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Pesticide Reregistration Rejection Rate Analysis Residue Chemistry / Environmental Fate Follow Up Guidance For Conducting Rotational Crop Studies

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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Guidance on How to Conduct Studies on Rotational Crops.

FROM: Ed Zager, Chief
Chemistry Branch II: Reregistration Support
Health Effects Division (H7509C)

and

Debra Edwards, Ph.D., Chief
Chemistry Branch I: Tolerance Support
Health Effects Division (H7509C)

TO: Peter Caulkins, Acting Director
Special Review and Reregistration Division (H7508W)

and

Lawrence Culleen, Acting Director
Registration Division (H7505C)

THRU: Penelope A. Fenner-Crisp, Ph.D. , Director
Health Effects Division (H7509C) 2/23/93

Earlier this year the Chemistry Branches of HED took over responsibility for the review of data generated on rotational crops (Guideline No.'s 165-1 and 165-2). The attached paper was prepared by a team consisting of Dr. R. Perfetti, Dr. R. Loranger, Dr. W. Hazel, F. Suhre, M. Rodriquez and R. Quick in order to provide guidance to Registrants and Chemistry Branch personnel on how to conduct and review these studies. This document will be utilized by the Chemistry Branches in future reviews of rotational crop studies.

We recommend that this paper be provided to all interested parties.

cc (With Attachment): L. Rossi, S. Irene, RBP, RF, Petition Review Aids File and Rotational Crops File

GUIDANCE ON HOW TO CONDUCT STUDIES ON ROTATIONAL CROPS

INTRODUCTION

The Chemistry Branches of Health Effects Division (HED) have taken over the responsibility for review of studies which determine whether pesticide residues of concern result in rotational crops as a result of uptake from soil of previously treated fields (Guideline Nos. 165-1 and 165-2). This transfer was performed because the concern over residues in these situations is chiefly dietary. The following paper is intended to provide additional guidance to HED personnel and other interested parties as to the requirements and procedure for review of submitted studies.

HISTORICAL

Studies on "Confined Rotational Crops" (Guideline Number 165-1) and "Field Rotational Crops" (165-2) are conditionally required under 40 CFR 158 for uses of pesticides on terrestrial food crops and aquatic food crops. As stated in Subdivision N, a rotational crop use is any field-vegetable crop use, aquatic crop use or any other site use on which it is reasonably foreseeable that any food or feed crop may be produced after application of a pesticide. The purpose of these studies is to determine the nature and amount of pesticide residue uptake into rotational crops. The confined study uses radioactive material applied to a small plot (often laboratory/greenhouse). Results of these "hot" studies are used to determine whether field studies (using non-radioactive pesticide) are needed to measure residues in rotational crops grown under actual field conditions. Based on these data appropriate crop rotation restrictions (time from application to planting of rotational crop) may be established and the need for tolerances on the rotated crops determined.

Review of these studies has been conducted by the Environmental Fate and Ground Water Branch (EFGWB) in the Environmental Fate and Effects Division (or its predecessors in earlier organizations of OPP). Presumably this assignment was based on the importance of soil residues as a factor in determining levels of residues in rotational crops.

Traditionally the confined study has served as a worst-case indicator of whether residues could occur in rotational crops. The study is often conducted indoors using potted plants, conditions which would tend to reduce the dissipation of the pesticide in the soil. Until recently, if detectable residues of concern were found in the crop during the confined study after the proposed rotational crop interval, the field trials would normally be required to assess whether residues occur in rotational crops under actual growing conditions. In some cases registrants have volunteered to perform field studies to refute results of the confined study, especially if the registrant did not want a rotational crop

interval on the label. If detectable residues were found in the field studies for crops having a 12 month plantback interval (or after a shorter interval the registrant desired on the label), the registrant would be directed to seek a tolerance under the FFD&CA. In this case, a tolerance petition was submitted and responsibility for review shifted to the Chemistry Branch in HED.

