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

THE ADMINISTRATOR

MEMORANDUM

Subject: EPA Reg. No.: 524-308 acute toxicity review; DP Barcode# D216119, Case# 003372

From: Mark J. Perry, Biologist
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)

MJP 4-26-96

To: Robert Taylor, PM-25 / E. Mitchell
Registration Division (7505C)

Applicant: Monsanto Company
Suite 1100
700 14th Street, N.W.
Washington, DC 20005

FORMULATION FROM LABEL:

	% by wt.
Active Ingredient(s): Glyphosate, N-(phosphono-methyl)glycine, in the form of its isopropylamine salt	41.0
Inert Ingredient(s):	59.0
Total:	100%

BACKGROUND

Monsanto has submitted acute dermal, dermal irritation and dermal sensitization studies in support of reregistration. These data were submitted to replace previously unacceptable studies performed with this product. The subject product, Roundup, is a liquid herbicide which contains glyphosate at 41.0%.

Acute studies were performed by Bio/dynamics and Pharmaco

LSR; assigned MRID/Accession numbers are 434345-02, 434345-04 and 434049-02.

RECOMMENDATION:

1. Acute Dermal; Category IV / Acceptable

2. Dermal Irritation; Category IV / Acceptable

3. Dermal Sensitization; Non-sensitizer / Acceptable

LABELING

1. The recommended signal word is "danger/Peligro."

2. Restricted use classification is 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.

3. If this product is intended for residential use, child-resistant packaging is recommended.

4. The recommended precautionary statements are as follows:

Corrosive. Causes irreversible eye damage. Harmful if swallowed. Do not get in eyes or on clothing. Wear long-sleeved shirt and long pants, socks and shoes and goggles or face shield. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash clothing before reuse.

5. The recommended statements of practical treatment are as follows:

IF IN EYES: Hold eyelids open and flush with steady, gentle stream of water for 15 minutes. Get medical attention.

IF SWALLOWED: Call a physician or Poison Control Center. Do not induce vomiting. Drink promptly a large quantity of milk, egg whites, gelatin solution, or if these are not available, drink large quantities of water. Avoid alcohol.

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

EPA Reviewer: M. Perry MJP, Date 4-26-96
Review Section __, Toxicology Branch __ (7505W)
EPA Secondary Reviewer: _____, Date _____
Review Section __, Toxicology Branch __ (7505W)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit
OPPTS 870.1200 [81-2]

DP BARCODE: D216119 SUBMISSION CODE:
P.C. CODE: 103601 TOX. CHEM. NO.:
EPA REG. NO.: 524-308

TEST MATERIAL (PURITY): MON-2139 (41.56% isopropylammonium glyphosate)

SYNONYMS: Roundup Export Herbicide
CITATION: Blaszcak, D., and C. Auletta (1994) Acute dermal toxicity study in rats/MON-2139 Herbicide. Bio/dynamics, Inc., East Millstone, NJ. Laboratory Study Number BD-87-283/4547-87. October 10, 1994. MRID 43434502. Unpublished.
SPONSOR: Monsanto Agricultural Company, St. Louis, MO

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 43434502), five young adult New Zealand White rabbits/sex were dermally exposed to undiluted MON-2139 (45.56% isopropylammonium glyphosate) at 5,000 mg/kg (¢2X limit concentration) for 24 hours; the test substance applied uniformly to at least 10% of the total body surface. Animals were observed for clinical signs and mortality for up to 14 days postdosing.

Dermal LD_{50} Males = greater than 5,000 mg/kg (observed)
Females = greater than 5,000 mg/kg (observed)

MON-2139 is classified as **TOXICITY CATEGORY IV** based on the LD_{50} in both sexes.
All animals survived the 14-day observation period. Nasal discharge, oral discharge, dry oral discharge, wet rales, dry fecal staining, and/or a decrease in food consumption were observed from 4 hours to 10 days following application. In addition, severe dermal irritation characterized by necrosis, eschar formation, fissuring and/or exfoliation of the eschar tissue, was observed at most (6/10) treatment sites. The body

weights of all animals decreased between 0 and 7 days, and increased (9/10) or remained unchanged (1/10) between 7 and 14 days. Necropsy of animals sacrificed after 14 days revealed discoloration of the lungs in 10/10 animals and a reddened uterus in 5/5 female animals. The study author reported that these findings were "similar to those seen in control animals in this laboratory or were considered to represent normal physiological variation [page 6]."
This study is classified **acceptable**, and satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: MON-2139
   Description: Clear amber liquid
   Lot/Batch #: XLH-301
   Purity: 45.56% isopropylammonium glyphosate
   Bulk density: 1.17 g/mL
   CAS #: 38641-94-0 (The Pesticide Manual, 10th ed.)

