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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

EXPEDITE REVIEW

Subject: EPA ID # 524-UGN: Dithiopyr - Review of Dithiopyr (MON-7200) Reproduction Study in Rat, MRID 416956-01 (R. D. No. 1023) and Review of the Toxicology Data Base for Dithiopyr

Tox. Chem. Number: 717C
Project Number: 1-0193
Submission Number: S386328

From: Paul Chin, PhD Paul Chin 3/7/91
Section 2
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To: Joanne Miller, PM 23
Registration Division (H7505C)

Thru: Marion P Copley, DVM, DABT Marion Copley 4/3/91
Section Head
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Health Effects Division (H7509C)

I. CONCLUSION:

The Toxicology Branch I has reviewed "Dithiopyr (MON-7200) Reproduction Study in Rat" (MRID 416956-01, R. D. No. 1023). The reproduction study received core-minimum classification and it satisfies the guideline requirement for a reproduction study (83-4). The results of the evaluation of this study are as follows:

[The Data Evaluation Report for this study is appended to this memorandum.]

Parental Toxicity:
NOEL = 25 ppm (1.7 mg/kg/day in males; 1.91 mg/kg/day in females).
LEL = 250 ppm (16.4 mg/kg/day in males; 18.6 mg/kg/day in females)
based on decreased body weight gain (F1 males), increased relative liver weight (F0 males and F1 females), and increased absolute kidney weight (F0

females). Histopathological evidence of liver, kidney, thyroid, and adrenal toxicity in parental animals was observed at 2500 ppm, the high dose group (both sexes, both generations).

Reproductive Toxicity:

NOEL = equal to or greater than 2500 ppm, the highest dose tested in F0 and F1 parental animals.

No compound-related adverse effects were observed on reproductive parameters such as mating, fertility, gestation indices, and length of gestation.

Offspring Toxicity:

Body weights of F1 and F2 pups (both sexes) in the high dose group were decreased as compared to controls. Histopathological examination of the liver revealed diffuse hepatocellular swelling at 250 and 2500 ppm (both sexes, F1 and F2 pups). Liver toxicity observed was a significantly increased incidence of 'white spots' located on the outer margins of livers of F1 and F2 mid dose male pups culled on day 4 of lactation as compared to controls. The incidence was also found in pups (both sexes, both generations) of the high dose group. There were no indications of treatment related effects on mean number of pups/litter, sex ratio or pup viability in both generations.

Dose levels in the feed tested: 0, 25, 250, or 2500 ppm
Test species [strain]: rat [Charles River Crj:CD (SD)]

CORE CLASSIFICATION: Core minimum. This study satisfies the guideline requirements for a two-generation reproduction study (83-4) in rats.

II. ACTION REQUESTED

Review Dithiopyr (MON-7200) Reproduction Study in Rat, MRID 416956-01 (R. D. No. 1023).

Note: A tentative conclusion based on a cursory review of the two-generation reproduction study (MRID 416956-01) in rats with dithiopyr (MON-15100 or MON-7200) is found in the memorandum from Paul Chin, HED, to Joanne Miller, Registration Division, dated Dec. 19, 1990.

cc: Flora Chow, Science Analysis Coordination Branch, HED, H7509C
Norman Cook, Ecological Effects Branch, Environmental Fate and Effects Division, H7507C

III. Product information:

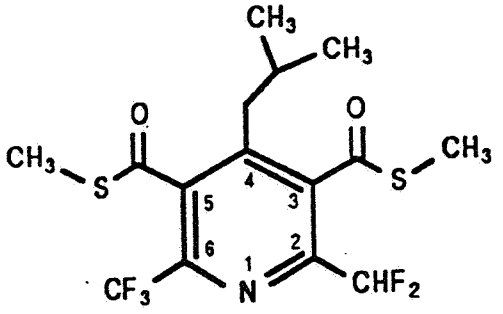
MON-15100 technical grade "dithiopyr" active ingredient is a selective herbicide for the preemergence and postemergence control of listed annual grasses and annual broadleaf weeds in established cool and warm season turfgrasses found in lawns and ornamental turf.

