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

NOV 30 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Alachlor (Lasso), EPA Reg.#524-316. Protocol - Percutaneous Absorption in Monkey. CASWELL#11

TO: Robert Taylor, PM#25
Registration Division (TS-767C)

FROM: Amal Mahfouz, Ph.D.
Toxicologist, Section V
Toxicology Branch/HED (TS-769C)

Amal Mahfouz 10/30/84

THRU: Laurence D. Chitlik, DABT
Section Head, Sections V & VI
Toxicology Branch/HED (TS-769C)
and
William L. Burnam, Chief
Toxicology Branch/HED (TS-769C)

LDC 11/23/84
11/30/84

Action Requested:

In a letter dated 9/6/84 Monsanto Company requested the review of the attached 3 protocols:

"1. Lasso Herbicide Application Exposure Study Biological Monitoring 1984 Field and Sample Protocol.

2. Percutaneous Absorption Study of Lasso Herbicide (MCB/9 Formulation) in Rhesus Monkeys.

3. Pharmacokinetic Study of Alachlor in Rhesus Monkeys Following Intravenous Administration."

The above studies had for objectives the following two items:

- To determine the level of alachlor metabolites in the monkey's urine upon dermal exposure to selected dosages of alachlor. These dosages would be selected based on new data on the applicator exposure to Lasso and Lasso EC.

- To identify the monkey's urinary metabolites for alachlor so that it can be used in the determination of these metabolites in the applicator's urine and the extrapolation of these data to actual human dermal exposure.

Recommendations:

1. The selection of the dosages used in the monkey protocols were based on the new data generated by the registrant from the applicator exposure study (see the above section under protocol #1). This protocol should be reviewed by the Exposure Assessment Branch (EAB). The Toxicology Branch needs to know if the exposure values in this study are adequate or underestimated. These values have to be verified by EAB and documented as mg/kg/day during the application period.

2. This reviewer notes that the determination of Alachlor/Metabolites in urine as indicator of dermal absorption in the exposure monitoring studies should take in consideration the following facts:

- The metabolism studies in rats indicated that the largest percentage of Alachlor/Metabolites were eliminated within 48 hours of the initial exposure. The amount of eliminated products were almost equally distributed in urine and feces. If data generated from the monkey studies are similar to the rat metabolism studies, the values calculated from urine analyses in the applicator monitoring studies should take in consideration these findings.

- The present method for the determination of Alachlor metabolites in/on food items appears to be inadequate for the determination of the actual level of all residues of concern as explained in the RCB's memo of 4/23/84 (pages 10 and 11) by Martin Kovacs. It appears that the method only measures the diethyl amine moiety. Thus the method used in the urine monitoring studies should clearly indicate if all residues of concern (as stated by RCB) will be determined in the exposure studies.

3. The submitted protocols for the monkey studies are adequate if the above issues (#1 and #2) are taken in consideration in the performance of these studies and if the amount of Alachlor applied per surface area of the monkey would correspond to the actual human dermal exposure in the field (see attached copy of submitted protocols).

Note: A copy of the "Procedure for Studying Dermal Absorption" by EPA's Robert P. Zendzian (Pharmacologist) is attached to this memo as a reference. Also a copy of the submitted protocols were forwarded to Dr. Zendzian for information, so far, he had no comments on these protocols.

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Title: Lasso® Herbicide Applicator Exposure Study
Biological Monitoring - 1984 - Field and Sample Protocol

Objective: Apply Lasso® herbicide according to common agricultural practice and collect urine from applicators for eventual biological monitoring of exposure to alachlor.

Protocol No.: 84-24-R-1A April 18, 1984

Test Substance: Alachlor formulated as Lasso® EC or Lasso® ME herbicide.

Sponsor: Monsanto Agricultural Products Company
Technology Division
800 N. Lindbergh Blvd.
St. Louis, MO 63167

Study Director: Andrew J. Klein, Ph.D.

Principal Investigator: Thomas R. Bade, Ph.D.

Quality Assurance Officer: Harry L. Hyndman, Ph.D.