2. Vehicle: None employed

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (8 weeks)
   Weight: 2.3-2.7 kg males; 2.4-3.2 kg females
   Source: Hazleton-Dutchland Laboratory Animals, Denver, PA
   Acclimation period: 17 days
   Diet: Purina Rabbit Chow HF (#5326), ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates: October 15-29, 1987

2. Animal assignment and treatment: Fur from the dorsal area of the trunk (at least 10% of the total body surface) of five animals/sex was clipped 1 day prior to dermal administration of MON-2139 at 5,000

mg/kg (greater than 2X limit concentration); the test substance was applied uniformly to the entire clipped area. The trunk of each animal was wrapped with gauze followed by an impervious plastic sleeve secured with tape. The animals were also fitted with Elizabethan collars. The coverings were removed 24 hours postdosing, and the test sites were wiped free of excess test material. The rabbits were observed for gross toxicity, behavioral changes, and/or mortality at 1, 2, and 4 hours following application and at least once daily thereafter for the remainder of the 14-day study. Body weights were recorded at 0 (prior to application), 7, and 14 days postdosing. At 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable to this study.

II. **RESULTS AND DISCUSSION:**

A. Mortality: All animals survived the 14-day observation period.

Dermal LD_{50} Males = 5,000 mg/kg (observed)
Females = 5,000 mg/kg (observed)

B. Clinical observations: Nasal discharge, oral discharge, dry oral discharge, wet rales, dry fecal staining, and/or a decrease in food consumption were observed from 4 hours to 10 days following application. In addition, severe dermal irritation characterized by necrosis, eschar formation, fissuring and/or exfoliation of the eschar tissue, was observed at most (6/10) treatment sites. Individual clinical observations were not provided.

C. Body Weight: The body weights of all animals decreased between 0 and 7 days, and increased (9/10) or remained unchanged (1/10) between 7 and 14 days. Overall (0-14 days), the body weights of all animals remained within +/-0.3 kg from study initiation (range of -4.3 to 11% change).

D. Necropsy: Necropsy of animals sacrificed after 14 days confirmed dermal lesions in 3/10 animals, and revealed discoloration of the lungs in 10/10 animals and a reddened uterus in 5/5 female animals. The study author reported that these findings were "similar to those seen in control animals in this laboratory or were considered to represent normal physiological variation [page 6]."

E. Deficiencies: Individual clinical effects were not provided. However, the summarized data provided were adequate in establishing the onset and duration of clinical effects, and this deficiency is considered minor.

The body weight of one female rabbit was greater than the desired 3-kg limit, however, this deficiency is considered minor.

EPA Reviewer: M. Perry MJP, Date 4-26-96
Review Section __, Toxicology Branch __ (7505W)
EPA Secondary Reviewer: _____, Date _____
Review Section __, Toxicology Branch __ (7505W)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS 870.2500 [81-5]

DP BARCODE: D216119 SUBMISSION CODE:
P.C. CODE: 103601 TOX. CHEM. NO.:
EPA REG. NO.: 524-308

TEST MATERIAL (PURITY): MON-2139 (41.56% isopropylammonium glyphosate)

SYNONYMS: Roundup Export Herbicide
CITATION: Blaszcak, D., and C. Auletta (1994) Primary dermal irritation study in rabbits/MON-2139 Herbicide. Bio/dynamics, Inc., East Millstone, NJ. Laboratory Study Number BD-87-283/4548-87. October 10, 1994. MRID 43434504. Unpublished.
SPONSOR: Monsanto Agricultural Company, St. Louis, MO

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 43434504), six young adult New Zealand White rabbits (2 males/4 females) were dermally exposed to 0.5 mL of undiluted MON-2139 (41.56% isopropylammonium glyphosate) for 4 hours; the test substance was applied to two intact 1-in^2 sites/animal. Animals were observed for dermal irritation for up to 72 hours following patch removal. Irritation was scored by the Draize Evaluation of Dermal Irritation.

