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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM **EXPEDITED REVIEW**

Subject: EPA ID # 524-UGN: Dithiopyr - Response to Monsanto's Comments to Agency Questions on Two Developmental Toxicity Studies (MRID Nos. 410015-07 & 410015-08) Submitted for New Chemical Registration
Tox. Chem. Number: 717C
Project Number: 0-1282
Record Number: 264231

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

Paul Chin 6/14/90

To: Joanne Miller, PM 23
Registration Division (H7505C)

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

Marion Copley 6/14/90

Conclusion

The Toxicology Branch I concludes that the above developmental toxicity studies with dithiopyr have been adequately conducted. Thus, we are upgrading both the rat study (MRID 410015-07, Study No. ET-86-208) and rabbit study (MRID 410015-08, Study No. HL-88-110/241-218) from core-supplementary to core-minimum. These studies satisfy the guideline requirement No. 83-3 for a developmental toxicity study (two species). This memorandum will serve as a supplement to the DERs (HED Document No. 007863, dated April 18, 1990).

The toxicology data base for MON-15100/MON-7200 technical grade dithiopyr supports the registration of dithiopyr for non-food crop use. The only data gap identified is the 90-day feeding study, however, this gap would not delay registration of this pesticide. This study is required in order to be consistent with the current requirements for reregistration under FIFRA 88.

The mutagenicity study (MRID 410015-12, Study No. ET-86-79) which was previously classified as unacceptable has been upgraded to acceptable. This action is being handled by Irving Mauer, Toxicology Branch.

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Requested Action

The Registration Division requested that the Toxicology Branch determine the adequacy of the Monsanto's comments (dated May 8, 1990) to Agency questions posed in our reviews of the developmental toxicity studies in rats and rabbits referred to above.

Background

1. The Toxicology Branch reviewed the two developmental toxicity studies referred to above (HED Document No. 007863, dated 4/18/90). Both developmental studies were core-graded supplementary. However, these studies could be either upgraded to core-guideline or downgraded to invalid pending reevaluation of the additional information on bioavailability of MON-15100 (See section on ADDITIONAL INFORMATION NEEDED below).

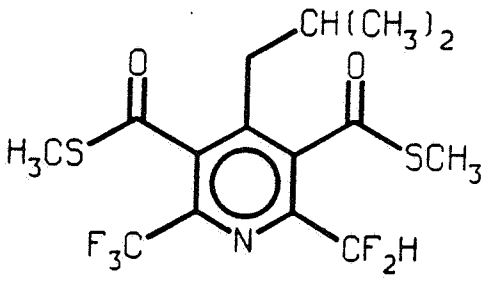
2. ADDITIONAL INFORMATION REQUESTED IN PREVIOUS DOCUMENT: Bioavailability data of MON-7200 in test animal

   The Agency must be assured that the apparent low toxicity of MON-7200 demonstrated in the developmental toxicity study in test animal (marginal maternal toxicity at 1 g/kg/day, HDT) is not the result of the poor availability of the test material in carboxymethylcellulose (CMC). Therefore, the registrant must provide the following data and information.

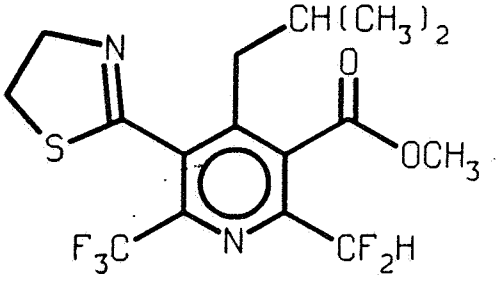
   a. The maternal liver weight from the developmental toxicity study in test animal.

   b. Data on the bioavailability of MON-7200 in the 0.5 - 1 % CMC, such as information on the degree of binding of the vehicle for MON-7200.

3. Structures for MON-7200 (dithiopyr) and MON-13200 (thiazopyr), a dithiopyr structural analog, are shown below.



MON-7200
(dithiopyr)



MON-13200
(thiazopyr)

Conclusion of Developmental Toxicity Studies:

The summary of the developmental toxicity studies with dithiopyr in rats and rabbits is as follows:

1. Developmental toxicity study in rats (MRID No. 41001507)

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.
Core classification: Core-minimum.