MON-15100 and MON-7200 are Monsanto designations for the same ingredient, ie., dithiopyr. Dithiopyr is a 3,5-pyridine dicarbothioic acid diester containing fluoroalkyl groups at the 2 and 6 positions on the ring. The chemical name for dithiopyr is: 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.

The Agency granted the extension of Experimental Use Permit 524-EUP-69 for both MON-15151 (12.7% a.i.) and MON-15104 (13.6% a.i.) formulations (dithiopyr end-use formulations under the Dimension Turf Herbicide trade name) to control annual grass and broad leaf weeds in turf grass.

The physical and chemical characteristics of dithiopyr are presented below:

Color:	Tan to light brown
Physical state:	Solid
Odor:	Sweet
Melting Range:	51-54 °C
Solubility:	water----- 1.4 ppm at 25 °C
	acetone--- > 33.3 g/100 ml
Vapor pressure:	4 X 10^{-6} mm Hg at 25 °C
pH:	5.1



Structure for MON 7200 (dithiopyr)

IV. Requirements (CFR 158.135):

Updated: March 7, 1991

Technical:

	Required	Satisfied
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
81-7 Acute Delayed Neurotox.(hen)	N	-
82-1 Subchronic Oral (rodent)	Y[1]	Y
82-1 Subchronic Oral (nonrodent)	N	-
82-2 21-Day Dermal	Y	Y
82-3 90-Day Dermal	N	-
82-4 90-Day Inhalation	N	-
82-5 90-Day Neurotoxicity (hen)	N	-
82-5 90-Day Neurotoxicity (mammal)	N	-
83-1 Chronic Toxicity (rodent)	N	-
83-1 Chronic Toxicity (nonrodent)	N	-
83-2 Oncogenicity (rat)	N	-
83-2 Oncogenicity (mouse)	N	-
83-3 Teratogenicity (rodent)	Y	Y
83-3 Teratogenicity (nonrodent)	Y	Y
83-4 Reproduction	N	Y
83-5 Chronic/Oncogenicity	N	-
84-2 Mutagenicity - Gene Mutation	Y	Y
84-2 Mutagenicity - Struct. Chrom. Aber.	Y	Y
84-2 Mutagenicity - Other Genotoxic Effect	Y	Y
85-1 General Metabolism	N	N[2]
85-2 Dermal Penetration	N	N[3]
86-1 Domestic Animal Safety	N	-

IV. Requirements (CFR 158.135) (cont'd) Updated: March 7, 1991

Formulation:

	Required	Satisfied
MON 15151 (12.6-13.5% a.i.)		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
MON 15104(13.6% a.i.)		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y
MON 15159 (1.12% a.i.)		
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	N[4]
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	Y	Y

Y - Yes; **N** - No; **R** - reserved, if tolerances are needed this study will be required.

1 The toxicology data base for MON-15100/MON-7200 technical grade dithiopyr supports the registration of dithiopyr for non-food crop use. This study is required in order to be consistent with the current requirements for reregistration under FIFRA 88.

2 A monkey metabolism study following intravenous administration of MON-15100 was acceptable. However, this study alone does not fully satisfy the toxicology Test Guidelines data requirement for metabolism because metabolism data from a single dose or repeat oral doses of MON-15100 was not generated.

3 This study is supplementary because the loss of 17 to 33% of the administered dose was not adequately accounted for and improper solvent (acetone) was used to wash unabsorbed test material from the skin.

4 A significant amount of respirable particles in this formulation may be derived by the rubbing action between particles during transport. Therefore, there may be a significant potential to become an inhalation hazard from inhaling these fine particles from this product. An acute inhalation study with MON-15159 is required prior to final registration of the product for general consumer use. See HED Doc 007787, dated Feb. 28, 1990.

