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

FEB 17 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Diazinon Registration Standard - Response to Data Call-in on Storage Stability for Weathered Crop Materials.
EPA Registration No. 100-577.
(No MRID No.) [RCB # 2927]

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Registration Division (TS-767C)

and

Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Robert S. Quick, Section Head
Tolerance Petition Section I
Residue Chemistry Branch
Hazard Evaluation Division (TS-769C)

RM

Background

Ciba-Geigy Corporation, Agricultural Division, registrant of products containing diazinon as the active ingredient, has submitted (letter dated August 7, 1987) a protocol for the study of storage effects on diazinon residues in weathered crop materials. The protocol was submitted to comply with the Diazinon Registration Standard issued on August 22, 1986. Ciba-Geigy requests the Agency review and comment on the proposed protocol and concur on the time-extension request.

The Diazinon Registration Standard conclusion on storage stability was as follows (see page 21 of the Residue Chemistry Chapter):

"o All of the plant residue and animal feeding data requested in this Standard must be accompanied by information pertaining to the conditions and duration of sample storage prior to residue analysis and on the stability of diazinon under the storage conditions used."

The Agency felt it was prudent to add the following data requirements for diazinon storage stability (see footnote 7, pages 25 and 26 of the Residue Chemistry Chapter).

" 1. If the required metabolism data indicate the presence of residues of toxicological concern in plant and animal commodities, data depicting the stability of such residues in storage are also required.

"2. To support crop residue data, storage stability studies must be conducted on <u>both</u> <u>weathered</u> samples and <u>fortified</u> frozen samples of one representative crop from each crop grouping (40 CFR 180.34) on which registered uses of diazinon exist. Analyses of each crop must be conducted over a time period that includes the time interval that the raw agricultural commodity (RAC) is held in frozen storage prior to the crop residue analysis. To support residue data on processed commodities, <u>fortified</u> storage stability data are required for <u>all</u> processing studies submitted to the Agency. Analyses must be conducted over a time period that includes the frozen storage of the RAC prior to processing and <u>each</u> processed commodity prior to the residue analysis. Acceptable protocols must be submitted to the Agency ninety (90) days after receipt of this Notice. The protocols must be approved by the Agency prior to initiating the studies.

"a. <u>Storage stability data using weathered samples</u>. Data are required on the parent compound in which crop samples field-treated with a typical end-use product are frozen immediately upon harvesting. The integrity of the samples must be maintained by freezing. The samples must be analyzed for diazinon on the day they arrive at the analytical laboratory, and then stored frozen and analyzed periodically for diazinon during the time intervals specified in the Agency-approved protocols.

"b. Storage stability data using fortified samples. Data are required on diazinon and metabolites of concern in which a group of untreated samples of RACs and processed crops are fortified (spiked) with only diazinon (pure active ingredient) and other groups are fortified individually with each metabolite of concern. Immediately after fortification, the samples fortified with diazinon must be analyzed for diazinon and samples fortified with other metabolites of concern must be analyzed for only the metabolite with which the sample was fortified. Sample integrity must be maintained by freezing, and analyses for diazinon and metabolites must be conducted during the time intervals specified in the Agency-approved protocols.

"c. Storage stability data for livestock/poultry feeding studies. If cattle and poultry feeding studies are required, fortified storage stability studies will be required on all animal commodities (i.e., tissues, milk, and eggs) for which residue data are submitted to the Agency. Analyses must be conducted over a time period that includes the time interval that each commodity is held in frozen storage prior to residue analyses."

Storage stability problems have frequently been encountered in numerous petition reviews and in Registration Standards. In attempting to clarify ambiguities in interpretation of existing guidelines, and thereby aid registrants in submitting acceptable data packages on the magnitude of the residue to facilitate the Agency's review process, the Agency prepared (August 1987) a Policy Statement/ Position Document on storage stability. The title of the document is "Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data" and is currently available from the National Technical Information Service, ATTN: Order Desk, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). The order number is PB88 112362/AS.

Our conclusions and recommendations follow.

