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

007783

FEB 26 1990

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 524-EUP-69. MON-15100 (a.i.). Request for extension of Experimental Use Permit 524-EUP-69 (Dithiopyr Formulation on Turf) with new labeling for MON-15151 formulation and use of an alternate EC formulation: MON-15104

Tox. Chem. Number: 717C
Project Number: 9-1951
Record Number: 249202

To: Robert Y Ikeda, PM 23
Registration Division (H7505C)

From: Paul Chin, PhD
Section 2
Toxicology Branch I
Insecticide and Rodenticide Support (IRS)
Hazard Evaluation Division (H7509C)

Paul Chin 2/6/90

Thru: Marion P Copley, DVM, DABT
Section Head
Section 2, Toxicology Branch I (IRS)
Hazard Evaluation Division (H7509C)

Karl Baetcke, PhD.
Branch Chief
Toxicology Branch I (IRS)
Health Evaluation Division (H7509C)

K. P. Baetcke 2/15/90

Conclusions:

The Toxicology Branch I (IRS) has no objections to granting Experimental Use Permit 524-EUP-69 for both MON-15151 and MON-15104 formulations. The acute oral, acute inhalation, and acute dermal toxicity studies demonstrated that MON-15151 has low acute toxicity. However, MON-15151 is a severe dermal and eye irritant. All acute toxicity studies demonstrated that MON-15104

1 of 36

has low acute toxicity. Adequate precautions are described on the labels for both formulations, and no additional toxicity data are required prior to registration of the EUP. A repeat acute inhalation study with MON-15151 (R. D. No. 942 and MRID No. 41135602) has not been adequately reported and received core-supplementary classification (see DER attached). An acute inhalation study with MON-15104 was also supplementary. However, because of the low toxicity of MON-15151 and MON-15104 determined in other acute studies, the formulation products MON-15151 and 15104 are unlikely to be a significant hazard under the normal use conditions described in the application.

Action Requested:

Monsanto has applied for an extension of 524-EUP-69 to allow the continuation of testing of MON-15151 and MON-15104 (a new formulation) from October 24, 1989 until November 1, 1990.

Review the acute toxicity studies described below and determine any additional toxicity data requirements and/or the adequacy of the proposed label prior registration of the EUP for the use of MON-15151 and MON-15104 formulations.

Introduction:

The sponsor, Monsanto Co., has applied for an EUP for the use of MON-15151 (dithiopyr end-use formulation under the Dimension Turf Herbicide trade name) to control annual grass and broad leaf weeds in turf grass in 21 states on 1333 acres (not to exceed 4000). The application rates will vary from 0.25 to 1.5 lbs. a.i. per acre. Professionally qualified Monsanto employees will supervise the program and maintain records of the application sites of MON-15151. MON-15151 is to be applied by these Monsanto employees or by professional lawn care operators who participate in the EUP program.

On October 24, 1988, the Agency granted the EUP (524-EUP-69) for MON-15151 formulation for one year and allowed 1000 pounds a.i. to be applied to a maximum of 1333 acres of turf.

MON-15100 and MON-7200 are Monsanto designations for the same ingredient,ie., dithiopyr [3,5-pyridine-dicarbothioic acid, 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-S,S-dimethyl ester]. MON-15100 and MON-7200 are the designations for the active ingredient for registration in the United States and outside the United States, respectively.

2

Supporting Data:

Technical MON-7200 and MON-15151 Formulation

All toxicology data required for this Experimental Use Permit are acceptable as previously indicated (see memorandum from Anderson to Mountfort/Ikeda, dated October 13, 1988, HED Document No. 006873).

The personnel associated with the EUP and the application of MON-15151 are stated to be professional qualified Monsanto employees and will either make the application themselves or it will be applied by professional lawn care operators participating in the EUP. These workers should be advised of the potential hazards of new chemicals, and take the appropriate precautions.

The label is adequate.

Inert(s) clearance 180.1001 will be evaluated by the Registration Division.

Although the inhalation study is acceptable for the registration of this EUP, this acute inhalation study must be upgraded to core-minimum, in addition to the other requirements (See 40 CFR 158.135), prior to final registration of the product for general consumer use.

Thirteen acute toxicity studies on MON-7200 (the technical grade), and MON-15151 (the formulated product) in support of the EUP have been reviewed previously as indicated above. For each study, the study type/test substance/species/study number, accession number, conclusion, toxicity category, and core classification are listed below.
NOTE: A repeat inhalation study with MON-15151 (MRID No. 411356-02, Study No. 89-8189/BD-89-42) has not been adequately reported and received core-supplementary classification.

Technical MON-7200

1. Acute Oral Toxicity/Rat/MON-7200/87-0045/ET-87-121

MRID number 406386-07
LD50 > 5000 mg/kg.
Toxicity category IV
Core classification is minimum

3

2. Acute Oral Toxicity/Mouse/MON-7200/87-0046/ET-87-122

MRID number 406386-08
LD50 > 5000 mg/kg
Toxicity category IV
Core classification is minimum.

