14-day observation period.

**Gross Necropsy Findings:** No gross abnormalities were noted for any of the animals at the 0.51 mg/L exposure level when necropsied at the conclusion of the 14-day observation period. At the 2.08 mg/L exposure level gross necropsy of the six decedents revealed discoloration and edema of the lungs and/or corneal opacity. No gross abnormalities were noted for any of the four surviving animals at the 2.08 mg/L exposure level when necropsied at the conclusion of the 14-day observation period.

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

**Product Manager:** Marshall Swindell
**Reviewer:** Robert Turpin
**MRID No.:** 464561-06
**Study Completion Date:** June 7, 2004

**Report No.:** 15112
**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:** PSI 'B Photosensitizer Formulation (4X1-Liter) / Lot # 030904FG004 / clear, colorless liquid
**Dosage:** 0.5 ml
**Species:** Rabbit
**Age:** Young adult
**Sex:** Female - nulliparous and nonpregnant
**Weight:** NA
**Source:** Robinson Services, Inc.

**Summary:**

1. **Toxicity Category:** I

2. **Classification:** Acceptable

**Procedure (Deviations From §81-5):**

1. The laboratory reported that the Elizabethan collars were not removed at patch removal due to the severity of irritation observed at patch removal, and that this deviation did not affect the results of the study.

II. Relative humidity of animal housing was not reported.

III. The test substance was applied to a test area of 6 $cm^2$ on each animal, however, the gauze pad covered an area of only 1 inch x 1 inch.

**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, all three treated sites exhibited severe erythema, moderate edema, and blanching. By 24 hours, corrosion was evident at all dose sites. Therefore, the study was terminated and all animals were euthanized for humane reasons.

**Special Comments**: None.

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

**Product Manager**: Marshall Swindell **Reviewer**: Robert Turpin
**MRID No.**: 464561-07 **Study Completion Date**: June 7, 2004

**Report No.**: 15113
**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:

- 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**: PS1 'B Photosensitizer Formulation (4X1-Liter) / Lot # 030904FG004 / clear, colorless liquid
**Positive Control Material**: alpha-Hexylcinnamaldehyde Technical (HCA); Historical data (4/2/04)

**Species**: Guinea pig
**Weight**: Females - 324-381 grams **Age**: Young adults
**Source**: Elm Hill Breeding Labs

**Method**: Buehler method

**Summary**:

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

2. **Classification**: Acceptable

**Procedure (Deviation From §81-6)**:

- 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%, 25%, 12%, 6%, and 3%. Each concentration was applied to a test site using an occlusive 25 ml 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 reaction (erythema only) according to the scoring system provided.

Induction Phase: Once each week for three weeks, the induction phase was conducted by applying a mixture of the test substance in distilled water to the left side of each test animal using an occlusive 25 mm Hill Top Chamber. For the first induction, 0.4 mL of a 40% w/w mixture of the test substance in distilled water was applied. Due to the severity of irritation noted after this dose, the concentration of the test substance was reduced to a 30% w/w mixture of test substance in distilled water for the second and third inductions. In addition, all dose sites were relocated to an adjacent, naive area prior to the second induction dose. All induction 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 were gently cleansed of any residual test substance. Approximately 24 and 48 hours after each induction application, readings were made of local reactions (erythema) according to the scoring system provided.

Challenge Phase: 27 days after the first induction dose, 0.4 mL of a 3% 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 according to the scoring system provided.

## 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 | 0.28 | 0.13 |

| | | | | |
|---|---|---|---|---|
| Naive Control Animals | 0 / 10 | 0 / 10 | 0.15 | 0.00 |

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

## ACUTE TOX ONE-LINER

1. PC CODE: 063201/000595

2. CURRENT DATE: 8/4/05

3. TEST MATERIAL: Peridox (PS1 'B Photosensitizer Formulation (4X1-Liter))

| Study/Species/Lab/ Study#/Date | MRID No. | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| acute oral toxicity /Rat/Product Safety Labs(PSL)/15108/6-7-04 | 464707-01 | $LD_{50}$ (mg/kg) = 3,129 | III | A |
| acute dermal toxicity /Rat/PSL/15109/6-7-04 | 464561-04 | $LD_{50}$ (mg/kg) = >5,000 | IV | A |
| acute inhalation toxicity /Rat/PSL/15110/6-10-04 | 464561-05 | $LC_{50}$ (mg/L) = >0.51<2.08 | III | A |
| primary eye irritation / | Waived | Severe irritant | I | A |
| primary skin irritation /Rabbit/PSL/15112/6-7-04 | 464561-06 | Severe irritant | I | A |
| dermal sensitization /Guinea pig/PSL/15113/6-7-04 | 464561-07 | Not a sensitizer | --- | A |

A = Acceptable
U = Unacceptable
S = Supplementary
V = self-Validated