Proposed Starting Date: April 23, 1984

Proposed Completion Date: June 30, 1984

Approval _____ Study Director

_____ Principal Investigator

_____ Quality Assurance Officer

Summary of 1984 Lasso® Exposure Study

Canadian Location

1. Number of replicate field tests: 4
2. Field size: 160 acres (40 acres per test)
3. Herbicide formulations: Lasso® EC, Lasso® ME (1984 production)
4. Amount of herbicide: Enough to treat 80 acres, each formulation
5. Use rate: 4 lb/acre (or recommended)
6. Application type: preplant incorporated (or recommended)
7. Field equipment needed: open cab tractor, application/ incorporation equipment, uncontaminated station wagon
8. Personnel needed: 4 operators, one observer/control subject
9. Samples: only urine samples will be collected, according to protocol
10. Product Development involvement: advance planning of location, supply of herbicides and field equipment, two applicators who have not used any acetanilide products for at least one week prior to study.

US Location

1. Number of replicate field tests: 8
2. Field size: 160 acres (20 acres/test)
3. Herbicide Formulations: Lasso® EC, Lasso® ME (1984 production)
4. Amount of Herbicide: Enough to treat 80 acres each formulation.

5. Use rate: 4 lb/acre (or recommended)
6. Application type: preplant incorporated (or recommended)
7. Field equipment needed: open (or closed) cab tractor with application/incorporation equipment, uncontaminated station wagon
8. Personnel needed: 8 operators, one observer/control subject
9. Samples: only urine samples will be collected according to protocol
10. Product Development involvement: advance planning of location, supply of herbicide and field equipment, 4 applicators who have not used any acetanilide products for at least one week prior to study.

I. Introduction - Scope and Methods

A field applicator exposure study will be conducted in the spring of 1984 in order to assess the potential exposure of farmer/applicators to alachlor which could result from the routine use of Lasso® herbicide. Previous studies have addressed potential exposure via air monitoring and passive dosimetry (gauze patch analysis). These studies have provided a measure of exposure to the applicators clothing, but an actual dose or body burden could only be estimated. A direct measure of the dose can be made by following the excretion of alachlor residues in the urine of an exposed applicator. This study will concentrate exclusively on the determination of alachlor and its potential metabolites in urine collected from personnel exposed to Lasso® herbicide via ordinary agricultural practice. The study will also attempt to measure any differences in exposure to alachlor from the use of Lasso® EC and Lasso® ME formulations.

II. General Description of the Field Experiments - Experimental Design and Records

A. <u>Replicates</u>

The study will consist of 6 replicate applications of each formulation for a total of 12 experiments. The field application will take place in two locations, one in southern Ontario and another in the vicinity of Vincennes, IN.

B. Subjects

Monsanto employees will be used for all field experiments. Both Environmental Science and Product Development personnel will be used for the field experiment and sample collection. Care will be taken to exclude contact with acetanilide products for one week prior to and during urine collection.

C. Application

Application of the herbicide will be according to label directions to fields prepared for normal planting of corn/soybeans or to fallow ground. Each replicate experiment will consist of tank-fill and application/incorporation of sufficient Lasso® herbicide to treat 20 acres at 4.0 lb active ingredient/acre (40 acres at 4.0 lb active ingredient/acre in Canada). To provide a worst case exposure estimate, the tank mix step will use 2½ gallon jugs of Lasso® EC and ME. A different operator will be used for each replicate application. If possible, four or more application/incorporation replicates will be made each day. If application equipment is normally cleaned, the final applicator of each day will perform this task.

D. Data Collection/Records

A daily log will be maintained for each replicate experiment. Weather conditions will be recorded before each tank fill and after each application. The duration of each operation and any unusual conditions will be recorded. A video camera will be used to record all tank fills on tape. A daily personal log will be kept by each operator for the duration of the sampling period.

E. Schedule of Operations

Sufficient Lasso® herbicide will be available at the location to be treated. This material will not be delivered by a subject of any field experiment. At least 160 acres will be available for the Canadian and US locations. Four consecutive 40 acre applications alternating between EC and ME formulations will be made at the Canadian location, preferably on a single day. Four or more consecutive 20 acre applications will be made at the US location. Weather permitting, applications will be made on consecutive days.

F. Sample Collection

Control urine will be collected from each participant before any application of Lasso® is made. An Environmental Science chemist will be present as an observer at each location, but not participate in any herbicide applications. The observer will provide urine

samples and fortify them with alachlor metabolites to serve as field fortifications. All participants will collect all urine excreted for a 120 hr period, starting at the time of application. Each collection will be made in a borosilicate glass bottle, sealed and labeled with the subject's initials, experiment number, date and time of collection. The sample will be cooled or frozen by placing in a cooler as soon as possible. All samples will be shipped or otherwise transported to Environmental Science labs in St. Louis for storage and analysis.