3 Acute Dermal Toxicity/Rat/MON-7200/87-0047/ET-87-123

MRID number 406386-09
LD50 > 5000 mg/kg
Toxicity category III
Core classification is minimum

4. Acute Inhalation Toxicity/Rat/MON-7200/87-0048/ET-87-124

MRID number 406386-10
LD50 > 5.98 mg/l
Toxicity category III
Core classification is minimum

5. Primary Eye Irritation/Rabbit/MON-7200/4313-87/BD-87-131.
MRID number 406386-11
No corneal opacity; irritation reversible within 7 days.
Toxicity category III
Core classification is minimum

6. Primary Dermal Irritation/Rabbit/MON-7200/4312-87/BD-87-131.
MRID number 406386-12
Mild or slight irritation at 72 hours.
Toxicity category III
Core classification is minimum

7. Dermal Sensitization/Guinea Pig/MON-7200/4314-87/BD-87-130.
MRID number 406386-13
MON-7200 is not a dermal sensitizer in this study.
Toxicity category NA
Core classification is minimum

MON-15151 (Formulation)

8. Acute Oral Toxicity/Rat/MON-15151/4195-87/BD-87-132.
MRID number 406386-14
LD50 = 4100 mg/kg in males and 3000 mg/kg in females.
Toxicity category III
Core classification is minimum

9. Acute Dermal Toxicity/Rabbit/MON-15151/4196-87/BD-87-132.
MRID number 406386-15
LD50 > 5000 mg/kg
Toxicity category III
Core classification is minimum

10a. Acute Inhalation Toxicity/Rat/MON-15151/ML-87-145/EHL-87093
MRID number 406386-16
LC50 >3.5 and <5.0 mg/l for males and 3.3 mg/l for females.
Tentative Toxicity category III
Core classification is supplementary

10b. Acute Inhalation Toxicity/Rat/MON-15151/89-8189/BD-89-42
MRID number 411356-02
LC50 11 mg/l for males and 8.9 mg/l for females.
Toxicity category IV
Core classification is supplementary

11. Primary Eye Irritation/Rabbit/MON-15151/4198-87/BD-87-132.
MRID number 406386-17
Corneal corrosion reversible within 21 days, and possibly within 7 days; corneal opacity reversible within 7 days; irritation reversible within 7 days.
Toxicity category II
Core classification is minimum

12. Primary Dermal Irritation/Rabbit/MON-15151/4197-87/BD-87-132.
MRID number 406386-18
MON-15151 caused severe dermal irritation at 72 hours.
Toxicity category II
Core classification is minimum

13. Dermal Sensitization/Guinea Pig/MON-15151/4199-87/BD-87-133.
MRID number 406386-19
MON-15151 is a dermal sensitizer in this study.
Toxicity category NA
Core classification is minimum

MON-15104 (Formulation)

All toxicology data required for this Experimental Use Permit are acceptable.

The personnel associated with the EUP and the application of MON-15104 are stated to be professional qualified Monsanto

5

employees and will either make the application themselves or it will be applied by professional lawn care operators participating in the EUP. These workers should be advised of the potential hazards of new chemicals, and take the appropriate precautions.

The label is adequate.

Inert(s) clearance 180.1001 will be evaluated by the Registration Division.

Although the inhalation study is acceptable for the registration of this EUP, this acute inhalation study must be upgraded to core-minimum, in addition to the other requirements (See 40 CFR 158.135), prior to final registration of the product for general consumer use.

Six acute toxicity studies on MON-15104 in support of the EUP have been reviewed. For each study, the study type/test substance/species/study number, MRID number, conclusion, toxicity category, and core classification are listed below.

1. Acute Cral Toxicity/Rat/MON-15104/5352-88/BD-89-21

   MRID number 411300-04
   LD50 > 5000 mg/kg.
   Toxicity category IV
   Core classification is minimum

2. Acute Dermal Toxicity/Rabbit/MON-15104/5353-88/BD-89-21

   MRID number 411300-05
   LD50 > 5000 mg/kg
   Toxicity category IV
   Core classification is minimum

3. Acute Inhalation Toxicity/Rat/MON-15104/89098/MSL-9084

   MRID number 411300-06
   LD50 3.4 mg/l for males and 4.5 mg/l for females
   Toxicity category III
   Core classification is supplementary

4. Primary Eye Irritation/Rabbit/MON-15104/5355-88/BD-89-21.

   MRID number 411300-07
   No corneal opacity; irritation reversible within 24 hours
   Toxicity category IV
   Core classification is minimum

5. Primary Dermal Irritation/Rabbit/MON-15104/5354-88/BD-89-21.

   MRID number 411300-08
   Very slight to slight irritation at 72 hours.
   Toxicity category IV
   Core classification is minimum

6. Dermal Sensitization/Guinea Pig/MON-15104/5356-88/BD-89-21.
   MRID number 411300-09
   MON-15104 is not a dermal sensitizer in this study.
   Toxicity category NA
   Core classification is minimum

1

Primary Reviewer: Paul Chin, PhD Paul Chin 2/6/90 007783
Section 2, Tox. Branch 1 (IRS) (H7509C)
Secondary Reviewer: Marion Copley, DVM, DABT, Section Head
Section 2, Tox. Branch 1 (IRS) (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation (81-3)/Rat/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 411356-02

TEST MATERIAL: MON-15151, 13.5% MON 7200 (a.i.)

SYNONYMS: MON-15151 on Turf, 13.5% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Bio/dynamics, Inc., P.O. Box 2360, Mettlers Road, East Millstone, NJ 08875-2360

STUDY NO: 89-8189/BD-89-42

REPORT TITLE: Acute Inhalation Toxicity Study of MON-15151 in the Rat

AUTHOR(S): G. M. Hoffman

REPORT ISSUED: May 23, 1989.

