8-23-99

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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

August 23, 1999

MEMORANDUM

Subject: EPA File Symbol: 70829-E ClearOut 41
DP Barcode: D258468
Case No: 066104
PC Code: 103601 Glyphosate, isopropylamine salt

From: Byron T. Backus, Ph.D., Toxicologist Byron T. Backus 8/23/99
Technical Review Branch
Registration Division (7505C)

To: James Stone/Jim Tompkins, PM 25
Herbicide Branch
Registration Division (7505C)

Registrant: Chemical Products Technologies

**ACTION REQUESTED**: "Review acute studies submitted to support product registration. Note: using an unregistered source for a.i. glyphosate."

**BACKGROUND:**
The proposed product has the following label declaration:
Active Ingredient:
*Glyphosate, (phosphonomethyl) glycine, in the form of its isopropylamine salt.....41.0%
Inert Ingredients.....59.0%
*Contains 480 grams per liter or 4 pounds per U.S. gallon of the active ingredient, glyphosate, in the form of its isopropylamine salt. Equivalent to 356 grams per liter or 3 pounds per U.S. gallon of the acid, glyphosate.

This action includes a 6-pack of acute toxicity studies (MRIDs 44883104 through 44883109). All six studies were conducted at Product Safety Labs, East Brunswick, NJ.

**COMMENTS AND RECOMMENDATIONS:** The acute toxicity studies in MRIDs 44883104 through 44883109 have been reviewed, and have all been classified as acceptable. On the basis of the results of these studies, the following is the acute toxicity profile for the proposed product, EPA File Symbol 70829-E:

| | | |
|---|---|---|
| Acute Oral $LD_{50}$ | III | Acceptable |
| Acute Dermal $LD_{50}$ | III | Acceptable |
| Acute Inhalation $LC_{50}$ | IV | Acceptable |
| Primary Eye Irritation | IV | Acceptable |
| Primary Dermal Irritation | IV | Acceptable |
| Dermal Sensitization | No | Acceptable |

Based on the acute toxicity profile given above, the following is the precautionary labeling for this product, as obtained from the Label Review System:

Date: 08/23/99 LABEL REVIEW SYSTEM

ID #: 070829-00002 Clearout 41

AGRICULTURAL USE REQUIREMENTS:

DIRECTIONS FOR USE:

For early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water, wear: coveralls over long-sleeved shirt and long pants, socks and chemical resistant footwear and waterproof gloves.

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed or absorbed through skin. Avoid contact with eyes, skin or clothing. Wear long-sleeved shirt and long pants, socks and shoes and waterproof gloves.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

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 by a poison control center or doctor.

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.

The following should appear under the heading USER SAFETY RECOMMENDATIONS:

Wash hands before eating, drinking, chewing gum, using tobacco or using toilet.

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

**Product Manager:** 25
**MRID No.:** 44883104

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7165

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 19)

**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight (fasted):** Males: 191-203 g; Females: 148-175 g
**Source:** Ace Animals, Inc., Boyertown, PA

**Conclusion:**

1. **$LD_{50}$ (mg/kg):**
   **Males:** > 2000 mg/kg (no mortalities at this dose level)
   **Females:** > 2000 mg/kg (no mortalities at this dose level)
   **Combined:** > 2000 mg/kg (no mortalities at this dose level)
2. **The estimated $LD_{50}$ is** >2000 mg/kg
3. **Tox. Category:** III **Classification**: Acceptable

**Procedure (including deviations from 870.1100):** "The sample was administered as received... Each animal received 2,000 mg/kg of the test substance by intubation using a stainless steel ball-tipped gavage needle attached to an appropriate syringe... The day of administration was considered Day zero of the study."

**Results:**

| Dosage (mg/kg) | Number of Deaths/Number Tested | | |
|---|---|---|---|
| | Males | Females | Combined |
| 2000 | 0/5 | 0/5 | 0/10 |

**Observations:** "All animals survived and gained weight during the study. With the exception of soft feces noted in two rats on Day 1, all animals appeared active and healthy. There were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behavior."

**Gross Necropsy:** "Gross necropsy findings at terminal sacrifice were unremarkable."

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

**Product Manager:** 25
**MRID No.:** 44883105

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7166

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 20)

**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight:** Males: 193-218 g; Females: 178-210 g
**Source:** Ace Animals, Inc., Boyertown, PA

**Dermal $LD_{50}$ Testing:**

**Conclusion:**

1. **$LD_{50}$ (mg/kg):**
   **Males:** > 2000 mg/kg (no mortality at this dose level)
   **Females:** > 2000 mg/kg (no mortality at this dose level)
   **Combined:** > 2000 mg/kg (no mortality at this dose level)
2. **The estimated $LD_{50}$ is** > 2000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

**Procedure (including deviations from 870.1200):** "On the day prior to application, a group of animals was prepared by clipping...the dorsal area and trunk... Two thousand mg/kg of bodyweight of the test substance was applied evenly over a dose area of approximately 2 inches x 3 inches (approximately 10% of the body surface) and covered with a 2 inch x 3 inch, 4-ply gauze pad. The gauze pad and entire trunk of each animal were then wrapped with 3 inch Durapore tape to avoid dislocation of the pad and to minimize loss of the test substance... After 24 hours of exposure...the pads were removed and the test sites gently wiped with water and a clean towel to remove any residual test substance."