Recently, EFGWB has been using the results of the confined studies alone to determine whether tolerances are required for rotational crops. Under this revised process, EFGWB has deferred to Toxicology Branch when radioactive residues of the parent compound or closely related metabolites were found in the crops during the hot study. In other words, the field trials have been eliminated as an early step in determining the need for rotational crop tolerances. Under that procedure, if Toxicology Branch (TOX) concluded that the residues identified in the confined study were not toxicologically significant or, if they were toxicologically significant, but the levels present were not toxicologically significant, then no tolerance was required. However, if TOX concluded the opposite, the registrant was referred to the Chemistry Branches in HED.

Scientific Considerations

Confined Rotational Crop Studies: 165-1

The protocol for performing the three required confined rotational crop studies (small grain, leafy vegetable and root crop) is provided in Pesticide Assessment Guidelines Subdivision N. Acceptance Criteria were discussed in the Agency's Phase 3 Technical Guidance Document. Confined rotational crop studies are essentially metabolism studies; therefore, it is recommended that the publication entitled "Additional Guidance for Conducting Plant and Livestock Metabolism Studies" (7/16/92) be consulted before conducting a confined rotational crop study. (It should be noted that, in the case of confined rotational crop studies, the application rate is 1X, not an exaggerated rate.) . This paper will refer frequently to that document when discussing various phases of the subject experiments. A flow diagram describing the approach discussed in this paper is provided in Figure 1 at the end of this document.

The following should be considered when a confined rotational crop study is to be conducted. The test material should be the pure active ingredient radiolabeled (PAIRA) with ^{14}C in a non-labile position (e.g., in a ring). The parent compound only should be applied to the appropriate soil type (usually a sandy loam) at the maximum label rate (1X) and the required three rotated crops (small grain, leafy vegetable and root crop) should be planted at appropriate soil aging intervals (e.g, 1, 4, 7 or 9, and 12 months). Sampling of the soil is not required and need only be performed at the Registrant's discretion. The crops should be

harvested and the appropriate plant parts (see Pesticide Assessment Guidelines Subdivision O, Table II) should be sampled and combusted to determine the total radioactive residue (TRR). At this point, if each of the three crops demonstrate a TRR of <0.01 ppm in edible portions at one of the plantback or soil aging intervals then the Chemistry Branches will conclude that no further work and no tolerances are needed. An appropriate rotational crop restriction can be set at the shortest interval where no TRR is ≥0.01 ppm, provided that the Registrant is willing to place this interval on the label. If the TRR is <0.01 ppm in all three crops at the one month interval, then no plantback restriction will be needed on the label. If, however, in the three confined studies, the minimum intervals at which the TRR is <0.01 ppm differ, then the rotational crop restrictions will be set at the interval appropriate to each tested crop group with the longest interval being applied to all other (untested) rotated crops. The following example should be considered:

> The TRR for leafy vegetables is <0.01 ppm at the 1 month plantback interval, the root crop TRR is <0.01 ppm at the 4 month interval and the grain crop TRR is <0.01 ppm at the 9 month interval. The rotational crop restrictions would be 1 month for leafy vegetables, 4 months for root crops and 9 months for small grains and all other rotated crops.

It is the Registrant's prerogative to perform additional confined rotational crop studies on other crops to establish less restrictive intervals based on levels of radioactivity.

In rare cases, TOX may have concerns regarding the presence of a pesticide or metabolite at levels <0.01 ppm. Determination of the presence (or absence) of specific metabolites of concern at levels <0.01 ppm may be required in these cases.

If <u>any</u> of the plants in the confined studies exceed the trigger value (0.01 ppm) at the 12 month interval, then the nature of the residue in those test crops having a TRR >0.01 ppm must be determined. The Registrant is referred to the 7/16/92 guidance document discussed above (see also the comment regarding the application rate for confined rotational crop studies) for a description of the procedures which need to be followed to accomplish this determination. If any one of the three crops shows <0.01 ppm at a given interval but the Registrant desires a shorter interval on the label for that crop where the TRR is >0.01 ppm, then the composition of the TRR in that rotated crop (at the desired interval) should be determined as described above for the crop parts where the trigger value (i.e., 0.01 ppm) was exceeded. If several samples of the crop are available at the desired interval, the sample having the highest TRR should be utilized. In either of the above cases, this information is needed in order that

the Agency can make a conclusion as to whether the residue is an inadvertent residue of no concern or whether cold field trials are needed to make that determination.