CONCLUSIONS: MON-15151 was administered in an acute inhalation study for 4 hours to 5 rats per sex at 3.1, 5.5, or 6.9 mg/l. The LC50 was found to be 8.9 mg/l for females and 11 mg/l for males. The particle size of MON-15151 was reported as a mass median aerodynamic diameter (MMAD) of 1.6-2.8 micrometers (um) with a geometric standard deviation (GSD) of 1.9-2.4. Greater than 96% of the particles had a MMAD of 10 um or less and 10 to 21% of the test material had a MMAD of 1 um or less. Most of the animals which died, died within 2-5 days.

Toxicity category: IV.
Core classification: Supplementary because the description of "breathing zone" of the animals was not presented in sufficient detail to be assured that the test material was uniformly distributed to the animals within the chamber. However, the study may be upgradable if required additional information is submitted
LC50 = 11 mg/l for males.
LC50 = 8.9 mg/ml for females.

A. MATERIALS:

1. Test compound: MON-15151, 13.5% MON 7200 the active ingredient. Description amber liquid, Lot # DAY 8901-31F, Purity 13.5%.

2. Test animals: Species: Rat, Strain: Sprague Dawley, Age:8-11 wk, Weight: Males 248-347 g, Females 221-263 g, Source:Charles River Breeding Laboratories, Inc., Raleigh, NC 27610. Acclimatized 1 to 3 weeks.
3. Environment: Temperature - 70-80 degrees F, Humidity - 16-53%, Light:dark = 12:12.

4. Inhalation conditions: Exposure was by whole body (Fig 1) for 4 hours. The exposure chamber was a 100 liter Plexiglas with a glass front. Test chemicals were generated by a spray atomizer. Air flow rate was regulated at 20 l/min.

B. METHODS:

Concentrations of MON-15151 in the breathing zone were determined gravimetrically once per hour during each 4 hour exposure through removal of samples from the exposure chamber. The particle size range in the test atmosphere was determined in an Delron DCI-6 or an Anderson cascade impactor once per hour during each 4 hour exposure. The MMAD, GSD, and percent of particles 1 um or less and 10 um or less were calculated based on the amount of material collected on the impactor stages (glass slides) using a graphical analysis of an assumed lognormal distribution.

Nominal atmospheric concentrations was determined by the total amount of test material delivered to the chamber divided by the total volume of air passing through the chamber.

- Animals were observed hourly while in the chambers(if possible), immediately after dosing, twice daily for mortality and morbidity, and daily for a total of 15 days.
- Rats were weighed on day 1, 2, 3, 5, 8, and 15.
- Gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed on day 15. Gross necropsy included the nasal passages, trachea, external surface, all orifices, the cranial cavity, carcass, the brain and spinal cord, the thoracic, abdominal and pelvic cavities and their viscera, and the cervical tissues and organs.
- Lung tissues were examined histopathologically.
- Doses given and lethality are presented in the table under results.
- The quality assurance statement was signed by W. Harrison, Supervisor of Quality Assurance, on May 22, 1989.

9

C. RESULTS AND DISCUSSION:

The particle size of the test material was reported: MMAD of 1.6 to 2.8 um with a GSD of 1.9 to 2.4. The report stated that greater than 96% of the test material had a MMAD of 10 um or less in diameter and 10 to 21% of the test material had a MMAD of 1 um or less.

Test group	Gravimetrical conc. of MON-15151 mg/l	Number animals that died (Day of death) Male	Total	Female	Total
1. Low	3.1	1 (3)	1/5	1 (3)	1/5
2 Mid	5.5	0	0/5	2 (3)	2/5
3. High	6.9	2 (3,5)	2/5	2 (2)	2/5

The nominal concentrations of MON 15104 were 14, 17, and 37 mg/l for the 3.1, 5.5, and 6.9 mg/l exposure levels, respectively. The differences in nominal and gravimetric exposure concentrations are attributed to impaction or sedimentation of the aerosol on the surfaces in the exposure chamber.

Clinical observations during exposure and immediately or during 2 hours after exposure in most animals (70-90% of animals) included respiratory irritation (labored breathing and gasping), secretary irritation (lacrimation, nasal discharge, and salivation), and decreased activity/prostration. A few animals (10-30% of animals) exhibited reduced righting reflex, reduced muscle tone, ataxia and tremors. During the 7-day post-exposure period, surviving animals showed signs of toxicity similar to those seen immediately following exposure after which signs of toxicity subsided. However, 3-4/6 animals in the high dose group exhibited a corneal irregularity throughout the 14-day observation period that progressed to a corneal opacity in 3/6 animals during the second week.

The mean body weight for animals at all exposure levels were down significantly up to day 5 post exposure. However, all surviving animals were gaining weight and exceeded their pre-exposure weight by termination of the study.

Most of the animals which died, died within 2-5 days. Death was probably caused predominantly by respiratory failure, or possibly by CNS effects.

Gross necropsy indicated that the incidence of discolored lungs was higher among the spontaneously dying animals (5/8) comparing to the surviving animals (5/22). Microscopic examination of the lungs showed vascular congestion, pulmonary hemorrhages, pulmonary edema, and inflammation. These effects were most pronounced in the spontaneously dying animals at the 6.9 mg/l exposure group.

10

This study is rated core-supplementary because the description of "breathing zone" of the animals where samples for gravimetric determination of MON-15151 exposures were drawn was not presented in sufficient detail to be assured that the test material was uniformly distributed to the animals within the chamber. A clear description of the "breathing zone" and the experimental evidence demonstrating the uniform distribution of the test material is requested. The study report contained no data on the uniform distribution of the test material. However, the study may be upgradable if required additional information is submitted.