V. TOXICOLOGY PROFILE:

Updated: March 7, 1991

STUDY;CLASSIFICATION; CATEGORY;STUDY #; Technical Dithiopyr	RESULTS
81-1 Acute Oral LD_{50}-Rat; Minimum; IV; 87-0045/ET-87-121; MRID# 406386-07.	LD_{50} > 5000 mg/kg
81-1 Acute Oral LD_{50}-Mouse; Minimum; IV; 87-0046/ET-87-122; MRID#406386-08.	LD_{50} > 5000 mg/kg
81-2 Acute Dermal LD_{50}-RAt; Minimum; IV; 87-0047/ET-87-123; MRID#406386-09.	LD_{50} > 5000 mg/kg
81-3 Acute Inhalation LC_{50}-Rat; Guideline; IV; 87-0048/ET-87-124; MRID#406386-10.	LC_{50} > 5.98 mg/L
81-4 Primary Eye Irrit.-Rabbit; Minimum; IV; 4313-87/BD-87-131; MRID# 406386-11	No corneal opacity; irritation reversible within 24 hours
81-5 Primary Dermal Irrit.-Rabbit; Minimum; IV; 4312-87/BD-87-131; MRID# 406386-12	Slight erythema but no edema within 0.5 hour. No effects by 72 hours
81-6 Dermal Sensitization/ Guinea Pig; N/A; N/A; 4314-87/BD-87-130; MRID# 406386-13	Not a sensitizer
82-1 Subchronic oral Toxicity; Rat; Minimum; ET-86-187; MRID# 416895-01	NOEL = 10 ppm (0.662 mg/kg/day in females) LEL = 100 ppm (6.62 mg/kg/day in females) based on increased organ weights and diffuse hepatocellular swelling. Dose levels: 0, 10, 100, 1000, and 5000 ppm in the feed.

82-2 21-Day Dermal; Rat; Guideline; BD-89-168-89-3440; MRID 413056-01	NOEL = 500 mg/kg/day LEL = 1000 mg/kg/day based on increased liver weights in male and female rats. Dermal Effects: limited to transient mild irritation in some animals in all dose groups. Incidence was generally dose-related and higher in females than in males
83-3 Teratogenicity; Rat; Minimum; ET-86-208; MRID# 410015-07	Maternal NOEL = 300 mg/kg/day. Maternal LEL = 1000 mg/kg/day (decreased food consumption). Developmental Toxicity NOEL = 1000 mg/kg/day (the highest dose tested). Developmental Toxicity LEL = not established. Dose levels tested: 0, 30, 300, or 1000 mg/kg/day by gavage in rat [Charles River Crj:CD (SD) strain].
83-3 Teratogenicity; Rabbit; Minimum; HL-88-110/241-218; MRID# 410015-08	Maternal NOEL = 500 mg/kg/day. Maternal LEL = 1000 mg/kg/day (reduced body weight gain). Developmental Toxicity NOEL = 1000 mg/kg/day (the highest dose tested). Developmental Toxicity LEL = not established. Dose levels tested: 0, 150, 500, or 1000 mg/kg/day by gavage in rabbit (New Zealand White strain).
83-4 Multigeneration reproduction; Rat; Minimum; IET 87-0053/ET-88-3; IET 87-0004/ET-87-154; MRID# 416956-01	Dose levels in the feed tested: 0, 25, 250, or 2500 ppm in rat [Charles River Crj:CD (SD) strain]. No compound-related adverse effects were observed on **reproductive parameters** such as mating, fertility, gestation indices, and length of gestation in F0 and F1 parental animals. **Parental toxicity**: NOEL=25 ppm (M: 1.7 mg/kg/day; F: 1.91 mg/kg/day). LEL=250 ppm (16.4 mg/kg/day in M; 18.6 mg/kg/day in F based on decreased body weight gain in F1 (M), increased relative liver weight in F0 (M) and F1 (F), and increased absolute kidney weight in

