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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

Subject: EPA ID # 524-EUP-AO. Experimental Use Permit for the Selective Herbicide MON-15151 on Turf.

Tox. Chem. Number: 717C
Project Number: 8-0907
Record Number: 223193

To: Richard F Mountfort/
Robert Y Ikeda PM 23
Registration Division (TS-767C)

From: David G Anderson, PhD
Section 2
Toxicology Branch 1
Insecticide and Rodenticide Support
Hazard Evaluation Division (TS-769C)

Thru: Marion P Copley, DVM.
Acting Section Head
Section 2, Toxicology Branch 1
Insecticide and Rodenticide Support
Hazard Evaluation Division (TS-769C)

Judith Hauswirth, PhD.
Acting Branch Chief
Toxicology Branch I (IRS)
Health Evaluation Division (TS-769C)

Conclusions:

The Toxicology Branch I (IRS) has no objections to granting Experimental Use Permit 524-EUP-AO after one of the inert ingredients is cleared under 40 CFR 180.1001 (see Supporting Data, page 3 of this memorandum). The acute toxicity demonstrated by MON-7200 and MON-15151 is low, however MON-15151 is a severe dermal and eye irritant. Adequate precautions are described on the label, and no additional toxicity data is required prior to registration of the EUP. One of the required inhalation studies

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(On MON-15151) was supplementary. However, because of the low toxicity of MON-15151 determined in other acute studies, the pesticide is unlikely to be a significant hazard under the normal use conditions described in the application.

Introduction:

The sponsor, Monsanto Co., has applied for an EUP for the use of MON-15151 on Turf to control annual grass and broad leaf weeds in turf grass in 21 states, and on 1,333 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.

Action Requested:

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 product.

Supporting Data:

All toxicology data required for this Experimental Use Permit are acceptable except the inhalation study on the formulated product. However, data from other studies, and toxicity demonstrated in the supplementary inhalation study do not suggest a hazard from MON-15151 under the EUP conditions. The acute oral toxicity data indicated that both the technical grade (MON-7200) and the formulated product (MON-15151) have low acute toxicity, category IV and III, respectively. The acute dermal toxicity of both the technical grade and the formulated product is also low, category III. However, MON-15151 is a severe eye and dermal irritant, both category II, and MON-15151 is a dermal sensitizer. The supplementary inhalation study on MON-15151 indicated that the acute inhalation LC50 was 3.3 mg/l, which was less than for the MON-7200, LC50 = 5.89 mg/l. Although neither study demonstrated 25% of the test material to have MMAD < 1.0 micrometer, the inhalation study on MON-7200 indicated that 14.1% of the test material had a MMAD of < 1.17 micrometers, and the inhalation study on MON-15151 also suggest that 10-14% of the test material had a MMAD < 1.17 micrometers. With this low toxicity, and approximately 1/2 of the required amount of the test material with a MMAD < 1.17 micrometers, a repeat of the inhalation study appeared not to be necessary for this EUP.

The personnel associated with the EUP and the application of MON-15151 are stated to be professional qualified Monstanto 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. In addition, MON-15151 is further diluted approximately 1:15 (V/V) before spraying (maximum concentration).

The label is adequate.

[redacted] used in MON-15151, [redacted] (See CBI Appendix) has 180.1001 clearance. [redacted] (See CBI Appendix) has not been located. Monsanto has assured me that the documentation is being submitted. Until the documentation arrives, the EUP should be denied.

There is an apparent discrepancy in the concentration determined for Dayton batch No. 2 on MON-7200. technical in Japan (90.9%) and in the USA (91.5%). The apparent discrepancy does not affect the validity of the studies, and may not reflect real differences in the concentration.

As noted in the respective DERs, the concentration of the active ingredient in batch # Dayton 2 used in the acute oral, dermal, and inhalation studies with MON-7200 is 90.9% when analyzed in Japan, and when this same batch was used in the eye and dermal irritation and sensitization studies the concentration was 91.5% when analyzed in USA. This apparent discrepancy in concentration of the same batch is unknown but is reasonably claimed by the sponsor to be due the normal difference in analyses from two different laboratories. It was claimed not to be due to instability (Telephone conversation with Dennis P. Ward, PhD., Product Toxicology Specialist of Monsanto Agricultural Co., October, 1988).

Although the inhalation study is acceptable for the registration of this EUP, an acute inhalation study on MON-15151 must be repeated, in addition to the other requirements (See 40 CFR 158.135), prior to final registration of the product for general consumer use. A repeat acute inhalation study on MON-15151 is necessary in order to be assured that the appropriate toxicity category is assigned. The toxicity category could possibly be decreased from a tentative III to II by a repeat study appropriately conducted.

Thirteen acute toxicity studies on MON-7200 (the technical grade), and MON-15151 (the formulated product) in support of the EUP have been reviewed. For each study, the study type/test substance/species/study number, accession number, conclusion, toxicity category, and core classification are listed below.

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

Manufacturing process information is not included

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

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

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

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10. 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 LC50 = 3.3 mg/l for females.
Tentatively Toxicity category III
Core classification is supplementary because 25% of the particle size did not have an MMAD < 1.0 um. The study needs to be repeated for the following reasons.
a. Twenty-five percent of the particle size of the aerosol generated was not demonstrated to have a MMAD of < 1.0 um.
b. No histological examination of effected organs was reported.
c. In this study a vehicle control group should have been included.
d. The eye and dermal irritation studies demonstrated a toxicity category II, which represents increased toxicity over the studies conducted on the technical grade.
e. It could not be determined whether or not this increased irritation in the primary eye irritation study and primary dermal irritation study was directly due to the formulation substances used or due to the formulation substances resulting in increased membrane penetration of MON-7200.

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

CBI APPENDIX:

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CBI APPENDIX:

Dithiopyr Science Reviews

Page _____ is not included in this copy.

Pages __8__ through __9__ are not included in this copy.

The material not included contains the following type of information:

__X__ 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.

__X__ The product confidential statement of formula.

_____ Information about a pending registration action

_____ 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.

*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C)
Secondary reviewer: Marion Copley, DVM.
Section 2, Tox. Branch 1 (IRS)(TS-769C).

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DATA EVALUATION REPORT

STUDY TYPE: Acute Oral (81-1)/Rat/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-07

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 90.9% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Mitsukaido Laboratories, The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan.

STUDY NO.: 87-0045/ET-87-121.

REPORT TITLE: MON 7200 Acute Oral Toxicity Study in Rats.

AUTHOR(S): Koichi Ebino, DVM.

REPORT ISSUED: February 2, 1988.

CONCLUSIONS: MON-7200 was administered by gavage to 10 Sprague Dawley rats per sex per dose level at 2500, and 5000 mg/kg in an oral acute toxicity study. Two male and 1 female rats died at the highest dose level. Death occurred on day 1 (1 male and 1 female) and day 2 (1 male). No dose related effects were found at necropsy. One male which died was possibly missed dosed. The two other deaths may have been test substance related, but no cause was reported.