The Toxicity Category is IV.

11

Dithiopyr Science Reviews

Page __12__ is not included in this copy.

Pages _____ through _____ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

007783

Primary Reviewer: Paul Chin. PhD Paul Chin 1/25/90
Section 2, Tox. Branch 1 (IRS) (H7509C)
Secondary Reviewer: Marion Copley, DVM, DABT, Section Head
Section 2, Tox. Branch 1 (IRS) (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral (81-1)/Rat/MON-15104

TOX. CHEM. No: 717C

MRID No: 411300-04

TEST MATERIAL: MON-15104, 13.6% MON-15100(a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Bio/dynamics, Inc., P.O. Box 2360, Mettlers Road, East Millstone, NJ 08875-2360

STUDY NO: 5352-88/BD-89-21

REPORT TITLE: Acute Oral Toxicity Study in Rats. Test Material: MON-15104

AUTHOR(S): D. L. Blaszcak

REPORT ISSUED: May 10, 1989

CONCLUSIONS: MON-15104 was administered by gavage to 10 Sprague Dawley rats per sex per dose level at 2500, 3600 or 5000 mg/kg in an oral acute toxicity study. Clinical signs on the day of dosing included fecal staining (1 female at 3600 mg/kg and 1 female at 5000 mg/kg) and urinary staining and soft stool (1 female at 5000 mg/kg). Decreased food consumption was noted in animals at 2500 mg/kg and in 8 animals at 3600 mg/kg or 5000 mg/kg on the day after dosing. All animals were free of significant signs of toxicity from day 2 through day 14. No deaths occurred at 2500, 3600, or 5000 mg/kg.

Toxicity category: IV.
Core classification: Minimum.
LD50 > 5000 mg/kg for males and females.

13

A: MATERIALS:

1. Test compound: MON-15104, 13.6% MON-15100 the active ingredient. Description, amber liquid, Batch # XLI-496, Purity 13.6%.

2. Test animals: Species: Rat, Strain: Sprague-Dawley, Age: 9-12 wk, Weight: Males 255-350 g, Females 232-270 g, Source: Charles River Breeding Laboratories Inc., Wilmington, MA 01887. Acclimatized 21 days.

B. METHODS:

- Rats were fasted overnight before dosing.
- Test material was administered orally by gavage. The specific gravity of MON-15104 and volume of the doses were 960.9 mg/ml and 2.6, 3.7, and 5.2 ml for the 2500, 3600, and 5000 mg/kg dose levels, respectively. It is assumed that the doses administered were presented as the weight of MON-15104/kg and not weight of the active ingredient/kg body weight of the test animal.
- Animals were observed 1, 2, and 4 hours after dosing, and daily for a total of 14 days.
- Rats were weighed on day 0, 7, and 14.
- Gross necropsy was performed on all survivors which were sacrificed on day 14.
- Doses given and lethality are presented in the table under results and discussion.
- Quality Assurance Statement was signed by W. M. Harrison, Supervisor of Quality Assurance, on May 10, 1989.

C. RESULTS AND DISCUSSION:

Test Group	Dose of MON-15104 mg/kg	Number Animals that Died (day of death) Male	Total	Female	Total
1. Low (LDT)	2500	0	0/10	0	0/10
2. Mid (MDT)	3600	0	0/10	0	0/10
3. High (HDT)	5000	0	0/10	0	0/10

Animals were sacrificed on day 14.

14

Clinical signs on the day of dosing included fecal staining in 1 female at 3600 mg/kg dose group and urinary and fecal staining and soft stool in 1 female at 5000 mg/kg dose group. Decreased food consumption was noted in 3 animals at 2500 mg/kg and in 8 animals at 3600 mg/kg or 5000 mg/kg on the day after dosing. One male at 5000 mg/kg had an opacity in the left eye from day 2 through the termination of the study (day 14). All animals were free of significant signs of toxicity from day 9 through day 14. Changes in animals killed after 14 days were similar to those seen in control animals killed by CO_2 inhalation.

No deaths occurred at 2500, 3600, or 5000 mg/kg. Since these guidelines allow a limit dose of 5000 mg/kg, a repeat study is not required. The LD50 was stated in the report to be > 5000 mg/kg.

15

*Primary reviewer: Paul Chin, PhD. Paul Chin 1/25/90
Section 2, Tox. Branch 1 (IRS)(H7509C).
Secondary reviewer: Marion Copley, DVM, DABT, Section Head.
Section 2, Tox. Branch 1 (IRS)(H7509C). M Copley 1/31/90

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity (81-2)/Rabbit/MON-15104. 007783

TOX. CHEM. No.:717C

MRID No.: 411300-05.

TEST MATERIAL: MON 15104, 13.6% MON 15100 (a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Co.

TESTING FACILITY: Bio/dynamics, Inc., P.O. Box 2360, Mettlers Road, East Millstone, NJ 08875-2360

STUDY NO.: 5353-88/BD-89-21.

REPORT TITLE: MON 15104 Acute Dermal Toxicity Study in rabbits: Test Material: MON-15104

AUTHOR(S): D L Blaszcak

REPORT ISSUED: May 10, 1989

CONCLUSIONS: MON-15104 was administered dermally to 5 rabbits per sex for 24 hours at 5000 mg/kg. No effects were observed; no adverse clinical signs, weight gain reduction, mortality, or effects at necropsy were detected.

Toxicity category: IV.
Core classification: Minimum.
LD50 > 5000 mg/kg for males and females.

