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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

August 20, 1999

MEMORANDUM

Subject: EPA File Symbol: 70829-G ClearOut 41 Plus
DP Barcode: D258470
Case No: 066109
PC Code: 103601 Glyphosate, isopropylamine salt

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

Byron T. Backus
8/20/99

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 of ai 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 44883113 through 44883118). All six of these studies were conducted at Product Safety Labs, East Brunswick, NJ.

**COMMENTS AND RECOMMENDATIONS:** The acute toxicity studies in MRIDs 44883113 through 44883118 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-G:

| | | |
|---|---|---|
| Acute Oral $LD_{50}$ | III | Acceptable |
| Acute Dermal $LD_{50}$ | III | Acceptable |
| Acute Inhalation $LC_{50}$ | IV | Acceptable |
| Primary Eye Irritation | I | 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: 08/20/99 LABEL REVIEW SYSTEM

ID #: 070829-00003 Clearout 41 Plus

RESTRICTED USE CLASSIFICATION RECOMMENDED:

Due to eye irritation toxicity category.

The PM Team should decide if restricted use classification is necessary or if alternative labeling will allay the requirement for restricted use classification.

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, Wear goggles or face shield, and waterproof gloves.

SIGNAL WORD: DANGER PELIGRO

PRECAUTIONARY STATEMENTS:

Corrosive. Causes irreversible eye damage. Harmful if swallowed or absorbed through skin. Do not get in eyes or on clothing. Avoid contact with skin. Wear long-sleeved shirt and long pants, socks and shoes, goggles or face shield 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.

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 poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

The following "Note to Physician" statement is required for the subject product:

NOTE TO PHYSICIAN; Probable mucosal damage may contraindicate the use of gastric lavage.

The following should appear under the heading USER SAFETY RECOMMENDATIONS:

Wash hands before eating, drinking, chewing gum, using tobacco or using toilet. Remove contaminated clothing and wash clothing before reuse.

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

**Product Manager:** 25
**MRID No.:** 44883113

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7171

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

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

**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight (fasted):** Males: 189-208 g; Females: 143-172 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. Several rats exhibited diarrhea and anogenital staining eight hours after test substance administration, but recovered by Day 1 and appeared active and healthy for the remainder of the 14-day observation period.

**Gross Necropsy:** "No gross abnormalities were noted for the animals when necropsied at the conclusion of the study."

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

**Product Manager:** 25
**MRID No.:** 44883114

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7172

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

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

**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight:** Males: 201-219 g; Females: 194-202 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[a] | 0/10 |

[a]Due to a technical error, one animal was dosed with 0.31 mL rather than 0.35 mL (1771 mg/kg instead of 2000 mg/kg).

**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 when 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.:** 44883115

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7173

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

**Quality Assurance (40 CFR §160.12):** Included (p. 30)

**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.

**Species:** Rat: albino, Sprague-Dawley derived
**Age:** "young adult"
**Weight:** Males: 210-232 g; Females: 179-203 g
**Source:** Ace Animals, Inc., Boyertown, PA

**Conclusion:**

1. **$LC_{50}$ (mg/L):**
   **Males:** > 2.09 mg/L (no mortalities from 4-hr exposure to this level)
   **Females:** > 2.09 mg/L (no mortalities from 4-hr exposure to this level)
   **Combined:** > 2.09 mg/L (no mortalities after 4-hr exposure to this level)
2. **The estimated $LC_{50}$ is** > 2.09 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 |
| 2.09 ± 0.06 | 0/5 | 0/5 | 0/10 |

**Observations:** "In-chamber animal observations included ocular and nasal discharge, irregular respiration, hunched posture and hypoactivity. Upon removal from the exposure chamber, one male continued to appear hypoactive. Another male exhibited hypoactivity, a hunched posture, irregular respiration, dyspnea and was gasping." Test substance was noted on the fur of all rats. All animals had recovered by day 2.

**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]** |
| 2.09 ± 0.06 | 2.7 µm | 1.74 |

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

**Other Information:** The nominal concentration was 34.88 mg/L. Approximately 55% of the particles had an effective cut-off diameter $\leq$ 3.3 µm.

| Chamber Environment | |
|---|---|
| Chamber Volume | 150 L |
| Mean Total Airflow | 45.7 LPM |
| Temperature | 21-22°C |
| Relative Humidity | 41-68% |

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

**Product Manager:** 25
**MRID No.:** 44883116

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7174

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

**Quality Assurance (40 CFR §160.12):** Included (p. 25)
**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.
**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:** I
2. **Classification**: Acceptable

**Procedure (including deviations from 870.2400):** "One-tenth of a milliliter of the test substance, as received, was instilled into the right eye of three healthy rabbits..."