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

A. MATERIALS:

1. Test compound: MON 7200, technical. Description, light yellow solid, Batch # Dayton 2, Purity 90.9%, MPt 50 degrees C, Vp $4*10^{-6}$, solubility: 7 ppm in water, soluble in methanol, acetone, and chloroform.

2. Test animals: Species: Rat, Strain: SD (Crj:CD), Age:5 wk,

Weight: Males 133-158 g, Females 104-121 g, Source:Charles River, Inc., Shimofurusawa, Atsugi-shi, Kanagawa. Acclimatized 11 days. Rats were specific pathogen free. Caging rooms were semi-barrier-sustained.

B. METHODS:

- Rats were fasted overnight before dosing.
- Test material was administered orally by gavage in 20ml of 1% tween 80/kg body weight.
- Animals were observed 1, 3, and 6 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 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.
- The quality assurance statement was signed by Massahiro Hirano, Chief, Quality Assurance Unit, February 1, 1988.

C. RESULTS AND DISCUSSION:

Test group	Dose in mg/kg	Number animals that died (Day of death) Male	Total	Female	Total
1. Low (LDT)	2500	0	0/10	0	0/10
2. High (HDT)	5000	1(1),1(2)	2/10	1(1)	1/10

Animals sacrificed at day 14.

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

Body weight gain of each group was similar.

At gross necropsy, 1 male animal found dead at the HDT demonstrated a hydrothorax (probably due to missed dosing), and 1 female at terminal sacrifice demonstrated a subcutaneous nodule. No abnormalities were found in any other animal at any dose group including the other 2 animals found dead.

Although the acute testing guidelines were not followed, an additional test is not required because the toxicity category would not be expected to be altered. The study was conducted with 2 dose groups (2500 mg/kg and 5000 mg/kg) with 10 rats per sex per group, whereas 3 are required by the guidelines with 5 animals per sex per group. The guidelines also state that a limit test of 5000 mg/kg is acceptable if no animals die, whereas 2 of 3 animal deaths may have been due to the systemic toxicity of the test substance at the 5000 mg/kg dose level. It is obvious (from the possibly 2 dose related deaths in 20 animals at the HDT) that the LD50 > 5000 mg/kg. The LD50 was confirmed in mice.

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

*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT 006873

STUDY TYPE: Acute Oral (81-1)/Mouse/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-08

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 90.9% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Mitsukaido Laboratories, The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan.

STUDY NO.: 87-0046/ET-87-122.

REPORT TITLE: MON 7200 Acute Oral Toxicity Study in Mice.

AUTHOR(S): Koichi Ebino, DVM.

REPORT ISSUED: February 2, 1988.

CONCLUSIONS: MON-7200, technical was administered by gavage to 10 ICR mice per sex per dose level at 2500, and 5000 mg/kg in an oral acute toxicity study. One female mouse at the 2500 mg/kg dose level demonstrated body weight loss. One male demonstrated kidney cysts at necropsy at the 2500 mg/kg dose level, but no dose related effects were found at necropsy. It would appear that no dose related or treatment related toxicity occurred in this study. No deaths occurred.

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

A. MATERIALS:

1. Test compound: MON 7200, technical. Description light yellow solid, Batch # Dayton 2, Purity 90.9%, MPt 50 C, Vp $4*10^{-6}$, solubility: 7 ppm in water at 25 C, soluble in methanol, acetone, and chloroform. Test material was ground with a motar and pestal prior to homogenization.

2. Test animals: Species: Mice, Strain: ICR (Crj:CD-1), Age:5 wk, Weight: Males 27.2-34.3 g, Females 22.9-28.8 g, Source: Charles River, Inc., Shimofurusawa, Atsugi-shi, Kanagawa. Acclimatized 11 days. MICE were specific pathogen free. Caging rooms were semi-barrier-sustained.

B. METHODS:

- Mice were fasted 3 hours before dosing.
- Test material was administered orally by gavage in 20ml of 1% tween 80/kg body weight.
- Animals were observed 1, 3, and 6 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 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.
- The quality assurance statement was signed by Masahiro Hirano, DVM., Chief, Quality Assurance Unit on Feruary 1, 1988.

C. RESULTS AND DISCUSSION:

Test group	Dose in mg/kg	Number animals that died (Day of death) Male	Total	Female	Total
1. Low (LDT)	2500	0	0/10	0	0/10
2. High (HDT)	5000	0	0/10	0	0/10

Animals were sacrificed on day 14.

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

Body weight gain of each group was similar, except in 1 female (28.1)(initial body weight 28.8 g) at 2500 mg/kg dose group at 14 days

At gross necropsy, 1 male animal at the 2500 mg/kg dose level demonstrated cysts in each kidney at terimal sacrifice. No abnormalies were found in any other animal at any dose group.

No deaths occurred at 2500 mg/kg or 5000 mg/kg. Since the 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.

*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

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DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity (81-2)/Rat/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-09.

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 90.9% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothicate.

SPONSOR: Monsanto Japan Ltd.

TESTING FACILITY: Mitsukaido Laboratories, The Institute of Environmental Toxicology, Suzuki-cho 2-772, Kodaira-shi, Tokyo 187, Japan.

STUDY NO.: 87-0047/ET-87-123.

REPORT TITLE: MON 7200 Acute Dermal Toxicity Study in Rats.

AUTHOR(S): Koichi Ebino, DVM.

REPORT ISSUED: February 2, 1988.

CONCLUSIONS: MON-7200 was administered dermally in water to 10 Sprague Dawley rats per sex per dose level at 1000, and 5000 mg/kg. No effects were observed; no adverse clinical signs, weight gain reduction, mortality, or effects at necropsy were detected.

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

A. MATERIALS:

1. Test compound: MON 7200, technical. Description light yellow solid, Batch # Dayton 2, Purity 90.9%, MPt 50 degrees C, Vp $4*10^{-6}$, solubility: 7 ppm in water, soluble in methanol, acetone, and chloroform.

2. Test animals: Species: Rat, Strain: SD (Crj:CD), Age:7 wk, Weight: Males 223-280 g, Females 159-200 g, Source: Charles River, Inc., Shimofurusawa, Atsugi-shi, Kanagawa. Acclimatized 7-11 days. Rats were specific pathogen free. Caging rooms were

semi-barrier-sustained. 006873

B. METHODS:

- Test material was administered dermally. The test material was applied to filter paper, wetted with water and applied to a 4 by 5 cm skin site on the backs of the test rats for 24 hours. The remaining test material was washed off after 24 hours with soap and water. The area receiving the test material had been previously clipped and shaved. The manner in which the test material was held on the animal and whether or not the animal was restrained was not specified, however this deficiency does not alter the conclusions. The test material had been previously pulverized by dry ice and a mortar and pestle.
- Animals were observed 1, 3, and 6 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 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.
- Quality Assurance Statement was signed by Masahiro Hirano, DVM, Chief, Quality Assurance Unit, on February 1, 1988.

