17

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

MAR 23 1993

TO: Robert Taylor (25)
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Alachlor; EPA Reg.#524-316. Additional Information on Chronic Rat, Chronic Mouse, and Monkey Absorption Studies. Accession Nos.: 247922 and 247937; CASWELL#11

Action Requested:

Review of the following addenda:

A. Addendum to Chronic Feeding Study in Rats (Accessions #70586-#70590) and 18-Month Chronic Feeding in Mice (Accession #70168 and #70169), R.D. #432, Special Report MSL-2349, July 20, 1982; Submitted by Monsanto on 7/28/82. Accession#247922.

This report presents tables for in-life physical observations on the chronic rat (BD-77-421, 11/13/81) and the chronic mouse (BD-77-423, 6/18/81) studies (The original studies were reviewed separately in two memos each dated 6/16/82).

B. Addendum to Dermal Absorption Studies (Volume 8 of 9, Section IV, Accession#70592), RD#396, Special Report MSL-1983, July 27, 1982; Submitted by Monsanto on 7/29/82. Accession #70592.

This report presents the second phase of the study entitled 'Elimination of ^{14}C-Alachlor in Rhesus Monkeys Following a Single Topical Dose', MA-81-261B, 1126/1981 (The first phase of this study, intramuscular injection, was reviewed on pages 18 and 19 of our 7/20/82 memo).

Recommendations:

A. The submitted summary tables of the in-life physical observations on the chronic feeding rat and mouse studies (both performed by Bio/dynamics Inc.) provided additional data which are useful in determining the general health of the animals, i.e., in mice, distended abdomen was noted in both sexes in all experimental groups; in rats, incidence of animals with red, thick and swollen ears (both ears) was also reported in all experimental groups.

The distended abdomen findings were noted in other studies conducted at Bio/dynamics and at other facilities during the time frame this study was conducted and therefore may be considered animal supply related. The effects noted in the rat ears could be related to ear-tagging the animals for identification. However, no adequate explanation was provided by Bio/dynamics Inc. to justify the omission of these data from the final reports. In the future, the in-life physical observations data should be routinely included in the final reports submitted for review.

B. The additional data on the monkey absorption study indicated that 50% of the dermally applied dosage was absorbed within 24 hours and that 15.6% of the dermally applied dosage was eliminated in urine. The half-life for C^{14} Alachlor elimination in urine was 31 hours. However the study is still classified as supplementary because: 1. the area treated is very small (less than 10% of the body surface) to allow a comprehensive assessment of the compound elimination or retention; 2. the amount of the compound tested appears to be highly concentrated for the surface treated (1,475 ug/cm^2 as compared to 4 ug/cm^2 in the reference method); and 3. the parenteral excretion factor used to correct the dermal absorption data appears to be inadequate because this factor was generated by a relatively high dosage intramuscularly injected instead of an appropriate dosage intravenously injected as originally described in the reference method by Wester and Maribach; 1975.

Review

A. Addendum to Chronic Feeding in Rat (BD-77-412, 11/13/81) and Mouse (BD-77-423, 6/18/81). Studies Submitted by Monsanto on 7/28/82. Accession #247922.

This addendum is a monthly record of physical observations in the chronic rat and mouse studies with Alachlor. The testing laboratory indicated that symptoms were recorded weekly throughout the study and that the submitted summary tables of the in-life physical observations represented data of the last week of each month. The testing laboratory also noted that the recorded data were not cumulative for any given month.

These tables reflected the following additional symptoms in the rat study (see also our 6/16/82 review p. 8):

- Increased incidences of animals with chromodacryorrhea and alopecia in both treated and control groups. These effects occurred at a similar frequency in the treated and control males but at a higher frequency in treated female groups than the control group.

- Increased incidence of animals with red, thick and swollen ears (both sexes) in both treated and control groups. This finding appeared to be not compound-related, i.e. the animals were ear tagged for identification and this finding may have been associated with the ear tagging process.

The following additional symptoms were also noted in the mouse study (see also our 6/16/82 review p. 6):

- Abdominal distention was noted in all animal groups. This finding may be associated with the high incidence of amyloidosis reported in this study. However, the distended abdomen findings were noted in other studies conducted at Bio/dynamics (the testing laboratory that performed this study) and other facilities during the time frame this study was conducted and therefore may be considered animal supply related.

Conclusions:

The summary tables of the in-life physical observations for the rat and mouse studies reflected some symptoms that are helpful in assessing the general health of the animals during these studies,

i.e., red swollen ears in the rats, and distented abdomen in the mice. These findings were not accurately reported in the final reports; and no adequate explanation was provided to justify the omission of these data. In the future, Bio/dynamics Inc. should routinely include this kind of data in the final reports submitted for review.