RCB CONCLUSIONS

1. RCB Conclusion on the Study Purpose

The registrant's purpose for the study is consistent with RCB's objective for a storage stability study which is "Are the parent pesticide and its metabolite(s) that together comprise the total toxic residue which is to be regulated stable in the 'matrices of interest' during storage?"

2. RCB Conclusion on Blended or Unblended Samples

The registrant needs to state which form or condition of samples, i.e., blended, whole, or raw extract will be used in this study. The samples used in the storage stability study must be in the same form, blended or whole, as the samples used to determine the magnitude of the residue. The registrant needs to clarify "immediate freezing" as this implies storing samples whole (unblended). If the registrant plans to store some samples whole and some samples in blended form then storage stability data will be needed for both forms.

3. RCB Conclusion on Translation of Data from One Storage Stability Study to Other Samples

The registrant is planning to support continued registration of diazinon for use on commodities in more than four crop groups (legume, cereal, leafy and root, and tuber vegetable). RCB is unwilling to translate storage stability results from one crop group to another crop group. Thus, the registrant should provide storage stability data for at least one representative commodity from each crop group which he plans to support with diazinon residue data.

4. RCB Conclusion on Storage Stability Study Justification

The justification for this type of study is that data on the magnitude of the residue on raw or processed agricultural commodities are required by 40 CFR 158.125 to support the registration of any pesticide for use on a food or feed crop. Unless the field trial residue samples are quickly analyzed,

data are needed to validate the magnitude of the residue in the various commodities during periods of storage. RCB does not agree that justification is to validate results from metabolism studies and methods. The registrant should provide a copy of Ciba SOP 4.2 in the final report to RCB.

5. RCB Conclusion on Use of Fortified Samples and/or Weathered Residue Samples

The current Agency policy is "The registrant or petitioner may choose whether to use field-incurred residue samples of known value analyzed prior to storage or to use fortification samples in the storage stability study." (See Agency Position Document "Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data"). The registrant has to run either/or, but not both types of studies to satisfy the data requirement.

6. RCB Conclusion on the Analysis Schedule for the Storage Samples

While no specific analyses schedule is proposed in our Agency position document, Data Reporting Guideline for Storage Stability, or in the Standard Evaluation Procedure for Storage Stability we are in this case dealing with a pesticide that is prone to breakdown and/or has high volatility. RCB suggests additional analyses early in the test program, and also toward the end of the test.

7. RCB Conclusion on Analytical Method for the Storage Stability Study

RCB has no objection to waiting until the metabolism studies are completed before deciding on what new method, if any, to use. However, we point out there are adequate existing methods, including several FDA multiresidue protocols for diazinon, per se. It is possible that additional validation data for metabolites is all that would be necessary for these methods.

8. RCB Conclusion on Quality Control Proposed

RCB agrees each time test point should be validated by one control, duplicate fresh fortification of the control, and duplicate of the actual storage sample. The registrant should report each individual datum point gathered in addition to the average plus one standard deviation. RCB agrees to the proposed retention and storage of records.

9. RCB Conclusion on Fortification Levels for the Storage Stability Study

RCB cautions the registrant that level (magnitude) of residue in the study be high enough that slight changes are detected within the precision of the method.

10. RCB Conclusion on Preliminary Storage Stability Study

In this situation, where diazinon is known to be prone to breakdown and has high volatility, RCB suggests the registrant run the storage stability study in advance of any of the magnitude of the residue studies so that proper storage and maximum storage times can be determined before treated samples are collected and stored.

11. RCB Conclusion on Granting a Time Extension

While RCB has no objection to the 18-month time-extension request, granting a time extension is an administrative decision. We note this situation fulfills the PR Notice 85-5 guidance where a sequential data requirement exists; i.e., metabolism studies must identify what should be measured during storage and appropriate analytical methods developed before storage stability studies can be run.

RCB Recommendations

Prior to commencing any storage stability study RCB recommends the registrant first resolve all plant metabolism concerns and then validate appropriate analytical methods.

RCB recommends this entire review be forwarded to the registrant for his consideration of Conclusions 2, 3, 4, 5, 6, 7, 8, 9, and 10.