C. RESULTS AND DISCUSSION:

Test group	Dose in mg/kg	Number animals that died (Day of death) Male	Total	Female	Total
1. Low (LDT)	1000	0	0/10	0	0/10
2. High (HDT)	5000	0	0/10	0	0/10

Animals were sacrificed of day 14.

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

Body weight gain of each group was similar.

At gross necropsy, no detectable effects were found at either dose level in males or females at terminal sacrifice.

Since no animals died at 1000 or 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.

*Primary reviewer: David G Anderson, PhD. 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

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DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation (81-3)/Rat/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-10

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 90.9% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Japan Limited.

TESTING FACILITY: Mitsukaido Laboratories, The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan.

STUDY NO.: 87-0048/ET-87-124.

REPORT TITLE: MON 7200 Acute Inhalation Toxicity Study in Rats.

AUTHOR(S): M Yoshida, BSc.

REPORT ISSUED: February 2, 1988.

CONCLUSIONS: MON-7200 in DMSO was administered by nose only inhalation for 4 hours to 10 Fischer 344 rats per sex per dose level at 5.98 mg MON-7200/l, and to the DMSO control groups at 9.37 mg/l. The particle distribution size of the test material in DMSO was a MMAD of 3.7 um with geometric standard deviation of 2.5 um. That is, 90% or more of the exposure mist consisted of particles of aerodynamic diameters of 15 um or less and 85% or more consisted of particles of aerodynamic diameters of 10 um or less.

The particle size distribution expressed as weight percent of each stage of the Andersen type cascade impactor indicates that 14.1% had a particle size (MMAD) of 1.17 um or less.

Nominal concentrations of the test material and the vehicle control in the exposure chambers were 84.03 and 87.48 mg/l, respectively.

No deaths occurred and the only dose related effects were redness around the nose and mouth.

Toxicity category: III.
Core classification: Minimum.
LC50 = > 5.98 mg/l for males and females.

A. MATERIALS:

1. Test compound: MON 7200, Description light yellow solid, Batch = Dayton 2, Purity 90.9%, MPt 50-51 C, Vp $4*10^{-6}$, solubility: 7 ppm in water, soluble in methanol, acetone, and chloroform, contaminants: list in CBI appendix.

2. Test animals: Species: Rat, Strain: Fischer (F344/DuCrj), Age:8 wk, Weight: Males 197-226 g, Females 133-147 g, Source:Charles River, Inc., Kanagawa. Acclimatized 7 days, or more. Rats were specific pathogen free. Caging was on isolated-ventilation racks.

3. Environment: Temperature - 24 degree C, Humidity - 55 %, Light:dark = 14:10, Air changes - 15 time per hour.

4. Inhalation conditions: Exposure was by snout only (Fig 1) for 4 hours. Test material (50:50 = MON-7200:DMSO) exposure was generated by an atomizer (AKI Jet 04, H. Ikeuchi & Co., Ltd., Aichi, Japan). Air flow rate was regulated at 20 l/min.

B. METHODS:

Concentrations of the MON 7200, technical were determined 7 times every 0.5 hour during exposure through removal of 1 liter of the exposure atmosphere from the chamber (1.4 l/min.). The test atmosphere was trapped on a glass filter and weighed to determine the weight of the sample. The filter was then extracted with acetonitrile to analytically determine pesticide residue. This residue was determined by gas chromatography. The amount of MON-7200 was determined from a standard curve previously prepared from standard active ingredient, MON-7200, (99.9%). (Recovery of MON-7200 was about 97.2% when 40 mg of the MON-7200 DMSO mixture was added to the filter.) Back calculation for the percent recovery, and the percent MON-7200 in MON-7200 technical were used to calculate the concentration of MON-7200 technical in the atmosphere.

Actual concentrations of DMSO were determined 7 times every 0.5 hour by a midget impinger containing 10 ml of ethanol. The DMSO in the ethanol was determined by spectroscopy at 210 nm. Nominal atmospheric concentrations of DMSO was determined by dividing the consumed DMSO in 4 hours by the air flow.

Animals (10 rats/sex/group) were exposed nose only to MON-7200 in DMSO at 12.06 mg/l (5.98 mg MON-7200 and 6.08 mg DMSO/l) in 1 exposure for 4 hours, or DMSO at 9.37 mg/l for 4 hours. Air flow during the exposure was 20 l/minute, and considered 10-20 times larger than the respiratory volume of 20 rats. This rate represented about 80 air changes/hour. Chamber temperature was 24.4 - 26.5 degrees C. Chamber humidity was 17-28%; the value was lower than the animal rooms because of the need for the generating conditions and the hygroscopicity of DMSO.

- Animals were observed immediately 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 animals that died on study and on all survivors which were sacrificed on day 14. Organs and tissues preserved were the lung, larynx, trachea, heart, liver kidney, spleen, and head including the nasal cavity and oral cavity.
- Doses given and lethality are presented in the table under results.
- The quality assurance statement was signed by Masahiro Hirano, Chief, of the Quality Assurance Unit on February 1, 1988.

Particle size analysis - Particle size distribution was determined by an Andersen personal sampler (Kanomax Japan Inc.). The mass trapped at each stage was determined from 1 liter sampled at 1.4 l/minute, 3 times every hour during exposure. The weight % at each stage to the total mass trapped was calculated. The cumulative weight percent was plotted on probit-logarithmic paper to obtain the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the test substance mist.

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

The particle distribution size of the test material in DMSO was MMAD of 3.7 um with geometric standard deviation of 2.5 um. That is 90% or more of the exposure mist consisted of particles of aerodynamic diameters of 15 um or less and 85% or more consisted of particles of aerodynamic diameters of 10 um or less. No data was presented for these estimations. Analysis of the last table (Appendix 4, Particle Size Distribution -Weight % of Each Stage of Andersen type Cascade Impactor.) indicates that 14.1% had a particle size (MMAD) of 1.17 um or less.

Nominal concentrations of the test material and the vehicle control in the exposure chambers were 84.03 and 87.48 mg/l, respectively.

Test group	Dose of MON-7200 for 4 hr.	Number animals that died (Day of death or sac.) Male	Total	Female	Total
1. MON-7200 & DMSO	5.98 mg/l 6.08 mg/l	0	0/10	0	0/10
2. DMSO	9.37 mg/l	0	0/10	0	0/10

Animals were sacrificed of day 15.