2. Developmental toxicity study in rabbits (MRID No. 41001508)

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
Core classification: Core-minimum.

Toxicology Branch Evaluation of Monsanto's Comments

Questions raised by the Toxicology Branch (Items A and B) and Monsanto's comments are listed below; Toxicology Branch comments follow each item.

Item A. Maternal Liver weight data

Toxicology Branch Request

Liver weight data (liver weights and liver/body weight ratios) are needed because the liver was the common target organ in a 21-day dermal toxicity study in rabbits with MON-7200 or the pilot dietary study in rats with MON-13200. The liver weight increase observed in these studies is apparently related to the absorbed dose of the test substance from 2 different routes of administration.

Monsanto Comment

Monsanto has not routinely included determination of liver weights in protocols for developmental toxicity studies since it is not required by the Pesticide Assessment Guidelines (83-3). As such liver weights were not measured on the developmental toxicity studies with dithiopyr. Acceptance of these studies should not be contingent on fulfilling a request that is not a part of the Guidelines.

Toxicology Branch Response

Monsanto's comments adequately satisfied Toxicology Branch request.

Item B. Bioavailability Data

Toxicology Branch Request

Carboxymethylcellulose (CMC), a widely used suspending agent, binds some chemicals. The CMC used in the developmental toxicity study may sufficiently bind MON-7200 and cause a decrease in the availability of test material for absorption in test animals. Therefore, the registrant should demonstrate the availability of MON-7200 for absorption when test material is suspended in CMC.

Monsanto Comment

We have evaluated all data bearing on this issue and have concluded that dithiopyr is unlikely to bind to CMC and that the observed low maternal toxicity is not a reflection of poor bioavailability. We offer 3 lines of evidence in support of this conclusion:

1. Physical chemical properties of dithiopyr make binding to CMC unlikely:

   No significant binding of dithiopyr to CMC would be expected to take place at physiological pH's found in the GI tract. The electron withdrawing properties of dithiopyr's fluoroalkyl groups will leave the ring nitrogen electron deficient. Thus, protonation of the nitrogen would only take place at very low pH's (< 2). At pH < 2.5, CMC will exist as the free acid; the carboxyl group would not be ionized.

   The calculated molar ratio for the dosing solutions used on the rat and rabbit studies are 6,250 and 20,000, respectively. Therefore, the lack of potential for chemical interaction with CMC, combined with the large molar excess of dithiopyr, indicate that the test chemical was available for systemic absorption.

2. Low level maternal toxicity would be expected based on the results of acute and subacute studies with dithiopyr:

   - Rat acute oral LD_{50} > 5,000 mg/kg
   - Mouse acute oral LD_{50} > 5,000 mg/kg
   - Rat acute dermal LD_{50} > 5,000 mg/kg

- Rat 4-week feeding study at levels of 0, 300, 1,000, 3,000, 10,000 and 30,000 ppm; vehicle - rodent feed. After 4 week terminal kill, liver weights increased in females at the 10,000 ppm feeding level (equivalent to approximately 2345 mg/kg/day).

3. A dithiopyr structural analogue (MON 13200) produced comparable maternal toxicity on pilot developmental toxicity studies that employed aqueous and corn oil vehicles:

   Dose levels of 400 mg/kg/day in the rat study (employed corn oil as the dosing vehicle) and dose levels of 250 mg/kg/day in the rabbit study (employed 1 % CMC as the dosing vehicle) produced significant maternal toxicity (e.g. body weight loss and/or maternal lethality). These studies indicate that MON 13200 is bioavailable from both dosing vehicles, since comparable maternal toxicity is observed in the 2 species.

Toxicology Branch Response

Monsanto's comments to this item are satisfactory. Monsanto's data demonstrate that the low maternal toxicity displayed by dithiopyr is not a reflection of poor bioavailability or vehicle inhibition of absorption.