The Registration Division needs to respond to conclusion 11 and decide on granting the requested time extension.

Detailed Considerations and Discussion

Petitioner's Response

In his cover letter the registrant states the following:

> Storage Stability Data
>
> EPA Submission Date 11/08/88
> (Protocol Due in 90 Days)
> Proposed Submission Date 5/90
>
> Protocols for storage stability studies using both weathered samples and fortified samples are enclosed. The proposed deadline allows development of appropriate and validated analytical methods with which to determine storage stability. The study would be initiated in 4/89 when the analytical methods have been developed and would run for one year.

The document to be considered in this review is titled "Residue Stability Study Under Freezer Storage Conditions for Diazinon Residues in Weathered Crop Materials" under the direction of M.W. Cheung and L.G. Ballantine. The Ciba project code is 302925. The protocol is not dated, nor has it been signed by the principal managers of the proposed project.

RCB Comments

RCB acknowledges there are two protocols under separate review. This review is concerned with this storage stability data for diazinon residues on weathered crops. In a separate RCB review we will comment on the storage stability protocol using fortified samples.

The registrant's study objective is consistent with the Agency's primary question "Are the parent pesticide and its metabolite(s) that together comprise the total toxic residue which is to be regulated stable in the 'matrices of interest' during storage?" While proposing only a 1-year study the registrant has tentative plans to extend the project longer, if appropriate.

The residue data will be presented for diazinon and metabolite(s) of the Toxicology Branch concern identified in upcoming ^{14}C-diazinon plant metabolism studies.

In the Test System the registrant proposes the use of weathered crop matrices, frozen immediately from four crop groups such as legume, cereal, leafy, and root and tuber vegetables. RCB points out the registrant should handle his storage stability samples exactly like the field-incurred residue samples. At a minimum this is storage in the same freezer, same type of container, and for the same length of time. The registrant proposes immediate freezing of samples which implies unblended samples; thus, the field-incurred residue samples should also be unblended. In storage stability studies the registrant has the option to use either unblended samples, or blended, or even raw sample extracts provided the field-incurred residue samples are stored in like manner. Field-incurred residue samples stored in one or more conditions, such as whole samples and blended samples, for over 2 weeks before analysis will require storage stability data to validate each condition of sample storage. The registrant needs to address our concerns as to what form(s) samples will be stored.

There are four proposed separate storage stability studies, one each for a representative commodity of a different crop grouping. Hopefully, this will be a series of storage studies on unrelated crops all showing similar results so that future petitions and studies required for registration on related commodities can reference these acceptable studies in lieu of conducting additional storage stability studies. RCB does foresee a potential problem. The registrant plans to support continued registration of diazinon on commodities in more than these four crop groupings. At this time RCB is not willing to translate storage stability data to commodities in a different crop grouping. Thus the registrant should plan on a storage stability study for at least one representative commodity for each crop group which he plans to support with diazinon residue data.

RCB agrees that the purpose of the study is to determine stability of diazinon residues under freezer storage conditions. We do not agree the justification is to validate results from metabolism and method validation. Instead, data on the magnitude of the residue for crops, meat, milk, poultry, eggs, fish, and processed commodities are required by 40 CFR 158.125 to support the registration of any pesticide intended for use on a food or feed crop under the amended Federal Insecticide, Fungicide, and Rodenticide Act. Therefore, unless field trial residue samples are quickly analyzed (14 days or less), data will be needed from the registrant/petitioner to validate the magnitude of residue levels in the various commodity matrices of interest during such a storage period.

Storage at -15 °C is acceptable. The registrant should supply a copy of the Coca Laboratory (the test facility) practices as outlined in Ciba SOP 4.2 in the final report to RCB.

In the section on experimental design, RCB interprets the registrant's proposed course of action to be both a weathered samples field-incurred residues and a fortified control residues storage stability study(ies). In spite of what the Registration Standard Guidance Package states, current Agency policy is, "The registrant or petitioner may choose whether to use field-incurred residue samples of known value analyzed prior to storage, or to use fortification samples in the storage stability study." (See Agency Position Document "Effects of Storage (Storage Stability) on Validity of Pesticide Residue Data"). Thus, the registrant has to run either/or, not both types of studies to satisfy the data requirement. Of course, we would not object if the registrant provides storage stability data from both types of studies.