Immediately after exposure animals were observed to have wetness about the nose, mouth, abdominal fur and back. This wetness disappeared by day 1. Slight reddish brown staining

around the nose and mouth which developed, disappeared by day 5, but appeared intermittently in some males and females. In addition red stains appeared around the eyes of 1 male on the day of exposure and on 1 female on day 2. The animals in the vehicle exposure test demonstrated almost identical signs. No other clinical signs were noted in any animal.

Body weight gain of each group was similar.

At gross necropsy, no abnormalities were noted in any animal exposed to the test material or the vehicle.

No deaths occurred prior to terminal sacrifice in either test group or the vehicle control group.

D. DISCUSSION:

The MMAD of the aerosol generated was 3.7 um, with a GSD of 2.5. Although 25% of the generated aerosol did not have a MMAD of 1.0 um or less, and did not meet the criteria of the inhalation guidelines, the study need not be repeated because:

1. The toxicity category is IV in an acceptable acute oral toxicity study.
2. There was little to no skin irritation demonstrated by an acceptable study.
3. There was only minor eye irritation demonstrated by an acceptable study.
4. No rats died when exposed for 4 hours to the test material at 5.98 mg/l.
5. 14.1% of the test material had a MMAD of 1.17 um or less.

The LC50 was stated in the report to be > 5.98 mg/l, greater than the limit dose of 5 mg/l.

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*Primary reviewer: David G Anderson, PhD. David G Anderson 11/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 1/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation (81-5)/Rabbit/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-12

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 91.5% 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.: 4312-87/BD-87-131.

REPORT TITLE: Primary Dermal Irritation Study in Rabbits (4-Hour Exposure/Semi-Occlusive Covering) on Test Material: MON 7200.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: January 7, 1988.

CONCLUSIONS: MON-7200 (0.5 g solid) was administered to each of two 1 by 1 inch square patches on 4 female and 2 male rabbits and observed and scored at 0.5, 24, 48, and 72 hours. Slight erythema (grade 1), but no edema was noted at 0.5 hours or at any time after administration. Erythema (grade 1) was seen in 1 male at 0.5, 24, and 48 hours after administration. No other effects were observed at 1, 24, 48, or 72 hours after administration.

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

A. MATERIALS:

1. Test compound: MON 7200, Description light tannish solid, Batch # Dayton 2, Purity 91.5%, analysis in USA.

2. Test animals: Species: Rabbit, Strain: New Zealand White,

A. MATERIALS:

1. Test compound: MON 15151 on Turf, 12.7% MON-7200 Description amber liquid, Batch # XLH-221, Purity 12.68%, contaminants: list in CBI appendix.

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age:8 wk, Source:Summit Farms, Hazleton, PA. Acclimatization: 35 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 hours 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 Florence S Gilson, Supervisor of Quality Assurance on November 20, 1987.

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

At 0.5 hours, 5 of the 6 rabbits demonstrated grade 1 to 2 erythema and grade 2 to 4 edema at both test sites. At 24 hours, all rabbits responded with grade 2 to 4 erythema and grade 1 to 2 edema at both sites, in addition to superficial necrosis in 2 rabbits at both sites. At 48 hours, the erythema had progressed to grade 4, but appeared to reach a maximum at 72 hours which remained until day 7. By day 10, 1 animal responded with grade 2 erythema and 6 with desquamation. By day 14, only 1 rabbit was responding with some desquamation. The erythema reaction reached the maximum of 4 at 72 hours and day 7 but the edema reaction reached a grade of 4 at 0.5 hours with a slow decline. Edema was absent at day 10. The necrosis persisted through day 7 in 5 of the 6 animals tested, but it had reversed by day 10.

D. DISCUSSION:

Moderate to severe dermal irritation was produced by MON-15151 at 48 hours to day 7. Only superficial necrosis affecting the epidermis only as stated in the submitted report was exhibited which was reversible within 10 days. Thus, although there is evidence of necrosis and corrosiveness, the deep layers were apparently not affected.

Toxicity category II.

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*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT 006873

STUDY TYPE: Dermal Sensitization (81-6)/Guinea Pig/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-13.

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 91.5% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Co.

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

STUDY NO.: 4314-87/BD-87-130.

REPORT TITLE: A Closed-patch Repeated Insult Dermal Sensitization Study in Guinea Pigs (Buehler Method) Test Material MON-7200.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: February 17, 1988.

CONCLUSIONS: MON-7200 was administered dermally in water 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, grade 1, after the third induction. No adverse clinical signs, weight gain reduction, or mortality were observed.

Toxicity category: NA.
Core classification: Minimum.
MON-7200 technical is not a dermal sensitizer in the Buehler Test.

A. MATERIALS:

1. Test compound: MON 7200, technical, Description light tanish solid, Batch # Dayton 2, Purity 91.5%, analysis in USA.

2. Test animals: Species: Guinea Pigs, Strain: Hartely Albino, Age:5-6 wk, Weight: Males 354-419 g, Females 328-380 g, Source:Hazleton-Dutchland Laboratory Animals, 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 wetted with water was found to be non-irritating.

Induction Phase - 0.3 cc 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 1, 24, 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 1, 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 not signed by an officer of the Quality Assurance Unit, however it was signed by the Study Director, DL Blaszcak, on February 17, 1988.

C. RESULTS: (Numbered table 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, 2 animals responded with ± reactions and 5 with grade 1 erythema at 24 hours. Also at the third exposure, 2 animals responded with grade 1 erythema and 3 animals responded with ± at the 48 hour reading. These results alone could mean that the test material was causing slight sensitization or accumulative slight irritation.

2. Challenge phase - Table III and IV present the results from the challenge phase and the irritation control. The failure of the animals to respond to the challenge dose, indicated that MON-7200 is not a sensitizer in this test.

D. DISCUSSION: During the induction phase the animals responded with grade 1 erythema which was probably due to accumulated irritation because none of the animals responded to the challenge dose.

MON-7200 is not a dermal sensitizer in the Buehler Test.

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*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

006873

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation (81-4)/Rabbit/MON-7200.

TOX. CHEM. No.:717C

MRID No.: 406386-11

TEST MATERIAL: MON 7200, technical

SYNONYMS: MON-15151 on Turf, 91.5% 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.: 4313-87/BD-87-131.

REPORT TITLE: Eye Irritation Study in Rabbits, Test Material: MON 7200.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: January 7, 1988.

CONCLUSIONS: MON-7200 (0.1 cc solid, approximately 64.1 mg) was administered to 1 eye of each of 4 female and 2 male rabbits and observed for 72 hours. Slight redness (grade 1), chemosis (grade 2), and discharge (grade 1) was seen at 1 hour after administration. Redness (grade 1) was seen in 1 animal at 24 hours after administration. No other effects were observed at 1, 24, 48, or 72 hours after administration.