Equipment and Personnel List

I. Equipment and Personnel to be supplied by Product Development.

A. Canadian Location

1. Open cab tractor with application/incorporation equipment
2. Lasso® EC herbicide in 5 gal cans
3. Lasso® ME herbicide in 2½ gal plastic jugs
4. One station wagon or van uncontaminated with acetanilide herbicides
5. Dry ice
6. Two applicators

B. US Location

1. Open (or closed) cab tractor with application/ incorporation equipment
2. Lasso® EC herbicide in 5 gal cans
3. Lasso® ME herbicide in 2½ gal plastic jugs
4. Four applicators (2 each day)

II. Equipment and Personnel to be supplied by Environmental Science

A. Canadian Location

1. Borosilicate glass sample bottles
2. Sample log sheets
3. Labeling equipment
4. Shipping containers for samples
5. Goggles
6. Protective gloves

7. Stapler and staples
8. Tape
9. Scissors
10. Standard solution of alachlor metabolites
11. Microliter syringes
12. Plastic bags
13. Aluminum foil
14. Marking pens
15. Wire tags
16. Notebooks
17. Wind meter
18. Compass
19. Thermometer
20. Hygrometer
21. Stopwatch
22. Calculator
23. Tools
24. Two applicators
25. One control subject
26. Polaroid camera and film
27. Video recording equipment

B. US Location

1. Items 1 through 23 above
2. One uncontaminated van, one rental car
3. Dry ice or other cooling media
4. Plastic coolers or insulated shipping container
5. Four applicators

Protocol Amendment

Title: Lasso® Herbicide Applicator Exposure Study Biological Monitoring - 1984 - Field and Sample Protocol

Protocol No.: 84-24-R-1A

Amendment Author: Andrew J. Klein

Date: May 8, 1984

Reason for amendment: To specify collection of gauze patches from applicators at the Canadian location.

Amendment Approval

Andrew J. Klein
Study Director

Tom Seidl
Principal Investigator

Larry L. Hyndman
Quality Assurance Officer

Amendment: See Attached

A1-I Introduction - Scope and Methods

Gauze patch samples (passive dosimetry) will be taken from the four applicators and a control subject at the Canadian location. These samples are needed to address possible requests for additional data from regulatory officials in Canada.

A1-II General Description of the Field Experiments - Experimental Design and Records

A. Replicates

Two replicate experiments in Southern Ontario (4 experiments, 2 each with Lasso® EC and ME) will include gauze patch monitoring for alachlor. A negative control will be performed for each formulation (a total of 2 experiments) by placing gauze patches on a control subject.

B. Subjects

The applicators will include three Monsanto employees provided by Product Development and one subject from Environmental Science. The observer will be provided by Environmental Science.

C. Schedule of Operations

Gauze patches will be placed on each subject immediately prior to tank fill. Gauze patches will be placed outside clothes on each subject's cap, chest, back, thigh and each wrist. Additional patches will be placed underneath clothing on the chest and thigh for a total of eight patches. The patches will be worn throughout the course of the tank fill, application/incorporation and cleanup. The control subject will be at least several hundred feet removed from all operations with herbicides. Field fortifications of gauze patches will be made before each tank mix step and remain exposed to the weather for the same amount of time as the patches on the subjects of the experiments.

D. Sample Collection

Gauze patches will be collected from the applicators, control and fortifications immediately following the completion of a particular experiment in a manner which

minimizes the potential for contamination. Each pad will be placed in an individual clean metal can labelled with the subject's initials, experiment number and date and time of collection. The cans will be transferred to a container filled with dry ice for eventual shipment to Environmental Science labs in St. Louis for storage. The gauze pad samples will be analyzed as required.

Amendments to Equipment and Personnnel List for the Canadian Location

I. Equipment and Personnel to be supplied by Product Development

A. Lasso® EC herbicide in 2½ gallon plastic jugs

B. Three applicators

II. Equipment and Personnel to be supplied by Environmental Science

A. One Applicator

B. One control subject

C. One experiment observer

D. Prepared gauze pads for passive monitoring

E. An uncontaminated step van for gauze pad application and fortifications

F. Labeled sample cans for gauze pads