**Results:**

| Observations | Number "positive"/number tested | | | | | | |
|---|---|---|---|---|---|---|---|
| | Hours | | | | Days | | |
| | 1 | 24 | 48 | 72 | 7 | 14 | 21 |
| | Unwashed eyes | | | | | | |
| Corneal Opacity | 0/3 | 3/3 | 3/3 | 3/3 | 3/3 | 2/3 | 2/3 |
| Iritis | 2/3 | 3/3 | 3/3 | 3/3 | 1/3 | 0/3 | 0/3 |
| Conjunctivae: | | | | | | | |
| Redness[1] | 3/3 | 3/3 | 3/3 | 3/3 | 1/3 | 0/3 | 0/3 |
| Chemosis[1] | 3/3 | 3/3 | 2/3 | 2/3 | 1/3 | 0/3 | 0/3 |
| Discharge[1] | 3/3 | 3/3 | 2/3 | 2/3 | 1/3 | 0/3 | 0/3 |

[1]Score of 2 or greater considered as a positive effect.

**Summary:** Grade 1 corneal opacity was still present in 2/3 eyes on Day 21.

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

**Product Manager:** 25
**MRID No.:** 44883117

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7175

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

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

**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.

**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):** "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 ethanol, water and a clean towel to remove any residual test substance"

**Results:** "One hour after patch removal, very slight edema and/or erythema was observed at all treated sites [all sites scored "1" for erythema, and 2/3 scored "1" for edema]. The incidence of irritation decreased with time. All rabbits were free of dermal irritation within 48 hours.

The primary irritation index = 0.5.

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

**Product Manager:** 25
**MRID No.:** 44883118

**Reviewer:** Byron T. Backus, Ph.D.
**Study Completion Date:** April 8, 1999
**Study No.:** 7176

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

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

**Test Material:** Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.
**Positive Control Material:** 1-chloro-2,4-dinitrochlorobenzene

**Species:** Guinea pig; Albino, Hartley (14 males, 6 females)
**Age:** "young adult"
**Weight (at initiation):** Males: 331-412 g; Females: 338-409 g.
**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:** The maximum 24-hour score following induction was "1," while the maximum 48-hour score was "0.5." There was no indication of an increase in either degree or incidence of irritation from the first to third induction treatment. Following challenge, 5/20 previously induced guinea pigs showed a score of "0.5" at 24 hours (and "0.5" was the maximum irritation observed), while 1/20 showed a score of "0.5" at 48 hours. Similar results were observed with the naive controls (3/10 scored "0.5" at 24 hrs; 2/10 scored "0.5" at 48 hrs; all other scores were zero). The study report includes results of positive control testing (utilizing DNCB). According to the positive control validation, this was a concurrent study. This is consistent with the animal numbers, which ranged from 9710 to 9739 for the guinea pigs which served had been 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.

## ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D258470
2. **PC CODE:** 103601 Glyphosate, isopropylamine salt;
3. **CURRENT DATE:** August 20, 1999
4. **TEST MATERIAL:** EPA File Symbol: 70829-G; Clearout 41 Plus, Lot #981711, identified as containing 41% glyphosate IPA, an amber liquid.

| Study/Species/Lab Study #/Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Acute oral toxicity/rat/Product Safety Labs/ 7171/APR-8-1999 | 44883113 | $LD_{50}$ > 2000 mg/kg (males, females, combined); no mortalities at this dose level; symptoms in a few animals consisted of diarrhea & ano-genital staining, which was gone 24 hrs after dosing. | III | A |
| Acute dermal toxicity/rat/Product Safety Labs/7172/APR-8-1999 | 44883114 | $LD_{50}$ > 2000 mg/kg (males, females, combined); no mortalities or symptoms of systemic toxicity. | III | A |
| Acute inhalation toxicity/rat/Product Safety Labs/7173/APR-8-1999 | 44883115 | $LC_{50}$ > 2.09 mg/L (whole body exposure), no mortalities from 4-hr exposure to this concentration. | IV | A |
| Primary eye irritation/rabbit/Product Safety Labs/7174/APR-8-1999 | 44883116 | At 72 hours, all eyes were positive for corneal opacity, iritis and conjunctivitis. Some improvement, but 2/3 unwashed eyes still showed corneal opacity on day 21. | I | A |
| Primary dermal irritation/rabbit/Product Safety Labs/7175/APR-8-1999 | 44883117 | Three rabbits used;PII = 0.5; at 1 hr 3/3 sites scored 1 for erythema; 2/3 scored 1 for edema. At 48 hrs, all scores were zero. | IV | A |
| Dermal sensitization/guinea pig/Product Safety Labs/7176/APR-8-1999 | 44883118 | A non-sensitizer | – | A |

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