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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

December 21, 2007

MEMORANDUM:

Subject: EPA Reg. No.: 352-516/DuPont Chlorsulfuron Technical
DP Barcode: 347587
Case No.: 0631

From: Marianne Lewis, Biologist **[sign. M.Lewis 12/21/07]**
Product Reregistration Branch
Special Review and Reregistration Division (7508C)

To: Bonnie Adler, CRM
Product Reregistration Branch
Special Review and Reregistration Division (7508C)

Applicant: E.I. du Pont de Nemours & Co.
DuPont Agricultural Products
Walker's Mill, Barley Mill Plaza
Wilmington, DE 19880-0038

FORMULATION FROM EPA Reg. No. 352-516 LABEL:

	% by wt.
Active Ingredient(s):	
Chlorsulfuron	98.0%
Inert Ingredient(s):	2.0%
Total	100.0%

BACKGROUND: In the 8 month response to the Chlorsulfuron RED, the registrant has submitted acute toxicity studies and a skin sensitization waiver request to support the reregistration of their product, EPA Reg. No. 352-516. The MRID's are as follows: 31406 (81-1), 31411 (81-2), 86825 (81-3), 31414 (81-4), 458337-04 (81-5). The studies were conducted by Haskell Laboratory for Toxicology & Industrial Medicine, DuPont Co. The test material used in each of the studies was the subject product.

RECOMMENDATIONS:

- Three (81-1, 81-2, 81-5) of the acute toxicity studies submitted are acceptable to support the reregistration of EPA Reg. No. 352-516.
- The skin sensitization study is waived. The subject product will be classified as a non sensitizer.
- The acute inhalation study is unacceptable. A new study should be submitted or cited.
- The primary eye irritation study is unacceptable. However, based on the information contained in the study, the Agency will classify the subject product as Toxicity Category II. If the registrant disagrees with this classification then a new study performed with the subject product should be cited or submitted for review.

Procedural Deviations:

Acute Inhalation Study (81-3): The particle sizes (MMADs) in this study ranged from 5.8 – 6.1 μm. The Agency's acceptable range for particle sizes is 1 – 4 μm. Any particles outside of the acceptable range will not reach the deep regions of the lungs which is the objective. This study is unacceptable. A new study conducted with the subject product should be cited or submitted.

Primary Eye Irritation Study (81-4): Only two animals were tested and one of the two was used as a 'washed' eye, meaning that the test material was only in the eye for 30 seconds prior to being washed out. This is unacceptable. The minimum number of animals to be used in this test is three (all unwashed – having the test material in the eyes for 24 hours prior to having it rinsed out). If a product is corrosive or the lab suspects it would be corrosive then one animal is sufficient. Another deviation is that the lab did not utilize a UV light when doing the sodium fluorescein method. Sodium fluorescein staining is not a mandatory procedure, but, if the lab does not use the UV light to detect the staining then the Agency will classify the study as unacceptable. It was noted in the report that both the washed and the unwashed eyes had fluffy debris at the bottom of the pupil-iris junction lasting through day 13. This is not normally seen in the eye studies seen by the Agency, indicating that this chemical related. Therefore, the Agency will classify the subject product as Toxicity Category II for the primary eye irritation study. If the registrant disagrees with this classification then a new primary eye irritation study should be conducted on the subject product and submitted for review.

The acute toxicity profile for EPA Reg. No. 352-516 is currently:

Acute Oral	IV	Acceptable
Acute Dermal	III	Acceptable
Acute Inhalation		Unacceptable
Primary Eye	II	Unacceptable
Primary Dermal	IV	Acceptable
Skin Sensitization	non sensitizer	Waived

NOTE: The labeling will be completed upon receipt of the required information.