B. Addendum to the Dermal Absorption Study In Monkeys (MA-810261, 11/28/81). Addendum Submitted by Monsanto on 7/29/82. Accession #247937.

This addendum to the absorption study in monkeys contains data that were "inadvertently omitted" from the initial submission as stated in Monsanto's letter of July 27, 1982. The following is a review of these newly submitted data (see also our initial review of this study on pages 18 and 19 of our 7/20/82 memo to Mr. Robert Taylor of the Registration Division):

Test Material:

C_{14}, labeled Alachlor was diluted with Lasso EC formulation (45% a.i.) to produce a test solution with a specific activity of 22.9 microcurie/millimole (molecular weight 269), i.e.,

25 microliters solution = 11.8* mg Alachlor = 1 microcuries

Six male Rhesus monkeys were used in this study. Twenty-five microliters (1.06 uc) of the testing solution were spread over a 7.9 cm^2 of the shaven abdomen of each animal. The treated area was left uncovered and the animals were restrained in metabolic chairs for 24 hours (Wester and Maibach, Tox. Appl. Pharmcol. 32:394-398, 1975). The test material was then removed as follows: twice with water, twice with acetone then twice again with water. The elimination of the compound was monitored for five days in urine. Urine was collected at 4, 8 and 12-hour intervals the first day, and at 12-hour intervals thereafter. Liquid scintillation spectrophotometry (LCS) was used to analyze the amount of Alachlor present in the dermal wash and in urine samples. All the reported data were already corrected for a parenteral excretion factor of 71.4%. This value was obtained in phase one of the study: elimination after intramuscular injection (see our memo of 7/20/82 p. 18 & 19).

*Note: The dosage applied dermally (11.8 mg) in phase two of this monkey study is 4x higher than the dosage injected intramuscularly (3 mg) in phase one of the study. The method used as a reference (Wester and Maibach, 1975) indicated that the dosages used in each route are similar and that the extrapolation was based on data from intravenous injection and not from intramuscular injection.

Results:

Apparently fifty percent of the dermally applied dose was absorbed within 24 hours. The data in this study indicated that 15.6% of the applied Alachlor was eliminated in urine within 5 days. Elimination was slow during the first 12 hours; maximum elimination occurred after 2 to 3 days of the initial treatment. The half-life for Alachlor elimination was 31 hours in this experiment.

A comparison between the dermally absorbed amount of Alachlor in phase two of the study (5.9 mg of the 11.8 mg initially applied, as estimated by this reviewer) and the amount injected intramuscularly in phase one of the study (3 mg) reflected a 2 fold difference in Alachlor concentration in the animal system in the second phase of the study. Yet, the data in this second phase were corrected for a parenteral excretion factor of 71.4% obtained from the first phase of the study.

Conclusions:

The data presented in this addendum (phase two of the Alachlor absorption study in monkeys) indicates that apparently 50% of the dermally applied dosage was absorbed within 24 hours and that 15.6% of this initial dosage was excreted in urine within five days. The half-life for C^{14} Alachlor elimination in urine was 31 hours.

These data appear to be inadequate to assess the percent dermal penetration of Lasso EC (45% a.i.) in monkeys due to the following rationale:

1. The dosage injected intramuscularly (3 mg) was 1/4 the dermally applied dosage (11.8 mg). It was indicated that the elimination values reported in the second phase of this study were corrected for incomplete urinary excretion with a parenteral excretion factor of 71.4% (obtained in the intramuscular injection phase of this study). However it is not clear if this extrapolation was appropriate due to the fact that a 4-fold difference in dosage was noted between the two phases of the study and that the extrapolation of data was based on an intramuscular injection and not based on an intravenous injection as indicated in Wester and Maibach's method (1975).

In summmary the utility of the data obtained in this second phase of the study is questionable.

2. The surface treated was 7.9 cm^2/animal; this area represents a very small percentage of the monkey's body surface (less than 10% of the body surface) to allow a comprehensive assessment of the compound elimination or retention.

In addition, the reference method (Wester and Maibach's method, 1975) indicated that the rate of dermal application was 4 ug/cm^2; in this study the rate of application was relatively high, 1,475 ug/cm^2; hence, the treated area may have been too small for an adequate dermal application.

Classification:

The classification of this study remains as Core Supplementary due to the issues discussed above in the conclusions section under 1 and 2.

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