A. MATERIALS:

1. Test compound: MON 15104, 13.6% MON-15100 the active ingredient, Description amber liquid, Batch # XLI-496, Purity 13.6%, Density 0.9609 g/ml

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age: 8 wk, Weight: Males 2.4-2.6 kg, Females 2.5-2.7kg, Source: Hazleton Research Animals, Inc., Denver, PA. Acclimatized 37 days.

16

B. METHODS:

- Test material, 5000 mg/kg, was administered dermally to 5 rabbits per sex. The test material was applied at 5.2 ml/kg, specific gravity of 960.9 mg/ml. The test material was applied directly to the shaved backs of the test animal, wrapped with gauze held in place by a plastic sleeve for 24 hours. The test animals were fitted with Elizabethan collars. The remaining test material was wiped from the site with a dry paper towel after 24 hours. It was stated in the report that the test material required no preparation before application. About 10% of the body surface area was shaved, but the area covered by the test material was not stated. It was implied that 10% of the body surface area received the test material.
- Animals were observed 1, 2, and 4 hours after dosing, and daily for a total of 14 days.
- Rabbits were weighed on day 0, 7, and 14.
- Gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed on day 14.
- Doses given and lethality are presented in the table under results and discussion.
- Quality Assurance Statement was signed by William Harrison, Supervisor of Quality Assurance Unit, on May 10, 1989.

C. RESULTS AND DISCUSSION:

Test group	Dose in mg/kg	Number animals that died (Day of death) Male	Total	Female	Total
1.	5000	0	0/5	0	0/5

All animals were terminated by day 14.

No clinical signs were noted in any animal.

At day 7, most animals exhibited slight body weight lossess (0.1-0.2 kg), but all gained weight between day 7 and 14.

At gross necropsy, one female exhibited lung discoloration and no detectable effects were found in 9 remaining animals at terminal sacrifice.

Since no animals died at 5000 mg/kg, a repeat test is not required. The guidelines allow a limit dose of 2000 mg/kg.

The LD50 was stated in the report to be > 5000 mg/kg.

17

*Primary reviewer: Paul Chin, PhD. Paul Chin 2/6/90
Section 2, Tox. Branch 1 (IRS)(H7509C).
Secondary reviewer: Marion Copley, DVM, DABT, Section Head.
Section 2, Tox. Branch 1 (IRS)(H7509C). [illegible] 2/5/90

007783

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation (81-3)/Rat/MON-15104.

TOX. CHEM. No.:717C

MRID No.: 411300-06

TEST MATERIAL: MON-15104, 13.6% MON 15100 (a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Monsanto Environmental Health Lab., 645 S. Newstead Ave., St. Louis, MI 63167

STUDY NO.: 89098/MSL-9084.

REPORT TITLE: Acute Inhalation Study of MON-15104.

AUTHOR(S): CL Bechtel.

REPORT ISSUED: May 26, 1989.

CONCLUSIONS: MON-15104 was administered in an acute inhalation study for 4 hours to 5 rats per sex at 1.8, 3.7, or 6.7 mg/l. The LC50 was found to be 4.5 mg/l for females and 3.4 mg/l for males. The particle size of MON-15104 was reported as a mass median aerodynamic diameter (MMAD) of 2.8-3.1 micrometers (um) with a geometric standard deviation (GSD) of 1.9. Greater than 97-98% of the test material had a MMAD of < 10 um in diameter and 4.4 to 5.2% of the particle sizes had a MMAD of < 1 um in diameter. Most of the animals which died, died within 2-3 days.

Toxicity category: III.
Core classification: Supplementary because 25% of the generated particle size was not < 1 um, and lack of raw data to substantiate the results of evaluation of various aerosol generation systems employed for this study. However, the study may be upgradable if required additional information is submitted.

LC50 = 3.4 mg/l for males.
LC50 = 4.5 mg/l for females.

14

A. MATERIALS:

1. Test compound: MON-15104, 13.6% MON 15100 the active ingredient. Description amber liquid, Batch # XLI-496, Purity 13.6%.

2. Test animals: Species: Rat, Strain: Sprague Dawley, Age:7 wk, Weight: Males 235 g, Females 173 g, Source:Charles River Breeding Laboratory, Portage, MI. Acclimatized NOT STATED.

3. Environment: Temperature - 64-79 degrees F, Humidity - 40-70%, Light:dark = 12:12.

4. Inhalation conditions: Exposure was by whole body (Fig 1) for 4 hours. The exposure chamber was a 300 liter New York University-style stainless steel with pyramidal top and bottom. Exposures were generated by a nebulizer (Laskin-style), Air flow rate was regulated at 69.4-70.4 l/min. Temperature, 25-26 degrees C. Humidity, 57-73%. Oxygen level, 20.5-21.0%.

B. METHODS:

Concentrations of MON-15104 in the breathing zone were determined hourly during each 4 hour exposure through removal of 5 to 20 l of the exposure atmosphere from the chamber, and passing it through acetone in a 25 ml glass impinger. The concentration MON-15100 in the sample war determined by gas chromatography, and the concentration of MON-15104 determined on the bases of 13.6% MON-15100 in MON-15104. The particle size range in the test atmosphere was determined in an Andersen cascade impactor one time during each 4 hour exposure. A sample was drawn for 5 min. at a rate of 1 CFM. The mass collected at each stage was determined gravimetrically and used to determine the MMAD.

Nominal atmospheric concentrations was determined by the total amount of test material delivered to the chamber divided by the total volume of air passing through the chamber.