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

Product Manager: Jim Tompkins, 25
MRID No.: 31406

Reviewer: Marianne Lewis
Study Completion Date: 8/17/79
Report No.: 399-79

Testing Facility: DuPont Co.
Author: G. Kennedy

Quality Assurance (40 CFR §160.12): conducted prior to GLP

Test Material: Chlorsulfuron, about 95%, suspended in corn oil

Species: ChR-CD rat
Age: young adult
Weight: not given
Source: not given

Conclusion:

1. **LD_{50} (mg/kg):** males: 5545 mg/kg (4723 - 6648 mg/kg)
   females: 6293 mg/kg (4113 - 9524 mg/kg)

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

Procedure (Deviations from §81-1): none

Results:

Dose mg/kg	(number deaths/number tested)		
	Males	Females	Combined
4000	1/10	3/10	4/20
5000	4/10	5/10	9/20
6000	7/10	3/10	10/20
7000	7/10	3/10	10/20
7500♀		8/10	
10000♀		8/10	

Observations:

Dose mg/kg	Time of Death*	Clinical Observations
4000		Diarrhea, wet/stained perineal area, salivation, stained face, hunched posture, lethargy
5000		Diarrhea, wet/stained perineal area, salivation, stained face, hunched posture, lethargy, eyes half closed, lacrimation, gasping
6000		Wet/stained perineal area, stained face, hunched posture, eyes half closed, weakness, piloerection, unkempt fur
7000		Wet/stained perineal area, stained face, hunched posture, eyes half closed, lethargy, prostration, chromodacryorrhea, hematuria, diarrhea
7500		Wet/stained perineal area, stained face/feet/body, hunched posture, eyes half closed, lethargy, chromodacryorrhea, weakness
10000		Diarrhea, Wet/stained perineal area, stained face, chromodacryorrhea, piloerection

*all deaths occurred w/in 1 – 4 days after dosing with moderate weight losses seen in the first 4 days and sporadic weight losses seen from day 5 to end of study.

Gross Necropsy: No observable abnormalities noted

Dose mg/kg	Gross Necropsy Observations
4000	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air
5000	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air, hydronephrosis, corneal opacity, discolored pancreas
6000	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air, small discolored testis
7000	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air, hydronephrosis, thick horns of uterus, oily material on axillary region skin
7500	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air, corneal opacity, yellow fluid in stomach
10000	Small pink thymus w/dark red mottling, dark heavy liver, heavy hyperinflated discolored lungs, small discolored spleen, g.i. tract filled w/fluid – distended w/air, corneal opacity,

DATA REVIEW FOR ACUTE DERMAL TOXICITY (§81-2, 870.1100)

Product Manager: Jim Tompkins, 25
MRID No.: 31411

Reviewer: Marianne Lewis
Study Completion Date: 8/24/79
Report No.: 415-79

Testing Facility: DuPont Co.
Author: G. Kennedy

Quality Assurance (40 CFR §160.12): conducted prior to GLP

Test Material: Chlorsulfuron, about 95%, moistened w/physiological saline
Species: albino rabbit
Weight: not given
Age: young adult
Source: not given

Summary:

1. **LD_{50} (mg/kg):** > 2000 mg/kg

2. **Toxicity Category:** III **Classification:** Acceptable

Procedure (Deviations From §81-2): none

Results: **Reported Mortality**

Dosage (mg/kg)	(number deaths/number tested)		
	Males	Females	Combined
2000	1/5		
3400	0/10	0/10	0/20

Observations: Twenty four hours prior to application of the test material the dorsal area and trunks were clipped free of hair. The test material was moistened with physiological saline. The test material was then applied to the abraided test sites under two 3 x 3 inch 12-ply gauze pads opened to full length. The trunks were then wrapped with Saran Wrap, Kling gauze bandage and Elastoplast adhesive bandage. After 24 hours, the wraps and pads were removed and the test sites were washed with water and dried.

Dose mg/kg	Time of Death	Clinical Observations
2000	1/5 on day 5	All had initial weight loss. Decedent – had skin irritation at test site
3400	N/A	Diarrhea, skin irritation at test site

Gross Necropsy Findings: Only 4 animals were examined for necropsy – no observable abnormalities were noted.