	F0 (F). Histopathological evidence of liver, kidney, thyroid, and adrenal toxicity was observed at HDT (M & F; F0 & F1). **Offspring Toxicity**: Body weights decrement in F1 and F2 pups (both sexes) at HDT. Histopathological examination of the liver revealed diffuse hepatocellular swelling at MDT and HDT (M & F; F1 & F2). Liver toxicity observed was a significantly increased incidence of 'white spots' located on the outer margins of livers of F1 and F2 pups (M) at MDT and F1 and F2 pups (M & F) at HDT. No compound-related adverse effects were observed on mean number of pups/litter, sex ratio or pup viability in both generations.
84-2 Mutagenicity/ Gene mutation; Acceptable; ML-87-11; MRID# 410015-09	Negative for reverse mutation in Salmonella (Ames) TA strains up to the dose limit of solubility (3000 ug/plate), with/without activation.
84-2 Mutagenicity/Gene mutation; Acceptable; SR-86-375; MRID# 410015-10	Negative for reverse mutation in Ames Salmonella strains up to the dose limit of solubility (5000 ug/plate), with/without activation.
84-2 Mutagenicity/CHO/HGPRT gene mutation; Acceptable; ML-87-10; MRID# 410015-11	Negative for inducing forward mutation at the HGPRT locus of Chinese hamster ovary cells exposed with/without activation up to cytotoxic dose levels (300 ug/ml/-S9; 30 ug/ml/+S9).
84-2 Mutagenicity/ Structural Chromosome Aberr. (CHL cells); Acceptable; ET-86-79; MRID# 410015-12	Negative for inducing structural chromosome aberrations in Chinese hamster lung cells exposed to the limit of solubility (0.33 and 1.0 mM).
84-2 Mutagenicity/ Other Genotoxic Effects; Acceptable; SR-87-9; MRID# 410015-13	Negative for inducing unscheduled DNA synthesis in primary rat hepatocytes exposed to the limit of solubility (1000 ug/ml), as measured by silver grain counts indicative of DNA damage/repair.

85-1 Metabolism; Monkey; Primate Research Inst./MSL-9719 & MSL-9720; MRID# 416646-01	MON-15100 was extensively metabolized and rapidly excreted in monkeys following intravenous administration of radiolabeled MON-15100 (^{14}C-MON-15100) at 0.01 and 5 mg/kg. Approximately 65 and 29% (high dose) and 56 and 30% (low dose) of the administered dose was excreted in the urine and feces, respectively within 72 hours after dosing. The urinary and plasma half-life values for ^{14}C-MON-15100 were 29 hours. The major metabolite (dicarbothioic acid) accounted for 28-37% and 10-14% of the dose in the urine and feces, respectively. Seven minor metabolites of MON-15100 in the urine and feces were diacid, monoacid 1, monoacid 2, and four peptide conjugates. This study is acceptable, however, a metabolism study after single or repeat oral doses of MON-15100 was not conducted.
84-2 Dermal Penetration; Monkey; Primate Research Inst./MSL-9807 & MSL-9808; MRID# 416646-01	The dermal penetration of MON-15100 was extremely low in monkeys following dermal administration of radiolabeled MON-15100 (^{14}C-MON-15100) at 4 and 40 mg/kg. The radioactivity recovered in combined urine and feces was 0.22% (low dose) and 0.06% (high dose) and in the application site skin was 0.001% of the dose at the end of the study. Most of the test material (67% to 83% from the high dose group) was removed from the application site of animals with acetone followed by soap and water after the 12 hour exposure period. In both urine and feces, the major metabolite was dicarbothioic acid (less than 1% of the dose) and seven minor metabolites were diacid, monoacid 1, monoacid 2, and four peptide conjugates. This study is supplementary because the loss of 17 to 33% of the administered dose was not adequately accounted for and improper solvent (acetone)

	was used to wash unabsorbed test material from the skin.
MON-15151 Formulation (12.6-13.5% a.i.)	
81-1 Acute Oral LD_{50}-Rat; Minimum; III; 4195-87/BD-87-132; MRID# 406386-14.	LD_{50} = 4100 mg/kg in males LD_{50} = 3000 mg/kg in females
81-2 Acute Dermal LD_{50}-RAt; Minimum; IV; 4196-87/BD-87-132; MRID# 406386-15.	LD_{50} > 5000 mg/kg
81-3 Acute Inhalation LC_{50}-Rat; Supplementary; III; ML-87-145/EHL 87093; MRID# 406386-16.	LC50 > 3.5 and < 5.0 mg/L for males and 3.3 mg/L for females
81-3 Acute Inhalation LC_{50}-Rat; Minimum; IV; 89-8189/BD-89-42; MRID# 411356-02.	LC50 11 mg/L for males and 8.9 mg/L for females
81-4 Primary Eye Irrit.-Rabbit; Minimum; II; 4198-87/BD-87-132; MRID# 406386-17	Corneal opacity reversible within 7 days; irritation reversible within 7 days; corneal corrosion reversible within 7-21 days.
81-5 Primary Dermal Irrit.-Rabbit; Minimum; II; 4197-87/BD-87-132;MRID# 406386-18	Severe dermal irritation at 72 hours, clearing within 14 days
81-6 Dermal Sensitization/ Guinea Pig; N/A; 4197-87/BD-87-133; MRID# 406386-19	A dermal sensitizer

MON-15104 Formulation
(13.6% a.i.)