- Animals were observed hourly while in the chambers(if possible), immediately after dosing, twice daily for mortality and morbidity, and daily for a total of 14 days.
- Rats were weighed on day 0, 2, 7, and 14.
- Gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed on day 14. Organs and tissues examined were the lung, trachea, and nasal cavity.
- If conducted, histology was not reported.
- Doses given and lethality are presented in the table under results.
- The quality assurance statement was signed by Arthur Uelner for the manager of Quality Assurance, on May 25, 1989.

C. RESULTS:

The particle size of the test material was reported as: MMAD of 2.8 to 3.1 um with a GSD of 1.9. The report stated that greater than 97-98% of the test material had a MMAD of < 10 um in diameter and 4.4 to 5.2% of the particle sizes had a MMAD of < 1 um in diameter. Due to the nature of the test material (MON-15104 [redacted] greater than 5.2% mass of particle less than 1 um in size was difficult to achieve. Various aerosol "generation systems evaluated included the Laskin-type flask system (3), Laskin-type tank/syringe drive systems, and various elutriation or particle discrimination methods. However, the system used in this study gave the best results and also provided the highest achievable analytical concentration which is required for acute inhalation studies." The weight percent of the particle size range at each stage of the Anderson impactor was not reported.

The report stated that the high nominal/analytical ratios (6.7 to 16.1) indicate a loss of the test material from the exposure atmosphere due to the observed occurrence of impaction on animals, cages, and the walls of the chamber.

Test group	*Analytical conc. of MON-15104 mg/l	Number animals that died (Day of death) Male	Total	Female	Total
1. Low	1.8	0	0/5	0	0/5
2. Mid	3.7	3 (3-4)	3/5	1 (2)	1/5
3. High	6.7	5 (2-3)	5/5	5 (2)	5/5

Surviving animals was sacrificed on day 14.
* The concentration of MON-15104 was calculated from the analytical concentration MON-15100, and 13.6% MON-15100 in MON-15104. Nominal concentrations of MON 15104 were 12, 52, and 108 mg/l for the 1.8, 3.7, and 6.7 mg/l exposure levels, respectively.

Clinical observations immediately after exposure included labored respiration, red ocular discharge, hypoactivity, red/pink nasal discharge, eyelids partially/completely closed, and salivation. At 1-6 days post exposure, animals demonstrated hypoactivity, labored breathing, rapid respiration, red/pink nasal discharge, swollen mouth, eyelids partially/completely closed, urine stained hair, loss of hair, gasping, rattling sounds, emaciation, and periocular encrustation. At 7-14 days post exposure, the animals demonstrated emaciation and loss of hair.

At day 2 post exposure, the mean body weight for 3.7 and 6.7 mg/l exposure group was down -13 to -34 g and -49 g, respectively. The mean weight for animals at the exposure level of 1.8 mg/l was unchanged. At day 7 post exposure all surviving animals were gaining weight and exceeded their pre-exposure weight, except for one male in 1.8 mg/l exposure group.

Inert ingredient information is not included

Most of the animals which died, died within 2-3 days, and only two animals died at day 4. Death was probably caused predominantly by respiratory failure.

D. DISCUSSION:

MON-15104 administered via inhalation for 4 hours to 5 rats per sex per group at 1.8, 3.7 or 6.7 mg/l, resulted in mortality in all animals at 6.7 mg/l and in 4 animals at 3.7 mg/l. Of the animals which died, 86% died in 2-3 days. Labored breathing, and sensory irritation was the most common observation. At day 2 post exposure, the mean body weight for 3.7 or 6.7 mg/l exposure group was down -13 to -49 g. At day 7 post exposure all surviving animals were gaining weight and exceeded their pre-exposure weigh. The MMAD of the aerosol generated was 2.8-3.1 micrometers, with a GSD of 1.9. Due to the nature of the test material, greater than 5.2% of particles less than 1 um in size was difficult to achieve.

This study adequately demonstrated that MON-15151 has low acute inhalation toxicity for the following reasons:

1. The toxicity category is IV in acceptable acute oral and acute dermal toxicity studies.
2. There was only minor eye irritation and very slight to slight skin irritation demonstrated by acceptable studies.

However, this is rated core-supplementary because 25% of the generated particle size was not < 1 um, and lack of raw data to substantiate the results of evaluation of various aerosol generation systems employed for this study. However, this study may be upgradable if required additional information is submitted.

The Toxicity Category is III.

21

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Primary Reviewer: Paul Chin. PhD Paul Chin 1/25/90
Section 2, Tox. Branch 1 (IRS) (H7509C)
Secondary Reviewer: Marion Copley, DVM, DABT, Section Head
Section 2, Tox. Branch 1 (IRS) (H7509C) MCopley 1/31/90

007783

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation (81-4)/Rabbit/MON-15104.

TOX. CHEM. No.:717C

MRID No.: 411300-07

TEST MATERIAL: MON 15104, 13.6% MON-15100 (a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Bio/dynamics, Inc., Mettlers Road, East Millstone, NJ 08875.

STUDY NO.: 5355-88/BD-89-21

REPORT TITLE: Eye Irritation Study in Rabbits, Test Material: MON 15104.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: May 10, 1989.

CONCLUSIONS: MON-15104 (0.1 ml liquid), was administered to 1 eye of each of 3 female and 3 male rabbits and observed for 72 hours. Slight redness (grade 1), slight chemosis (grade 1), and discharge (grade 2 to 3) was seen at 1 hour after administration which cleared within 24 hours. No other effects were observed at 1, 24, 48, or 72 hours after administration.