**Results:**

| Dosage (mg/kg) | Number of Deaths/Number Tested | | |
|---|---|---|---|
| | Males | Females | Combined |
| 2000 | 0/5 | 0/5 | 0/10 |

**Observations:** "All animals survived, gained weight and appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behavior."

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

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

**Product Manager:** 25
**MRID No.:** 44883106

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7167

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 29)

**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight:** Males: 228-243 g; Females: 178-202 g
**Source:** Ace Animals, Inc., Boyertown, PA

**Conclusion:**

1. **$LC_{50}$ (mg/L):**
   **Males:** > 2.13 mg/L (no mortalities from 4-hr exposure to this level)
   **Females:** > 2.13 mg/L (no mortalities from 4-hr exposure to this level)
   **Combined:** > 2.13 mg/L (no mortalities after 4-hr exposure to this level)
2. **The estimated $LC_{50}$ is** > 2.13 mg/L
3. **Tox. Category:** IV **Classification**: Acceptable

**Procedure (including deviations from 870.1300):** Exposure was whole body. The test material was aerosolized as received. "After establishing the desired generation procedures during pre-test trials, ten healthy rats were exposed to the test atmosphere for 4 hours..."

| Exposure Concentration ± S.D. (mg/L) (Gravimetrically Determined) | Number of Deaths/Number Tested | | |
|---|---|---|---|
| | Males | Females | Combined |
| 2.13 ± 0.08 | 0/5 | 0/5 | 0/10 |

**Observations:** "In-chamber animal observations included ocular discharge, hunched posture and hypoactivity. Apart from test substance on the fur, all animals recovered from the above symptoms upon removal from the exposure chamber and appeared active and healthy for the remainder of the study."

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

| Chamber Atmosphere[a] | | |
|---|---|---|
| **Grav. Conc. ± S.D. (mg/L)** | **Mean MMAD[b]** | **Average GSD[b]** |
| 2.13 ± 0.08 | 2.65 µm | 1.72 |

[a]Exposure was whole body.
[b]Average of two sample times (at 1.5 and 3 hrs)

**Other Information:** The nominal concentration was 46.53 mg/L. Approximately 58% of the particles had an effective cut-off diameter ≤ 3.3 µm.

| Chamber Environment | |
|---|---|
| Chamber Volume | 150 L |
| Mean Total Airflow | 45.6 LPM |
| Temperature | 21-23°C |
| Relative Humidity | 42-72% |

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

**Product Manager:** 25
**MRID No.:** 44883107

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7168

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 22)
**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA
**Dosage:** 0.1 mL
**Species:** Rabbit; Albino, New Zealand White
**Age:** "adult"
**Weight:** not stated
**Source:** Davidson's Mill Farm, South Brunswick, NJ

**Conclusion**:

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

**Procedure (including deviations from 870.2400):** "One-tenth of a milliliter of the test substance, as received, was instilled into the conjunctival sac of the right eye of the first and second rabbit by pulling the lower lid away from the eyeball. The upper and lower lids were then gently held together for about one second before releasing, to minimize loss of the test substance... Prior to test substance installation in the third rabbit, 1-2 drops of ocular anesthetic (Tetracaine Hydrochloride Ophthalmic Solution 0.5%) were placed into both the treated and control eye, due to signs of distress in the second rabbit..."

**Results:**

| Observations | Number "positive"/number tested | | | |
|---|---|---|---|---|
| | Hours | | | |
| | 1 | 24 | 48 | 72 |
| | Unwashed eyes | | | |
| Corneal Opacity | 0/3 | 0/3[a] | 0/3 | 0/3 |
| Iritis | 0/3 | 0/3 | 0/3 | 0/3 |
| Conjunctivae: | | | | |
| Redness[b] | 2/3 | 0/3 | 0/3 | 0/3 |
| Chemosis[b] | 0/3 | 0/3 | 0/3 | 0/3 |
| Discharge[b] | 1/3 | 0/3 | 0/3 | 0/3 |

[a]2% florescein sodium used to verify the absence of corneal opacity
[b]Score of 2 or more considered to be "positive."

**Summary:** At 24 hours, 2/3 eyes scored "1" for conjunctival redness (not considered positive). All scores were zero at 48 hours.

## DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500, formerly §81-5)

**Product Manager:** 25
**MRID No.:** 44883108

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7169

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 21)

**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA

**Dosage:** 0.5 mL

**Species:** Rabbit; Albino, New Zealand White
**Age:** "adult"
**Weight:** not stated
**Source:** Davidson's Mill Farm, South Brunswick, NJ

**Conclusion**:

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

**Procedure (including deviations from 870.2500):** Three rabbits were used. "On the day before application, a group of animals was prepared by clipping...the dorsal area and the trunk... Five-tenths of a milliliter of the test substance was applied to one 6 $cm^2$ intact dose site on each animal and covered with a 1 inch x 1 inch, 4-ply gauze pad. The pad and entire trunk of each animal were then wrapped with semi-occlusive 3 inch Micropore tape to avoid dislocation of the pad. Elizabethan collars were placed on each rabbit... After 4 hours of exposure to the test substance, the pads and collars were removed and the test sites gently wiped with water and a clean towel to remove any residual test substance"

**Results:** "One treated site was free from dermal irritation throughout the study. One hour after patch removal, two animals exhibited very slight [grade "1"] erythema. Irritation cleared from both affected sites within 24 hours. All scores for edema were zero.

The primary irritation index = 0.2.

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

**Product Manager:** 25
**MRID No.:** 44883109

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 2, 1999
**Study No.:** 7170

**Testing Facility:** Product Safety Labs, East Brunswick, NJ
**Author:** Wnorowski, G.

**Quality Assurance (40 CFR §160.12):** Included (p. 32)

**Test Material:** ClearOut 41, Lot #981411, an amber liquid, identified as containing 41% glyphosate IPA
**Positive Control Material:** 1-chloro-2,4-dinitrobenzene

**Species:** Guinea pig; Albino, Hartley (14 males, 6 females for induction; 6 males and 4 females as naive controls)
**Age:** "young adult"
**Weight (at initiation):** Males: 304-397 g; Females: 363-391 g (induced animals only)
**Source:** Davidson's Mill Farms, South Brunswick, NJ

**Method:** Buehler

**Conclusion**:

1. **This product is a non-sensitizer.**
2. **Classification**: Acceptable

**Procedure (including deviations from 870.2600):** The test substance, as received, was topically applied [0.4 mL to the left side of each test animal using an occlusive 25 mm Hill Top Chamber®] to twenty healthy test guinea pigs, once each week for a three week induction period. Thirteen days after the last induction dose, a 0.4 mL challenge dose of the test substance at its highest non-irritating concentration (100%) was applied to a naive site on each guinea pig. A naive control group (ten animals) was maintained under the same environmental conditions and treated with the test substance at challenge only. Twenty-four and 48 hours after each induction and challenge dose, the animals were scored for erythema.

**Results:** All scores (both at 24 and 48 hours) following induction and challenge treatments (both with the previously exposed animals and the naive controls) with the Clearout 41 were zero. The study report includes results of positive control testing (utilizing DNCB). According to the report, this was a concurrent study. This is consistent with the animal numbers, which ranged from 9740 to 9759 for the guinea pigs which were induced with the test material or served as naive controls, and which ranged from 9770-9784 for the 10 animals induced with DNCB and their five naive controls. The results of the positive control study (6/10 animals with a score of at least "1" at 24 and 48 hours following challenge with 0.04% w/w solution DNCB in acetone; a maximum score of "0.5" observed in 5 naive controls) were consistent with those expected from a dermal sensitizer. [The positive control study was also concurrent to the dermal sensitization study with 70829-G, ClearOut 41 Plus.]

## ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D258468
2. **PC CODE:** 103601 Glyphosate, isopropylamine salt;
3. **CURRENT DATE:** August 23, 1999
4. **TEST MATERIAL:** EPA File Symbol: 70829-E; Clearout 41, Lot #981411, an amber liquid identified as containing 41% glyphosate IPA

| Study/Species/Lab Study #/Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Acute oral toxicity/rat/Product Safety Labs/ 7165/APR-2-1999 | 44883104 | $LD_{50}$ > 2000 mg/kg (males, females, combined); no mortalities at this dose level; symptoms in a few animals consisted of soft feces, which was gone 48 hrs after dosing. | III | A |
| Acute dermal toxicity/rat/Product Safety Labs/7166/APR-2-1999 | 44883105 | $LD_{50}$ > 2000 mg/kg (males, females, combined); no mortalities or symptoms of systemic toxicity. | III | A |
| Acute inhalation toxicity/rat/Product Safety Labs/7167/APR-2-1999 | 44883106 | $LC_{50}$ > 2.13 mg/L (whole body exposure), no mortalities from 4-hr exposure to this concentration. | IV | A |
| Primary eye irritation/rabbit/Product Safety Labs/7168/APR-2-1999 | 44883107 | No corneal opacity or iritis observed. At 1 hr, 2/3 eyes were positive for conjunctival redness, and 1/3 was positive for discharge. At 24 hrs, 2 eyes scored "1" for conjunctival redness (not considered a postive response). All scores were zero at 48 hrs. | IV | A |
| Primary dermal irritation/rabbit/Product Safety Labs/7169/APR-2-1999 | 44883108 | Three rabbits used;PII = 0.2; at 1 hr 2/3 sites scored 1 for erythema. All scores at 24 hrs and subsequently were zero. All scores for edema were zero. | IV | A |
| Dermal sensitization/guinea pig/Product Safety Labs/7170/APR-2-1999 | 44883109 | A non-sensitizer | – | A |

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**