81-1 Acute Oral LD_{50}-Rat; Minimum; IV; 5352-88/BD-89-21; MRID# 411300-04.	LD_{50} > 5000 mg/kg
81-2 Acute Dermal LD_{50}-RAt; Minimum; IV; 5353-88/BD-89-21; MRID#411300-05.	LD_{50} > 5000 mg/kg
81-3 Acute Inhalation LC_{50}-Rat; Minimum; III; 89098/MSL-9084; MRID#411300-06.	LC_{50} > 3.4 mg/L for males LC_{50} > 4.5 mg/L for females
81-4 Primary Eye Irrit.-Rabbit; Minimum; IV; 5355-88/BD-89-21; MRID# 411300-07	No corneal opacity; irritation reversible within 24 hours
81-5 Primary Dermal Irrit.-Rabbit; Minimum; IV; 5354-88/BD-89-21;MRID# 411300-08	Very slight to slight irritation at 72 hours, clearing within 10 days
81-6 Dermal Sensitization/ Guinea Pig; N/A;5356-88/BD-89-21;MRID# 411300-09	Not a sensitizer

MON 15159 Formulation
(1.12% a.i.)

81-1 Acute Oral LD_{50}-Rat; Minimum; IV; FD-89-182/89.2503.090; MRID# 412023-04	LD_{50} > 5000 mg/kg for males and females LD_{50} = 5000 mg/kg (ODT)
81-2 Acute Dermal LD_{50}-RAt; Minimum; IV; FD-89-182/89.2503.091; MRID# 412023-05	LD_{50} > 5000 mg/kg LD_{50} = 5000 mg/kg (ODT)
81-4 Primary Eye Irrit.-Rabbit; Minimum; III;FD-89-182/89.2503.092; MRID# 412023-06	Corneal opacity and irritation reversible within 7 days.

81-5	Primary Dermal Irrit.- Rabbit; Minimum; IV; FD-89-182/89.2503.093; MRID# 412023-07	Non-irritating
81-6	Dermal Sensitization- Guinea Pig; N/A;FD-89-182/89.2503.094; MRID# 412023-08	Not a dermal sensitizer by the Buehler method. Concentrations: Induction - 0.5 g of MON-15159 in 80% alcohol; Challenge - same conc.

VI. DATA GAPS:

MON 15159

81-3 Acute Inhalation Toxicity

Technical grade dithiopyr

One study which is being under review is a 90-day dog feeding.

VII. ACTION TAKEN TO REMOVE DATA GAPS AND OBTAIN ADDITIONAL INFORMATION:

NOTE: It is recommended that this memorandum be submitted to the registrant in its entirety.

VIII. REFERENCE DOSE (RFD):

The Toxicology Branch ADI committee will initiate the review process for dithiopyr.

IX. PENDING REGULATORY ACTIONS:

There are no pending regulatory actions against this pesticide at this time that Toxicology Branch I (TBI) is aware of.

X. TOXICOLOGIC ISSUES:

The carcinogenic potential of dithiopyr, its metabolites and degradation products have been evaluated. Results of analysis by SACB[4] using the TOPKAT software package confirmed Monsanto's conclusion that TOPKAT predicts dithiopyr and related compounds to have a low carcinogenic potential. Additional evaluation was performed by the SAR team in the Office of Toxic Substances. The SAR team has a low moderate concern for the carcinogenic potential of these compounds.[5]

[4] D. Van Ormer (31 October 1990). Carcinogenicity (SAR) Analysis of Dithiopyr. HED Project. No. INTRA - 0094. Memorandum to P. Chin.

[5] J. Cotruvo (4 December 1990). OTS Structure Activity Team (SAR) health hazard evaluation of a new pesticide. Memorandum to P. Fenner-Crisp.