Eye Irritation, toxicity category: IV.
Core classification: Minimum.

A. MATERIALS:

1. Test compound: MON 15104, 13.6% MON-15100 the active ingredient, Description amber liquid, Batch # XLI-496, Purity 13.6%, Density 0.9609 g/ml

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age: 8 wk, Weight: NOT REPORTED. Source: Summit View Farms, Hazleton, PA. Acclimatized 27 days.

23

B. METHODS:

- Test material was administered at 0.1 ml liquid in 1 eye, unwashed for 24 hours. Residual material was washed out at 24 hours.
- Animals were observed 1, 24, 48, and 72 hours after dosing, and scored according to the method of Draize (1959).
- Rabbits were not weighed.
- Gross necropsy was not performed.
- Fluorescein used to confirm ulceration or no ulceration.
- Doses given and lethality are presented in the table under results and discussion.
- Quality Assurance Statement was signed by W. Harrison, Supervisor of Quality Assurance on May 10, 1989.

C. RESULTS AND DISCUSSION: (Numbered tables were copied from the submitted report)

		Rating; Time after admin. (hours)			
Rabbit #		1	24	48	72
7254F	Redness	1	0	0	0
	Discharge	2	0	0	0
7255F	Redness	1	0	0	0
	Discharge	3	0	0	0
7256F	Redness	1	0	0	0
	Discharge	2	0	0	0
7257M	Redness	1	0	0	0
	Chemosis	1	0	0	0
	Discharge	3	0	0	0
7258M	Redness	1	0	0	0
	Chemosis	1	0	0	0
	Discharge	2	0	0	0
7259M	Redness	1	0	0	0
	Chemosis	1	0	0	0
	Discharge	2	0	0	0

No other involvement was noted.

Since a negative reaction for chemosis and redness (a positive reaction for chemosis and redness is grade 2 or higher) was seen in all animals at the 1 hour reading, which completely cleared within 24 hours, and no opacity occurred, the toxicity category for eye irritation is IV.

34

Appendix A

Grades for Ocular Lesions

I. CORNEA:

A. Opacity - degree of density: (area most dense taken for reading)

No opacity	0
Slight dulling of normal luster	+ **
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	1 *
Easily discernible translucent areas; details of iris slightly obsured	2 *
Nacrous area, no details of iris visible, size of pupil barely discernible	3 *
Opaque cornea, iris not discernible through opacity	4 *

B. Total area of cornea involved: (Total area exhibiting any opacity, regardless of degree)**

One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

C. Stippling: (appearance of pinpoint roughening)**

No stippling	0
One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

D. Ulceration: (absence of a gross patch of corneal epithelium)

No ulceration	0
One quarter (or less) but not zero	1 **
Greater than one quarter, but less than half	2 **
Greater than half, but less than three quarters	3 **
Greater than three quarters, up to whole area	4 **

II. IRIS:

A. Values:

Normal	0
Slight deepening of the rugae or slight hyperemia of the circumcorneal blood vessels	+ **
Markedly deepened folds (above normal), congestion, swelling, moderate circumcorneal hyperemia or injection (any or all of these or combination of thereof), iris still reacting to slight (sluggish reaction is positive)	1 *
No reaction to light, hemorrhage, gross destruction (any or all of these)	2 *

III. CONJUNCTIVAE:

A. Redness: (refers to palpebral and bulbar conjunctivae)

Vessels normal	0
Some vessels definitely hyperemic (injected above normal)	1
Diffuse, crimson red, individual vessels not easily discernible	2 *
Diffuse beefy red	3 *

B. Chemosis: (lids and/or nictitating membranes)

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2 *
Swelling with lids about half closed	3 *
Swelling with lids more than half closed	4 *

C. Discharge:

No discharge	0
Any amoung different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs and considerable area around eye	3

D. Necrosis or Ulceration or palpebral and bulbar conjunctivae or nictitating membrane**

Not present	0
Necrosis present	N *
Ulceration present	U *

* Score considered positive.
**Not included in EPA grading system, values assigned if findings present.

25

Primary Reviewer: Paul Chin. PhD Paul Chin 1/25/90
Section 2, Tox. Branch 1 (IRS) (H7509C)
Secondary Reviewer: Marion Copley, DVM, DABT, Section Head
Section 2, Tox. Branch 1 (IRS) (H7509C) Marion Copley 2/1/90

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation (81-5)/Rabbit/MON-15104.

TOX. CHEM. No.:717C

007783

MRID No.: 411300-08

TEST MATERIAL: MON 15104, 13.6% MON-15100 (a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Bio/dynamics, Inc., Mettlers Road, East Millstone, NJ 08875.

STUDY NO.: 5354-88/BD-89-21.

REPORT TITLE: Primary Dermal Irritation Study in Rabbits (4-Hour Exposure/Semi-Occlusive Covering) on Test Material: MON 15104.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: May 10, 1989.

CONCLUSIONS: MON-15104, 0.5 ml was administered dermally in a dermal irritation study to two 1 inch squares of shaved skin of 3 rabbits per sex and observed at 0.5, 24, 48, 72 hours, and at 7 and 10 days. Very slight or slight erythema occurred with little or no edema in all animals during the period of 0.5 hours to 7 days after administration. These mild irritation disappeared by day 10 and 2 rabbits demonstrated desquamation on day 10. The primary irritation index of MON 15104 is 1.1.

