PMSD/ISB

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

AUG 3 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No. 100-524. Diazinon.
Protocol for a Sheep ^{14}C Dermal Metabolism Study.
DEB#: 5575 HED#: 9-1850 MRID#: N/A

FROM: Maxie Jo Nelson, Ph.D., Chemist
Dietary Exposure Branch
Tolerance Petition Section I
Health Effects Division (H7509C)

THRU: Robert S. Quick, Section Head
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Tolerance Petition Section I
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TO: G. LaRocca, PM Team 15
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Registration Division (H7505C)

BACKGROUND

In compliance with the Diazinon Data Call-In, Ciba-Geigy Corporation (registrant of products containing diazinon as the active ingredient) is required to conduct a dermal residue ^{14}C-metabolism study in sheep to support the reregistration of diazinon.

The conduct of the requisite study was discussed between Ciba-Geigy and DEB (Dr. R. Perfetti) personnel in a recent conference (5/89).

In accord with the understanding reached at that meeting, Ciba-Geigy has designed and submitted by transmittal letter of 5/30/89 a proposed protocol for a "Dermal Absorption of ^{14}C-Diazinon in Sheep" study for DEB review.

The protocol is identified as Ciba-Geigy Corporation, Agricultural Division, Metabolism Department, Protocol 137-89, Project No. 302925, Study No. M89-302-003A.

Ciba-Geigy indicates the protocol has been designed following the suggestions made by Dr. R. Perfetti. This has been verified by discussion (7/28/89) between this reviewer and Dr. Perfetti.

DISCUSSION

The biological phase of the study will be conducted at the Ciba-Geigy Vero Beach Research Center, FL. The chemistry, analytical, and characterization phases of the study will be conducted in the Ciba-Geigy Agricultural Division, Metabolism Department facilities in Greensboro, NC.

Biological Phase. The proposed study will entail use of three sheep (Dorsett Ewes), 1.5-2 years of age, weighing ca 50 kg each. Two will be used as test animals and one as the control.

The animals will be individually housed and acclimated (5 days) in metabolism cages prior to initiation of the study. No dietary (diet or drinking water) restrictions will be imposed for the study.

The transmittal letter (5/30/89) indicates that approximately 20% of the sheeps' body area will be shaved prior to dermal application.

Following the acclimation period, each of the two test sheep will receive a daily dermal dose of 2.27 g. of ^{14}C-diazinon (specific activity approximately 3.67 μCi/mg) at 24-hour intervals for three consecutive days.

The daily dermal dose is equivalent to a use rate of 0.5 lb ai/ 100 gallons, which the transmittal letter states is the maximum labeled rate of application to sheep.

Applications of ^{14}C-diazinon will be made in an appropriate solvent (acetone) to maximize absorption.

The daily treatment regimen of the control animal is not given.

Urine and feces will be collected from each of the three animals daily, beginning two days prior to test initiation and ending at sacrifice.

Sacrifice of the three sheep will occur four hours after administration of the last daily treatment.

The following samples will also be collected at sacrifice: leg muscle, omental fat, kidney, liver, heart, and skin (treated area).

Care will be taken to ensure the proper labeling, shipping (frozen or refrigerated, as appropriate), and storage of all biological samples, radiochemicals, etc..

Chemistry, Analytical, and Characterization Phases. Duplicate subsamples of each collected sample will be prepared and subjected to liquid scintillation counting for a determination of the radioactivity present.

Since characterization of the radioactive species present in tissue/organ samples containing >0.01 ppm of ^{14}C-radioactivity (in terms of ^{14}C-diazinon equivalents) is a primary objective of the study, selected samples exceeding this level will be subjected to isolation and partitioning techniques devised to maximize recovery of radioactivity, and the isolates will be analyzed for their metabolite content using appropriate chromatographic techniques (TLC, HPLC) suitable for defining the metabolite profile.

Metabolites present in sufficient amount will be further isolated and purified for characterization and identification by mass spectroscopic analysis and by other analyses deemed appropriate.

Reference standards of diazinon and its metabolites will be used to facilitate the identification of radioactive components.

Appropriate written records will be kept and a full report of the study findings will be prepared and submitted to the Agency.

DEB COMMENTS

Neither the transmittal letter of 5/30/89 nor the accompanying protocol state what type, if any, of daily dermal treatment will be administered to the control sheep in this study. The control animal should be treated in a manner identical to that of the two test sheep, except that the solution dermally applied to the control sheep should contain no ^{14}C-diazinon (the solvent, acetone, should be included in the solution applied to the control sheep). The protocol should be revised to clarify the daily dermal treatment regimen for the control sheep.

Although the transmittal letter states that ca 20% of the body area of the sheep will be shaved prior to dermal applications, the protocol does not state this. The protocol should be revised to clarify this point, to specify the location(s) of the body area(s) to be shaved, and to indicate the control sheep will receive the same shaving treatment as the two test sheep.

The protocol (p. 5) states that "the (daily dermal) dose will be administered by appropriate methods". We request additional details be provided/specified in the protocol as to how the dose will be administered.

The Diazinon Registration Standard (p. 79: footnote 3 of Table A, §158.240-Residue Chemistry) specifies that "[^{14}C] ring-labeled diazinon" is to be used in the sheep dermal metabolism study. The protocol does not specify in which area(s) of the molecule the ^{14}C labeling occurs in the radioactive diazinon prepared for dermal administration in this study. This should be stated, and ^{14}C ring-labeled diazinon should be used in the conduct of this study.

We also bring to the registrant's attention the following statements from the Diazinon Registration Standard (p. 80: footnote 3 of Table A, §158.240 - Residue Chemistry): (#1) "...studies must be conducted utilizing sufficiently high doses to permit complete characterization of residues" in biological samples; (#2) "Tissues of [^{14}C] diazinon-dosed animals must also be analyzed by methods approved for enforcement to verify whether compounds of toxicological concern have been adequately characterized." These concerns will also need to be adequately addressed by the conduct of this study.

RECOMMENDATION

The PM should forward DEB's comments, **intact**, as stated above, to Ciba-Geigy for incorporation into the protocol and the study.

cc: Reviewer (M. Nelson), Reading File, Circulation (7), Diazinon Registration Standard File, Diazinon Subject File, ISB/PMSD (E. Eldredge).

H7509C:DEB:Reviewer(MJN):CM#2:Rm804:557-7423:typist(mjn): 1005DIAZ.PRO:8/1/89.

RDI:SectionHead:RSQuick:8/1/89:BranchChief:RDSchmitt:8/3/89.