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

A. MATERIALS:

1. Test compound: MON 7200, Description light tannish solid, Batch # Dayton 2, Purity 91.5%, analysed in USA.

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

B. METHODS: 006873

- Test material was administered at 0.1 cc solid, approximately 64.1 mg, in 1 eye, unwashed for 24 hours. Residual material 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.
- Fluoroscein 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 Florence S Gilson, Supervisor of Quality Assurance on January 7, 1988.

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

		Rating; Time after admin. (hours)			
Rabbit #		1	24	48	72
32342F	Redness	1	1	0	0
	Chemosis	2	0	0	0
3246F	Redness	1	1	0	0
	Chemosis	2	0	0	0
	Discharge	1	0	0	0
3250F	Redness	1	1	0	0
	Chemosis	2	0	0	0
	Discharge	2	0	0	0
3254F	Redness	1	1	0	0
	Chemosis	2	0	0	0
3253M	Redness	1	1	0	0
	Chemosis	2	0	0	0
	Discharge	1	0	0	0
	Iris	+	0	0	0
3255M	Redness	1	1	0	0
	Chemosis	2	0	0	0
	Discharge	1	0	0	0

No other involvement was noted.

Since a positive reaction for chemosis (a positive reaction for chemosis 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 iritation is III.

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*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT 006873

STUDY TYPE: Acute Oral (81-1)/Rat/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 406386-14.

TEST MATERIAL: MON-15151, 12.6% MON-7200.

SYNONYMS: MON-15151 on Turf, 12.6% 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.: 4195-87/BD-87-132.

REPORT TITLE: Acute Oral Toxicity Study in Rats. Test Material: MON-15151.

AUTHOR(S): DL Blaszcak

REPORT ISSUED: November 20, 1987.

CONCLUSIONS: MON-15151, 12.6% MON-7200 the a.i., was administered by gavage to 5 Sprague Dawley rats per sex per dose level at 2000, 3200, or 5000 mg/kg in an oral acute toxicity study. Eleven animals died on day 0, 1, or 2, and 2 on day 3 after dosing. Evidence of severe stomach and intestinal irritation or corrosion occurred in the form of probable blood discolored contents. Kidney damage may also have occurred because red, brown, and/or black fluid was found in the urinary bladder.

Toxicity category: III.
Core classification: Minimum.
LD50 = 4100 mg/kg for males, and 3000 mg/kg for females.

A. MATERIALS:

1. Test compound: MON 15151, 12.68% MON-7200 the a.i., Description amber liquid, Batch # XLH-221, Purity 12.68%.

2. Test animals: Species: Rat, Strain: Sprague Dawley, Age:9-12 wk, Weight: Males 297-343 g, Females 220-248 g, Source:Charles River Breeding Laboratories, Inc. Wilmington MA 01887.

Acclimatized 20-22 days.

B. METHODS:

- Rats were fasted overnight before dosing.
- Test material was administered orally by gavage. The specific gravity of MON-15151 and volume of the doses were 947.1 mg/ml and 2.1, 3.4, and 5.3 ml for the 2000, 3200, and 5000 mg/kg dose levels, respectively. It is assumed that the doses administered were presented as the weight of MON-15151/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 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 Florence S Gilson, Supervisor of Quality Assurance, on November 20, 1987.

C. RESULTS AND DISCUSSION:

Test group	Dose of MON-15151 mg/kg	Number animals that died (Day of death) Male	Total	Female	Total
1. Low (LDT)	2000	0	0/5	1 (2)	1/5
2. Mid (MDT)	3200	1 (3)	1/5	3 (2)	3/5
3. High (HDT)	5000	4(2,3)	4/5	1(2,3)	4/5
Animals were sacrificed on day 14.					
LD50 (mg/kg) and 95% confidence limits (mg/kg)		4100, 2740-5460		3000, 1765-4235	
Average			3600, 2802-4398		

Clinical signs on the day of dosing included ataxia, nasal and oral discharge, and hyperactivity. These and other signs in the 5000 mg/kg dose group included red oral discharge, hypopnea, wet rales, abdominal griping, and partially closed eyes. Additional signs in the 3200, and 5000 mg/kg dose groups were hypopnea, hypothermia, and prostration. Red urinary and urinary staining, and fecal staining was noted in some animals in the 2000 mg/kg dose group.

Body weight gain decreased in surviving animals. Animals decreased food consumption on the day of dosing which continued through day 3, and in some animals up to day 9.

At necropsy, several animals found dead, exhibited lung

discoloration, liver discoloration and/or accented lobular patterns, red, brown, or black fluid in the urinary bladder, changes in the stomach and intestines indicate of irritation and corrosive effects such as discolored walls, and red, brown and black material contents. Changes in animals killed after 14 days were considered normal for animals killed by CO_2.

The LD50 was stated in the report to be 4100 mg/kg for males and 3000 mg/kg for females. This degree of toxicity places MON-15151 on the low toxicity end of toxicity category III.

*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

006873

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity (81-2)/Rabbit/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 406386-15.

TEST MATERIAL: MON 15151, 12.6% MON-7200.

SYNONYMS: MON-15151 on Turf, 12.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Co.

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

STUDY NO.: 4196-87/BD-87-132.

REPORT TITLE: Acute Dermal Toxicity Study in Rabbits. Test Material: MON-15151.

AUTHOR(S): DL Blaszcak

REPORT ISSUED: November 20, 1987.

CONCLUSIONS: MON-15151 was administered dermally at 5000 mg/kg to 5 rabbits per sex for 24 hours. One female died on day 2 and one female demonstrated severe dermal reactions such as necrosis, eschar and exfoliation. All surviving animals demonstrated body weight decreases.

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

A. MATERIALS:

1. Test compound: MON 15151, 12.68% MON-7200 the active ingredient, Description amber liquid, Batch # XLH-221, Purity 12.68%.

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age: 8 wk, Weight: Males 2.5-2.9 kg, Females 3.0-3.2 kg, Source: Hazleton-Dutchland Laboratory Animals, Denver PA. Acclimatized 31 days.

B. METHODS:

- Test material, 5000 mg/kg, was administered dermally to 5 rabbits per sex. The test material was applied at 5.3 ml/kg, specific gravity of 947.1 mg/ml. The test material was applied directly to the shaved backs of the test animal, rapped 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 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.
- Rats 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 Florence S Gilson, Supervisor of Quality Assurance Unit, on November 20, 1987.

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	1 (2)	1/5

All animals were terminated by day 14.

Severe dermal effects, such as necrosis, eschar formation, and exfoliation occurred from day 1-14 in 1 female rabbit only.

One male and 1 female developed wet rales and urinary staining, respectively. The detail of the data in the report did not allow correlation of these symptoms with the dermal effects or the death.

Antemortem signs exhibited by the one female which died included red staining in the ano-genital area, hypoactivity, dyspnea, and lack of mobility.

Body weight gain decreased in some animals by day 7, but generally increased day 7-14. Occasional food consumption decreases occurred.

At gross necropsy, no unusual effects were found in surviving males or females at terminal sacrifice.