Toxicity category IV.
Core classification: Minimum.

3k0

A: MATERIALS:

1. Test compound: MON-15104, 13.6% MON-15100 the active ingredient. Description, amber liquid, Batch # XLI-496, Purity 13.6%.

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age:8 wk, Source:Summit Farms, Hazleton, PA. Acclimatization: 27 days.

B. METHODS:

-To approximately 1 by 1 inch square patches of shaved skin at each of two sites per rabbit on 3 rabbits per sex, test material, 0.5 ml, was applied under gauze and rapped with tape for 4 hours. The sites previously had been clipped free of hair. After 4 nours the sites were washed free of test material with gauze and water, and observed and scored (Draize, 1959) at 0.5, 24, 48, and 72 hours after test material was removed. Rabbits were not weighed. Gross necropsy was not performed.

- Quality Assurance Statement was signed by W. Harrison, Supervisor of Quality Assurance on May 10, 1989.

C. RESULTS AND DISCUSSION: (Numbered tables were copied from the submitted report.) Table I presents the results.

At 0.5 hours, 3 of the 6 rabbits demonstrated grade 1 erythema and grade 1 edema. At 24 hours, all rabbits responded with grade 1 erythema and 3 rabbits with grade 1 edema. At both 48 and 72 hours, 5 rabbits responded with grade 1 to 2 erythema and 3 rabbits with grade 1 edema. By day 7, 3 animals responded with grade 1 erythema and 4 with desquamation. By day 10, only 2 female rabbits were responding with desquamation and all animals were free of signs of dermal irritation.

Toxicity category IV.

27

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Section 2, Tox. Branch 1 (IRS) (H7509C)
Secondary Reviewer: Marion Copley, DVM, DABT, Section Head
Section 2, Tox. Branch 1 (IRS) (H7509C) MCopley 2/1/90

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization (81-6)/Guinea Pig/MON-15104.

TOX. CHEM. No.:717C

007783

MRID No.: 411300-09.

TEST MATERIAL: MON 15104, 13.6% MON 15100 (a.i.)

SYNONYMS: MON-15104 on Turf, 13.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Bio/dynamic, Inc., Mettlers Road, East Millstone NJ 08875

STUDY NO.: 5356-88/BD-89-23.

REPORT TITLE: A Closed-patch Repeated Insult Dermal Sensitization Study in Guinea Pigs (Buehler Method), Test Material : MON-15104.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: May 10, 1989.

CONCLUSIONS: MON-15104 was administered dermally to 5 guinea pigs per sex in a induction phase and a challenge phase by the Buehler method. No evidence of dermal sensitization was found, however during the induction phase there was evidence of accumulative dermal irritation, +/- reactions after the third induction. No adverse clinical signs, weight gain reduction, or mortality were observed.

Toxicity category: NA.
Core classification: Minimum.
MON-15104 technical is not a dermal sensitizer in the Buehler Test.

31

A. MATERIALS:

1. Test compound: MON-15104, 13.6% MON-15100 the active ingredient. Description, amber liquid, Batch # XLI-496, Purity 13.6%.

2. Test animals: Species: Guinea Pigs, Strain: Hartely Albino, Age:5-6 wk, Weight: Males 325-385 g, Females 304-382 g, Source:Hazleton Research Animals Inc., Denver, PA. Acclimatized 16 days.

B. METHODS:

- Test material which was reported to require no preparation was administered dermally. A slightly irritating concentration of test material for induction and a non-irritating concentration for challenge was selected from a range-finding study for 24 and 48 hours. The 100% test material was found to be non-irritating for both induction and challenge.

Induction Phase - 0.3 ml of test material, moistened with 0.9% saline, was applied in Hilltop Chambers to the clipped backs of 5 guinea pigs per sex for the test group. The chamber was left in place for 6 hours, after which remaining material was removed from the test site and examined at 24 and 48 hours. This Induction procedure was conducted 3 times over a period of 3 weeks.

Challenge Phase - 14 days after the final induction exposure, similar procedures were conducted one time for 6 hours with each of the 5 guinea pigs from the test group and the control group, but on the other side of the backs used for induction exposure, or control exposure. The control animals had not been previously exposed to the test material. The sites were read after 24 and 48 hours for erythema, with or without edema, necrosis and eschar formation.
- In addition animals were observed weekly.
- Animals were weighed pretest and at termination.
- Gross necropsy was not performed.
- Quality Assurance Statement was signed by W. Harrison, Supervisor of the Quality Assurance Unit, on May 10, 1989.

C. RESULTS: (Numbered tables were copied from the report)

No clinical signs were noted in any animal at either dose level.

Body weight gain of each group was similar.

1. Induction readings - Table II presents the results. Beginning with the third exposure, 7 animals responded with +/- reactions (mild irritation) at 24 hours and 8 animals responded with +/- at the 48 hour reading. These results alone could mean that the test material was causing slight sensitization or accumulative irritation.

33

2. Challenge phase - Tables III and IV present the results from the challenge phase and the irritation control. The challenge with MON 15104 caused grade 1 erythema in 1 animal in the irritation test group at the 48 hour reading and no dermal irritation was observed in any of the irritation control group. The failure of the animals except for one animal to respond to the challenge dose, indicated that MON-15104 is not a sensitizer in this test.

D. DISCUSSION: During the induction phase the animals responded with +/- reactions which was probably due to accumulated irritation because only one animal responded to the challenge dose.

MON-15104 is not a dermal sensitizer in the Buehler Test.

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