Thirty minutes following patch removal, very slight to moderate/severe erythema was observed at all (12/12) test sites, and very slight edema was observed at 3/12 sites. After 24 hours, irritation had lessened to very slight to well-defined erythema at 11/12 sites and very slight edema at 1/12 sites. All dermal irritation subsided by 72 hours.
In this study, **MON-2139 is a very mild dermal irritant**, and is classified as **TOXICITY CATEGORY IV** for primary dermal irritation based on the mild irritation which subsided by 72 hours.

This study is classified as **acceptable**, and satisfies the

guideline requirement for a primary dermal irritation study (81-5) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: MON-2139
   Description: Clear amber liquid
   Lot/Batch #: XLH-301
   Purity: 45.56% isopropylammonium glyphosate
   Bulk density: 1.17 g/mL
   CAS #: 38641-94-0 (The Pesticide Manual, 10th ed.)

2. Vehicle: None employed

3. Test animals: Species: Rabbits
   Strain: New Zealand White
   Age: Young adult (8 weeks)
   Weight: Not provided
   Source: Summit View Farms, Hazleton, PA
   Acclimation period: 28 days
   Diet: Lab Rabbit Chow HF (#5326), ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates: October 6-9, 1987

2. Animal assignment and treatment: Fur on the backs of six young adult animals (2 males/4 females) was clipped 1 day prior to dermal administration of 0.5 mL MON-2139 to two intact sites nearest the head per animal. The test substance was applied beneath a 1-in^2 gauze secured with non-irritating tape. The trunk of each animal was wrapped with gauze secured with porous tape, and the animals were fitted with Elizabethan collars. The coverings were removed 4 hours following application, and the sites were gently wiped with water-moistened gauze. The rabbits were observed for dermal irritation 0.5, 24, 48, and 72 hours following patch removal. Erythema and edema were scored separately using the Draize

Evaluation of Dermal Irritation. Adjacent areas of untreated skin were used as controls.

II. RESULTS AND DISCUSSION:

A. Clinical observations: Thirty minutes following patch removal, very slight to moderate/severe erythema (scores of 1-3) was observed at all (12/12) test sites, and very slight edema (score of 1) was observed at 3/12 sites. After 24 hours, irritation had lessened to very slight to well-defined erythema (scores of 1-2) at 11/12 sites and very slight edema at 1/12 sites. All dermal irritation subsided by 72 hours. Based on the results of this study, MON-2139 is a very mild dermal irritant.

B. Deficiencies: Individual observations for the entire day of dosing were not conducted; however, the observation intervals selected in this study were adequate in determining a toxicity category for MON-2139, and this deficiency is considered minor.

The sizes of the application areas were not directly specified. Since the sites were covered with 1-in^2 gauze patches, it is likely that the area was approximately this size, which fulfills guideline requirements.

EPA Reviewer: M. Perry MDP, Date 4-26-96
Review Section __, Toxicology Branch __ (7505W)
EPA Secondary Reviewer: _____, Date _____
Review Section __, Toxicology Branch __ (7505W)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea pig
OPPTS 870.2600 [81-6]

DP BARCODE: D216119 SUBMISSION CODE:
P.C. CODE: 103601 TOX. CHEM. NO.:
EPA REG. NO.: 524-308

TEST MATERIAL (PURITY): MON-0139 (47.6% glyphosate acid)

SYNONYMS: None specified
CITATION: Blaszcak, D. (1994) Closed-patch repeated insult dermal sensitization study in guinea pigs with MON 0139 (Buehler Method). Pharmaco LSR, Inc., East Millstone, NJ. Laboratory Study Number 94-1006. Sponsor Study Number PL-94-128. October 7, 1994. MRID 43404902. Unpublished.
SPONSOR: Monsanto Agricultural Company, St. Louis, MO

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 43404902) conducted with MON-0139 (47.6% glyphosate acid), five young adult Dunkin Hartley albino guinea pigs/sex were tested using methods based on those derived by Buehler. Results of two studies using dinitrochlorobenzene (DNCB) were included in the report to confirm the validity of the protocol used.