Since a limit dose of 2000 mg/kg is allowed, and it is very

unlikely that the toxicity category would be changed by a repeat study either at the lower limit dose level of 2000 mg/kg or if conducted on the normally required 3 dose levels, another study is not required.

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

*Primary reviewer: David G Anderson, PhD. David G Anderson 10/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C)
Secondary reviewer: Marion Copley, DVM Marion Copley DVM 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

006873

DATA EVALUATION REPORT

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

TOX. CHEM. No.:717C

MRID No.: 406386-16

TEST MATERIAL: MON-15151, 12.7-12.8% MON 7200.

SYNONYMS: MON-15151 on Turf, 12.7-12.8% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Agricultural Co.

TESTING FACILITY: Monsanto Agricultural Co., 800 N Lindbergh Blvd., St. Louis, MI 63167.

STUDY NO.: ML-87-145/EHL-87093.

REPORT TITLE: Acute Inhalation Toxicity Study of MON-15151.

AUTHOR(S): CL Bechtel.

REPORT ISSUED: December, 1987.

CONCLUSIONS: MON-15151 was administered in an acute inhalation study for 4 hours to 5 rats per sex at 2.9, 3.5, 5.0, or 7.9 mg/l, the LC50 was found to be 3.3 mg/l for females and >3.5 but <5.0 mg/l for males. The particle distribution size of MON-15151 was reported only as the MMAD of 2.9-3.2 micrometers with a GSD of 1.9. Most of the animals died within 0-2 days.

Tentative toxicity category: III.
Core classification: Supplementary because 25% of the generated particle size was not < 1.0 micrometer, and other factors noted in the discussion.
LC50 = >3.5 <5.0 mg/l for males.
LC50 = 3.3 mg/ml for females.

A. MATERIALS:

1. Test compound: MON-15151, 12.7-12.8% MON 7200 the active ingredient. Description amber liquid, Batch # XLH-221, Purity 12.7-12.8%.

2. Test animals: Species: Rat, Strain: Sprague Dawley, Age:8

wk, Weight: Males 262 g, Females 194 g, Source:Charles River Breeding Laboratory, Portage, MI. Acclimatized NOT STATED.

3. Environment: Temperature - 70-74 degrees F, Humidity - 35-60%, Light:dark = 12:12.

4. Inhalation conditions: Exposure was by whole body (Fig 1) for 4 hours. The exposure chamber was 300 liter New York University-style stainless steel with pyramidal top and bottom. Exposures were generated by an nebulizer (Laskin-style), Air flow rate was regulated at 63.6-73.0 l/min. Temperature, 20.4-25.0 degrees C. Humidity, 69.6-84.2%. Oxygen level, >20.5%.

B. METHODS:

Concentrations of MON-15151 in the breathing zone were determined hourly during each 4 hour exposure through removal of 5 l of the exposure atmosphere from the chamber, and passing it through acetone in a 25 ml glass impinger. The concentration MON-7200 in the sample was determined by gas chromatography, and the concentration of MON-15151 determined on the bases of 12.8% MON-7200 in MON-15151. 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 mean mass aerodynamic diameter (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 eyes, lung, skin, 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 Steven M Haag for the manager of Quality Assurance, on December 21, 1987.

C. RESULTS:

The particle distribution size of the test material was MMAD of 2.9 to 3.2 micrometers (um) with geometric standard deviation (GSD) of 1.9 um. The report stated that greater than 96% of the particle sizes had a MMAD of < 10 um in diameter. The weight percent of the particle size range at each stage of the Andersen

impactor was not reported. Thus, the percent mass of particles less than the MMAD of 1.0 um can not be determined.

Test group	*Analytical conc. of MON-15151 mg/l	Number animals that died (Day of death) Male	Total	Female	Total
1. Low (LDT)	2.9	0	0/5	1 (2)	1/5
2. Mid1(MTD1)	3.5	1 (1)	1/5	3 (1-4)	3/5
3. Mid2(MDT2)	5.0	5 (1-2)	5/5	5 (0-2)	5/5
4. High (HDT)	7.9	5 (0-1)	5/5	5 (0-1)	5/5

Surviving animals was sacrificed on day 14.
* The concentration of MON-15151 was calculated from the analytical concentration MON-7200, and 12.8% MON-7200 in MON-15151.

Clinical observations immediately after exposure included listlessness (misuse or disuse of legs), tremors, twitching, and respiratory difficulties. At 1-3 day post exposure animals demonstrated emaciation, hypoactivity, prostration, tremors, misuse of limbs, and labored breathing, and brownish ocular and nasal discharge, and 25 of the 26 deaths occurring in the study. At 4-14 days post exposure animals demonstrated red/brown nasal encrustation, and labored breathing, and 1 death.

Most of the animals which died, died within 0-2 days, and only one animal died after day 2 (day 4), thus death was probably caused predominantly by respiratory failure, or possibly by CNS effects.

Gross necropsy indicated corneal opacity, red/purple/black lungs in animals of the three highest dose groups among males which died prior to sacrifice, and in all groups among females which died. Incidences of stomachs with red/purple/black colored foci, abnormal digit color (red/purple/black), and abnormal skin color (brown/yellow/tan) also occurred in dosed groups. Animals which survived to day 14 were not remarkable at necropsy.

D. DISCUSSION:

MON-15151 administered via inhalation for 4 hours to 5 rats per sex per group at 2.9, 3.5, 5.0, or 7.9 mg/l, resulted in mortality in all animals at 5.0, and 7.9 mg/l and in 4 animals at 2.9, and 3.5 mg/l. Of the animals which died, 96% died in 0-2 days. Labored breathing, and sensory irritation was the most common observation. The MMAD of the aerosol generated was 2.9-3.2 micrometers, with a GSD of 1.9. Weight percent of the dose in each particle size range was not reported. Thus, it cannot be determined whether or not 25% of the generated aerosol had a MMAD of 1.0 um or less. Without this information, it is assumed that

the study did not meet the criteria of the inhalation guidelines. The acute inhalation toxicity of MON-15151 could be much greater than the current LC50 would indicate. The study needs to be repeated for the following reasons;

a. Twenty-five percent of the particle size of the aerosol generated was not demonstrated to have a MMAD of < 1.0 um.
b. No histological examination of effected organs was reported.
c. In this study a vehicle control group should have been included.
d. The eye and dermal irritation studies demonstrated a toxicity category II, which represents increased toxicity over the studies conducted on the technical grade.
e. It could not be determined whether or not this increased irritation in the primary eye irritation study and primary dermal irritation study were directly due to the formulation substances used or due to the formulation substances resulting in increased membrane penetration of MON-7200.

The tentative toxicity category is III.

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*Primary reviewer: David G Anderson, PhD. David G Anderson 11/11/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley DVM 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT 006873

STUDY TYPE: Primary Eye Irritation (81-4)/Rabbit/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 406386-17.