The registrant proposes an analysis schedule of 0 day then 3, 6, and 12 months. There is no specific periodic sampling schedule in the position document, Data Reporting Guideline (DRG) Addendum for Storage Stability, or in our Draft Standard Evaluation Procedures (SEP) on Storage Stability. It is determined on a case-by-case basis. In this situation we are dealing with a pesticide that is prone to breakdown and/or has high volatility; thus, additional sampling early in the test program and toward the end are appropriate.

The registrant is proposing to use new method(s) to be developed after the metabolism studies are completed to quantitate residues of parent diazinon and the metabolite(s) of concern. RCB does not object to waiting until the metabolism studies are completed before deciding on new method(s). However, RCB points out there are adequate

existing methods, including several FDA multiresidue methods for diazinon, per se. It is possible additional validation recovery studies for the diazinon metabolites is all that would be necessary to make these methods applicable to detect diazinon metabolites.

The registrant proposes to analyze a set of five samples as follows: one control, duplicate of fortified controls, and duplicate of the actual stored samples, whether field incurred residues or fortified samples.

Fortification levels are proposed based on metabolism study results. RCB cautions that regardless of the fortification or any future proposed tolerance that the levels used in the storage stability should be high enough that slight changes are to be detectable within the precision of the analytical method. For example, a field-incurred residue of 0.01 ppm to 0.02 ppm determined by a method of 0.01 ppm precision would not be acceptable. Whereas using exaggerated rate application to get 1 ppm or fortification at 1 ppm with a method precision of 0.02 ppm to 0.05 ppm to be able to detect changes is acceptable for a storage stability study.

RCB has no objection to the proposed maintenance of records. As proposed the lab notebooks detailing the data actually generated are under the control of the chemist until the final report is accepted, then they are all archived.

The final report proposes to have an average recovery and one standard deviation. RCB suggests each individual datum point be listed that was used to determine the average also be reported along with supporting chromatographic data (not just representative chromatographic data).

While not in the proposed storage stability protocol RCB offer these suggestions for the registrant's consideration. In the situation where diazinon is known to breakdown and/or is highly volatile, it is advisable to run a storage stability study for the parent, and presently identified metabolites at higher levels (1 to 10 ppm), in advance of any of the magnitude of the residues studies so that proper storage and maximum storage times can be determined before treated samples are collected and stored. For studies to fill data gaps in the magnitude of the residue for diazinon, a storage stability study should also be run concurrently with the storage of any particular crop group samples.

Regarding the registrant's proposed time extension request to submit the results of the diazinon storage in May 1990 instead of November 1988 RCB's position is as follows:

PR Notice 85-5 (Policy Regarding Time Extensions for Submitting Additional Data to Support Existing Registrations, dated August 22, 1985) states that:

"... on a case-by-case basis consideration will be given to extension requests due to unavoidable analytical problems, and for sequential data requirements in cases where studies cannot be initiated until other studies are completed. Such is the case here where metabolism studies must be completed or methods are developed to measure any storage stability changes. However, the registrant is required to demonstrate the validity of the problem and show good faith efforts toward resolution."

Accordingly, RCB considers the registrant's request for a time extension reasonable to complete plant metabolism studies before developing appropriate analytical methods to determine residue levels in a storage stability study. While RCB has no objection to the time extension request, granting of a time-extension is an administrative decision.

TS-769C:RCB:Reviewer(FDG):CM#2:RM814B:557-0826:JOB:92093:
C.Disk:KENCO:11/12/87:dg:jh:edited:fdg:2/16/88.

cc:Diazinon Registration Standard File(Boodee),R.F.,Circu,
Reviewer(FDG),ISB/PMSD(Eldredge),Diazinon Subject File.

RDI:SectionHead:R.S.Quick(MJNfor):2/17/88:R.D.Schmitt:2/17/88.