No dermal irritation was observed during the induction phase or following the challenge application. Similarly, no dermal irritation was observed in naive control animals. Based on the results of this study, **MON-0139 is not a dermal sensitizer.** This study is classified as **acceptable**, and satisfies the guideline requirement for a dermal sensitization study (81-6) in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: MON-0139
   Description: Clear liquid
   Lot/Batch #: LUL-9404-5904-F
   Purity: 47.6% Glyphosate acid
   CAS #: Not specified

2. Vehicle and positive control: No vehicle was employed. Results of two studies (March 23-April 29 and June 7-July 14, 1994) using dinitrochlorobenzene (DNCB), a known sensitizer, were included in the report to confirm the validity of the protocol used: 0.5% DNCB in 80% ethanol and 0.3% DNCB in acetone were used for induction and challenge treatments, respectively.

3. Test animals: Species: Guinea pig
   Strain: Dunkin Hartley Haz:(DH)fBR, albino
   Age: 9-10 weeks (preliminary study) or 5-6 weeks (definitive study)
   Weight: 283-410 g males; 300-378 g females (definitive study)
   Source: HRP, Inc., Denver, PA
   Acclimation period: 9 days (preliminary study) or 16 days (definitive study)
   Diet: Agway Prolab Guinea Pig Diet, ad libitum
   Water: Filtered tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates: June 1-July 8, 1994 (preliminary and definitive studies)

2. Animal assignment and treatment: The study was conducted using methods based on those derived by Buehler [Buehler, E., Arch. Dermatol, Vol. 91, pp. 171-175 (1965); and Ritz, H. and E. Buehler, Current Concepts in Cutaneous Toxicity, pp. 25-40, Academic Press (1980)]. Based on the results of preliminary experiments conducted with MON-0139 at 10, 25, 50, or 100%, the test material was administered undiluted (100%) in the definitive study.

   For the induction phase, fur on the back and sides

of five animals/sex was clipped 1 day prior to dermal administration of 0.3 mL of MON-0139 to the right side of the midline using a Hill Top Chamber. Each chamber was covered with impermeable plastic, and secured with elastic adhesive bandage. Following a 6-hour exposure period, the chambers were removed, and any excess test substance was removed from the skin by gently wiping with distilled water and clean gauze. Application of the test substance was repeated weekly for a total of three applications.

For the challenge phase, a single treatment was applied using MON-0139 in the same manner as described, to the previously untreated left side of each animal 14 days following the final induction treatment. To serve as naive controls, an additional five animals/sex were included for the challenge treatment. The guinea pigs were observed for dermal irritation 24 and 48 hours following each induction and challenge exposure. Skin reactions were scored according to the following scale:

0 - No reaction
0.5 - Very slight erythema, usually non-confluent
1 - Slight erythema, usually confluent
2 - Moderate erythema
3 - Severe erythema, with or without edema

The animals were observed for mortality twice daily, and for general health once weekly. Body weights were recorded 1 day prior to the first induction treatment and 2 days following the challenge treatment.

II. RESULTS AND DISCUSSION:

A. Induction reactions and duration: No dermal irritation was observed during the induction phase.

B. Challenge reactions and duration: No dermal irritation was observed following the challenge application. Similarly, no dermal irritation was observed in naive control animals. Based on the results of this study, MON-0139 is not a dermal sensitizer.

C. Positive control: Results for the induction phases of the two studies were not provided.

Following the single challenge treatment, very slight to severe erythema (scores of 0.5-3), accompanied by edema, necrosis, white tissue, and/or foci of white tissue, was observed at all test sites of previously induced animals, compared to very slight erythema observed at up to 12/20 sites of naive control animals.

D. Deficiencies: None.

ACUTE TOX ONE-LINER

1. PC CODE: 103601

2. CURRENT DATE: 2/22/95

3. TEST MATERIAL: Glyphosate 41%

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
81-2, Rat, Bio/ dynamics, 4547-87, 10/10/94	434345-02	LD50 greater than 5000 mg/kg	IV	A
81-5, Rabbit, Bio/ dynamics, 4548-87, 10/10/94	434345-04	No irritation at 72 hours	IV	A
81-6, Guinea pig, Pharmaco LSR, 94-1006, 10/7/94	434049-02	Non-sensitizer	---	A

Core Grade Key:

A = Acceptable
S = Supplementary
U = Unacceptable