TEST MATERIAL: MON-15151, 12.7% MON 7200.

SYNONYMS: MON-15151 on Turf, 12.7% 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.: 4198-87/BD-87-132.

REPORT TITLE: Eye Irritation Study in Rabbits on Test Material: MON-15151.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: November 20, 1987.

CONCLUSIONS: MON-15151, 12.7% MON-7200, (0.1 ml liquid) was administered to 1 eye of each of 3 rabbits per sex, and observed at 1, 24, 48, 72 hours, 7 days, and 14 days. All six animals demonstrated moderate to severe ocular irritation and corneal ulceration; (redness, chemosis. and discharge), 5 demonstrated corneal opacity, dullness, or ulceration, and 6 demonstrated iridal damage at the 1, 24, and 48 hour reading. Corneal opacity had disappeared by day 7 in 4 of the animals demonstrating opacity, and in the 1 animal demonstrating dullness. No positive effects on the eye were observed at day 7 or 14. The observation of corneal ulceration which was apparently reversible within 7 days, and certainly with 21 days classifies MON-15151 as severely irritating.

Eye Irritation, toxicity category: II, in agreement with t' sponsor.
Core classification: Minimum.

A. MATERIALS:

1. Test compound: MON-15151, 12.68% MON 7200 the active ingredient. Description amber liquid, Batch # XLH-221, Purity

12.68%.

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age:8 wk, Source:Summit Farms, Hazleton, PA. Acclimatized 21 days.

B. METHODS:

- Test material was administered at 0.1 ml in 1 eye, unwashed for 24 hours. Local proparicaine anesthesia was used. Residual material was washed out at 24 hours.
- The eyes of the animals were observed, and scored by the Draize method, Draize (1959), at 1, 24, 48, 72 hours, 7 days, and 14 days after dosing, otherwise observations were made twice daily.
- Rabbits were not weighed.
- Gross necropsy was not performed.
- Fluorescein used to confirm and to demonstrate no ulceration.
- Eye irritation scores are presented in the table I.
- Quality Assurance Statement was signed by Florence S Gilson, Supervisor of Quality Assurance on January 7, 1988.

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

All six animals demonstrated moderate to severe ocular irritation and corneal ulceration; (redness, chemosis, discharge), 5 demonstrated corneal opacity, dullness, and ulceration, and 6 demonstrated iridal damage at the 1, 24, and 48 hour reading. Except for grade 1 redness in 4 animals and a + reaction in the iris of 1 animal, the eye irritation had completely reversed by day 7 and all had completely reversed by day 14. Grade 1 redness, and + reaction in the iris is not considered a positive eye response in the grading system used. The test material caused 2 rabbits to vocalize, and thus a local anesthetic was used on the remaining animals.

D. DISCUSSION:

The grade 3-4 ulceration seen in 5 of the 6 eyes studied persisted for 72 hours, but it was apparently reversible in all animals by day 7, and grade 1 erythema in 4 eyes, and a + reading in the iris of 2 eyes at day 7 was completely disappeared by day 14. The corneal ulceration, which was apparently reversible within 7 days was certainly reversible within 21 days, in this case classifies MON-15151 in toxicity category II, severely irritating.

There was no indication that a slit lamp was used to detect possible edema to the cornea which may not have been completely reversible within 7 days. The National Academy of Sciences (1977) indicate that subtle edema in the cornea may result prior to complete healing of the corneal epithelium, and this edema may only be apparent with aid of a slit lamp. Another primary eye irritation study on the formulated product may allow modification of the toxicity category.

E. REFERENCE:

1. NAS (1977) Principles and Procedures for the Toxicity of Household Substances. NAS publication 1138, page 45.

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*Primary reviewer: David G Anderson, PhD
Section 2, Tox. Branch 1 (IRS)(TS-769C)
Secondary reviewer: Marion Copley, DVM.
Section 2, Tox. Branch 1 (IRS)(TS-769C)

9/12/88

006873

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation (81-5)/Rabbit/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 406386-18

TEST MATERIAL: MON 15151, 12.7% MON-7200.

SYNONYMS: MON-15151 on Turf, 12.7% 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.: 4197-87/BD-87-132.

REPORT TITLE: Primary Dermal Irritation Study in Rabbits (4-Hour Exposure/Semi-Occlusive Covering) on Test Material: MON 15151.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: November 20, 1987.

CONCLUSIONS: MON-15151, 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, 10, and 14 days. Superficial (epidermis only) necrosis occurred within 24 hours in 2 animals and in all animals within 7 days. This necrosis was reversible by day 14. Moderate to severe erythema and edema occurred which disappeared by day 10. One male demonstrated grade 2 erythema and desquamation on day 10, but only desquamation on day 14. The test material should be classified as a category II, because of the necrosis seen in this study apparently affected the epidermis only and not the underlying dermis, and these effects were reversible within 14 days.

Toxicity category II.
Core classification: Minimum.

A. MATERIALS:

1. Test compound: MON 15151 on Turf, 12.7% MON-7200 Description amber liquid, Batch # XLH-221, Purity 12.68%, contaminants: list in CBI appendix.

2. Test animals: Species: Rabbit, Strain: New Zealand White, Age:8 wk, Source:Summit Farms, Hazleton, PA. Acclimatization: 35 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 hours 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 Florence S Gilson, Supervisor of Quality Assurance on November 20, 1987.

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

At 0.5 hours, 5 of the 6 rabbits demonstrated grade 1 to 2 erythema and grade 2 to 4 edema at both test sites. At 24 hours, all rabbits responded with grade 2 to 4 erythema and grade 1 to 2 edema at both sites, in addition to superficial necrosis in 2 rabbits at both sites. At 48 hours, the erythema had progressed to grade 4, but appeared to reach a maximum at 72 hours which remained until day 7. By day 10, 1 animal responded with grade 2 erythema and 6 with desquamation. By day 14, only 1 rabbit was responding with some desquamation. The erythema reaction reached the maximum of 4 at 72 hours and day 7 but the edema reaction reached a grade of 4 at 0.5 hours with a slow decline. Edema was absent at day 10. The necrosis persisted through day 7 in 5 of the 6 animals tested, but it had reversed by day 10.

D. DISCUSSION:

Moderate to severe dermal irritation was produced by MON-15151 at 48 hours to day 7. Only superficial necrosis affecting the epidermis only as stated in the submitted report was exhibited which was reversible within 10 days. Thus, although there is evidence of necrosis and corrosiveness, the deep layers were apparently not affected.

Toxicity category II.

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Section 2, Tox. Branch 1 (IRS)(TS-769C).
Secondary reviewer: Marion Copley, DVM. Marion Copley DVM 10/12/88
Section 2, Tox. Branch 1 (IRS)(TS-769C).