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

Product Manager: Jim Tompkins, 25
MRID No.: 86825

Reviewer: Marianne Lewis
Study Completion Date: 3/18/80
Report No.: 129-80

Testing Facility: DuPont Co.
Author: G. Kennedy

Quality Assurance (40 CFR §160.12): conducted prior to GLP

Test Material: Chlorsulfuron, about 95%,

Species: ChR-CD rat
Weight: males = 257 - 294 g; females = 210 - 259 g
Age: young adult
Source: not given

Summary:

Classification: Unacceptable

Procedure (Deviation From §81-3):

- MMADs exceed acceptable range

Results: **Reported Mortality**

Exposure Concentration	(number deaths/number tested)		
	Males	Females	combined
2.9 – 12.0 mg/L	0/10	0/10	0/20

Chamber Atmosphere		
Dose Level mg/L	MMAD	GSD
2.9 – 12.0	5.8 µm 6.1 µm	

Chamber Environment	Dose Level mg/L
	2.9 – 12.0
Chamber Volume	30 L
Airflow	Not given
Temperature (˚C)	22 – 23
Relative Humidity %	Not given

Clinical Observations: No observable abnormalities were noted.

Gross Necropsy Findings: Only 6 of the 20 test animals were subjected to necropsy. 6/6 chronic rhinitis, 1/6 focal atrophy of nasal gland, 2/6 focal squamous metaplasia of nasal mucosa, 1/6 cystic dilatation of submucosal glands of trachea, 1/6 interstitial pneumonia of lungs, 1/6 focal interstitial nephritis of kidneys, 1/6 mineralization in tubular lumens of kidneys, 1/6 pregnant

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

Product Manager: Jim Tompkins, 25
MRID No.: 31414

Reviewer: Marianne Lewis
Study Completion Date: 10/8/76
Report No.: 744-76

Testing Facility: DuPont Co.
Author: R. Morrow

Quality Assurance (40 CFR §160.12): conducted prior to GLP

Test Material: Chlorsulfuron, about 95%,
Dosage: 10 mg
Species: albino rabbit, 2 used
Sex: not given
Weight: not given
Age: not given
Source: not given

Summary:

Classification: Unacceptable

Procedure (Deviations From §81-4):

- Not enough animals tested
- UV light not used for sodium fluorescein staining

Results:

One rabbit eye was not washed. Other rabbit eye washed 30 seconds after instillation of test material for 1 minute. No corneal opacity was seen and no iritis was seen. From 1 to 4 hours, mild to minimal redness seen in both, minimal swelling in both and mild to minimal discharge seen in both.

Small clumps of fluffy debris were noticed in both treated eyes at the bottom of the pupil-iris junction. These persisted through day 13.

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

Product Manager: Jim Tompkins, 25
MRID No.: 458337-04

Reviewer: Marianne Lewis
Study Completion Date: 4/25/01
Report No.: DuPont-5994

Testing Facility: DuPont Co.
Author: C.Finlay

Quality Assurance (40 CFR §160.12): included

Test Material: Chlorsulfuron, 97.18%, white solid

Dosage: 0.5 g
Species: New Zealand albino rabbit
Age: young adult
Sex: 6 males
Weight: 1419 – 2092 g
Source: Covance Research Products

Summary:

1. **Toxicity Category:** IV **PII** = 0.46

2. **Classification:** Acceptable

Procedure (Deviations From §81-5): none

Results: Twenty four hours prior to application of the test material the scapular to lumbar region of the backs were clipped free of hair. The test material was moistened with approx. 2 mL of deionized water to form a thick paste which was applied to the intact test site (6 cm^2) and covered with a 2-ply, 1 x 1 inch square gauze pad secured with non-irritating tape. The pads and trunks were then overwrapped with porous tape and further secured with waterproof tape. After 4 hours the pads and wrappings were removed and the test sites were washed with warm water and patted dry.

At 1 hr., 1/6 very slight erythema, 4/6 well defined erythema, & 1/6 very slight edema. At 24 hrs., 1/6 very slight erythema. By 48 hrs., all had cleared.