DATA EVALUATION REPORT 006873

STUDY TYPE: Dermal Sensitization/MON-15151.

TOX. CHEM. No.:717C

MRID No.: 406386-19.

TEST MATERIAL: MON 15151, 12.6% MON-7200.

SYNONYMS: MON-15151 on Turf, 12.6% S,S-Dimethyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine dicarbothioate.

SPONSOR: Monsanto Co.

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

STUDY NO.: 4199-87/BD-87-133.

REPORT TITLE: A Closed-patch Repeated Insult Dermal Sensitization Study in Guinea Pigs (Buehler Method) Test Material MON-15151.

AUTHOR(S): DL Blaszcak.

REPORT ISSUED: February 17, 1988.

CONCLUSIONS: MON-15151, at 25%, was administered dermally in acetone to 5 guinea pigs per sex in a induction phase and at 20% and 10% MON-15151 concentration in a challenge and rechallenge phase, respectively, by the Buehler method. During the induction phase there was evidence of accumulative dermal irritation from 25% MON-15151, such as erythema, and necrosis. Some evidence of dermal sensitization was found during the challenge phase with the 20% concentration of MON-15151, which was partially masked by excessive irritation from the 20% solution. The initial evidence for dermal sensitization by the 20% solution was confirmed by the a rechallenge phase with a 10% solution of MON-15151, where no irritation was detected. No other adverse clinical signs, weight gain reduction, or mortality were observed.

Toxicity category: NA.
Core classification: Minimum.
MON-15151 is a dermal sensitizer.

A. MATERIALS:

1. Test compound: MON 15151, 12.6% MON-7200 the a.i. Description amber liquid, Batch # XLH-221, Purity 12.6%.

2. Test animals: Species: Guinea Pigs, Strain: Hartely Albino, Age:5-6 wk, Weight: Males 335-378 g, Females 336-379 g, Source: Hazleton-Dutchland Laboratory Animals, Denver, PA. Acclimatized 7-11 days.
3. Environmental: Temperature, 65-75 degrees F; Humidity, 30-70%; Light:dark = 12:12.

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. Based on the range-finding study 25% test material in acetone was found to be minimally irritating for induction, and 20% in acetone was found to be the maximum non-irritating concentration. A less irritating concentration of 10% was chosen for rechallenge.

- Guinea Pigs used (All animals previously untreated, unless otherwise specified):
Range-finding - 6 guinea pigs.
Induction and challenge - 5 guinea pigs per sex.
Irritation test - 5 guinea pigs per sex.
Rechallenge - same 5 guinea pigs per sex as induction and challenge group above, but at a different site 7 days later.
Irritation test for the rechallenge group - 5 guinea pigs per sex.

Induction Phase - 0.3 ml of test material in acetone (25% MON-15151 in acetone, 3.15% with respect to MON-7200) was applied in Hilltop Chambers to the clipped backs of 5 guinea pigs per sex for each of the induction group. The chamber was left in place for 6 hours, after which remaining material was removed from the test site and examined at 1, 24, 48 hours. This Induction procedure was conducted 3 times over a period of 3 weeks.

Challenge Phase - 14 days after the final induction exposure, 0.3 ml of 20% MON-15151 in acetone (2.52% with respect to MON-7200) was placed in a Hilltop chamber for 6 hours on the other side of the shaved backs of the 5 guinea pigs per sex used for induction exposure, and on the shaved backs of each of 5 guinea pigs per sex from the irritation test group. The irritation test group animals had not been previously exposed to the test material. The sites were read after 1, 24 and 48 hours for

erythema, with or without edema, necrosis and eschar formation.

Rechallenge Phase - 7 days after the final reading of the challenged animals, these animals were rechallenged to 10% MON-15151 in acetone (1.26% MON-7200 in acetone) in a Hilltop Chamber, 0.3 ml, for 6 hours, and treated and read similarly to the previously challenged group.

Irritation phase testing for the challenged and rechallenged animals - A separate group of animals were used to determine irritation during the challenge phase and during the rechallenge phase.

Irritation for the challenge phase - 0.3 ml of 20% MON-15151 in acetone (2.52% A.I. in acetone) on 5 guinea pigs per sex, previously unexposed.

Irritation for the rechallenge phase - 0.3 ml of 10% MON-15151 in acetone (1.26% A.I. in acetone) on 5 guinea pigs per sex, previously unexposed.

- In addition animals were observed weekly.
- Animals were weighed pretest and at termination.
- Gross necropsy was not performed.
- Quality Assurance Statement was signed by William M Harrison Supervisor of the Quality Assurance Unit on February 17, 1988.

C. RESULTS: (Tables were copied from the submitted 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 first exposure(25% MON-15151), 7 animals responded with a patch or foci of necrotic reactions and/or grade 1 erythema at the 48 hours, 1 animal responded with grade 2 erythema and 1 with grade 3 erythema and necrosis, and 1 animal responded with $\pm$ at 48 hours. By the second exposure all but 1 animal (grade 1 erythema) responded with grade 3 erythema and necrosis. The third induction exposure(at a new site) resulted in 5 animals with $\pm$, 3 with grade 1 erythema, 1 with grade 3 erythema, and 1 animal with edema, necrosis, and eschar formation, and 1 with desquamation at the 48 reading.

2. Challenge phase - Table III and IV present the results from the challenge phase and the irritation test groups. The challenge with 20% MON-15151 in acetone caused grade 1 erythema in 5 animals and grade 2 erythema in 1 animal at the 48 hour reading. No edema, necrosis, eschar formation or grade 3 erythema was noted. The irritation test group responded with 1 animal with grade 1 erythema at 48 hours.

3. Rechallenge phase - Table III and IV presents the results from the rechallenge phase. When the group was rechallenged with 10% MON-15151 in acetone, 5 animals responded with ±, and 1 with grade 1 erythema at the 48 hour reading, while no animal responded in the irritation test group treated with 10% MON-15151.

DISCUSSION:

MON-15151 is a dermal sensitizer. The dermal scores were higher for the challenge phase than for the irritation phase with the 20% MON-15151. Although the 20% MON-15151 concentration appeared to be too high for the challenge because it also caused irritation, the rechallenge with the 10% concentration caused grade 1 erythema in 1 female, and a ± response in the 5 remaining animals, but no dermal irritation. These latter responses add credibility to the initial case where the animals responded to the 20% concentration.

Comparison of MON-15151 and MON-7200 is difficult because the suspending media was different in the studies on the two products. The technical grade, MON-7200 in water, was not a dermal sensitizer in the Buehler test, but the formulated product in acetone is a dermal sensitizer in the same test. The role of the acetone and the formulation products in this difference is unknown. Both the acetone and the formulation products could be expected to increase dermal penetration. It should be noted that all the acute toxicity studies indicated that the toxicity was lower for the technical grade than for formulated product on a mg of A.I. per kg body weight basis.

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