If the metabolism in rotated crops appears to be different than that in the primary crop, that is, if different metabolites are observed in rotated crops than in primary crops, the Agency will make a determination as to whether the different rotational crop metabolites are of concern at the levels observed. If necessary, the HED Metabolism Committee will be consulted to expedite this decision.

The following are examples of the situations described above;

The primary (target) crop metabolism studies indicate that the parent and metabolites A, B, C, D and E are present in the plant. The Agency decides that only the parent and metabolite B need to be regulated in the tolerance expression. The following three scenarios might be encountered regarding rotational crops:

1) The confined rotational crop studies indicate that the TRR is >0.01 ppm and that parent and metabolites A, B, C and D are present. Limited rotational crop field trials will normally be required with analysis for parent and metabolite B if it is determined that these residues could be present at detectable levels. If, however, metabolites A, C and D are present at much higher levels in the rotational crops than in the primary crop, the HED Metabolism Committee <u>may</u> be consulted as to whether the other metabolites need to be quantitated.

2) The confined rotational crop studies show that the TRR is >0.01 ppm and that the radioactive residue consists of no parent and metabolites D and E. In this case the Agency would normally conclude that this is an inadvertent residue of no concern situation and no field trials would be required. A rotational crop restriction may be necessary. As above however, if metabolites D and E are present at much higher levels in the rotational crops than in the primary crop, the HED Metabolism Committee <u>may</u> be consulted as to whether these metabolites need to be quantitated.

3) The confined rotational crop studies indicate that the TRR is >0.01 ppm and that there is no parent present but that the major portion of the TRR consists of a new metabolite F. This will require a decision, as to whether there is toxicological concern over the new metabolite. At this point the HED Metabolism Committee may be consulted for an expedited decision. If it is concluded that the metabolite is of concern at the levels likely to be present, then F should be analyzed for in the limited rotational crop field trials. If it is decided that F is of no concern then, as in 2 above, this is an inadvertent residue of no concern situation and no field trials are necessary. However, a rotational crop restriction may be necessary.

It is recommended that the confined studies be submitted to the Agency as soon after completion as possible, so that the Agency can make a conclusion as to whether there is a potential inadvertent residue of concern (i.e., will limited field trials be needed ?) as expediently as possible. This will allow the Registrant to design the field trials in a more efficient manner (i.e., what compounds require analysis in the field trials).

Field Rotational Crop Studies (Limited and/or Extensive): 165-2

If the level of the total radioactive residue in the confined rotational crops exceeds 0.01 ppm at the desired rotational interval or at 12 months, and once the nature of the residue in the rotational crops is understood, then the Registrant should consider the Agency's position regarding the residue to be regulated in the primary crop (see discussion above) to decide whether the first tier of field trials should be initiated. That is, if the composition of the TRR in the rotational crops is such that residues which are regulated in the primary crop are observed at levels ≥0.01 ppm in the rotational crop (following the criteria set forth in the 7/16/92 document with the exception of exaggerated application rates), then field trials should be performed. For further guidance on the protocols for carrying out these trials see Pesticide Assessment Guidelines Subdivisions N and O as well as the following comments.

The limited field trials should be conducted on a representative crop (as defined in 40 CFR 180.34 (f)) at two sites per crop for the following 3 crop groups: root and tuber vegetables , leafy vegetables and cereal grains for a total of 6 trials. The 6 trials should be conducted on a specific crop in each of the three crop groups which the Registrant intends to have as a rotational crop on the label. The soil should be treated at the maximum label rate and the maximum number of applications and the appropriate crops should be planted after the minimum aging interval. The crops should be harvested and all of the plant parts prescribed in Subdivision O, Table II should be analyzed for the residues of concern observed in primary crops as well as any other residues of concern specific to rotational crops which fulfill the criteria set forth in the Confined Rotational Crop section of this paper. Detection limits for rotational crops should be comparable to those for primary crops.

If no detectable residue are observed in raw agricultural commodities in the limited field trials, then no tolerances will be needed. However plantback restrictions will normally be needed unless confined or field studies show no detectable residues of concern at a 30 day plantback interval.

If the limited field studies above indicate that detectable residues will occur, then rotational crop tolerances will be required. The requirement for number of trials would be the same as

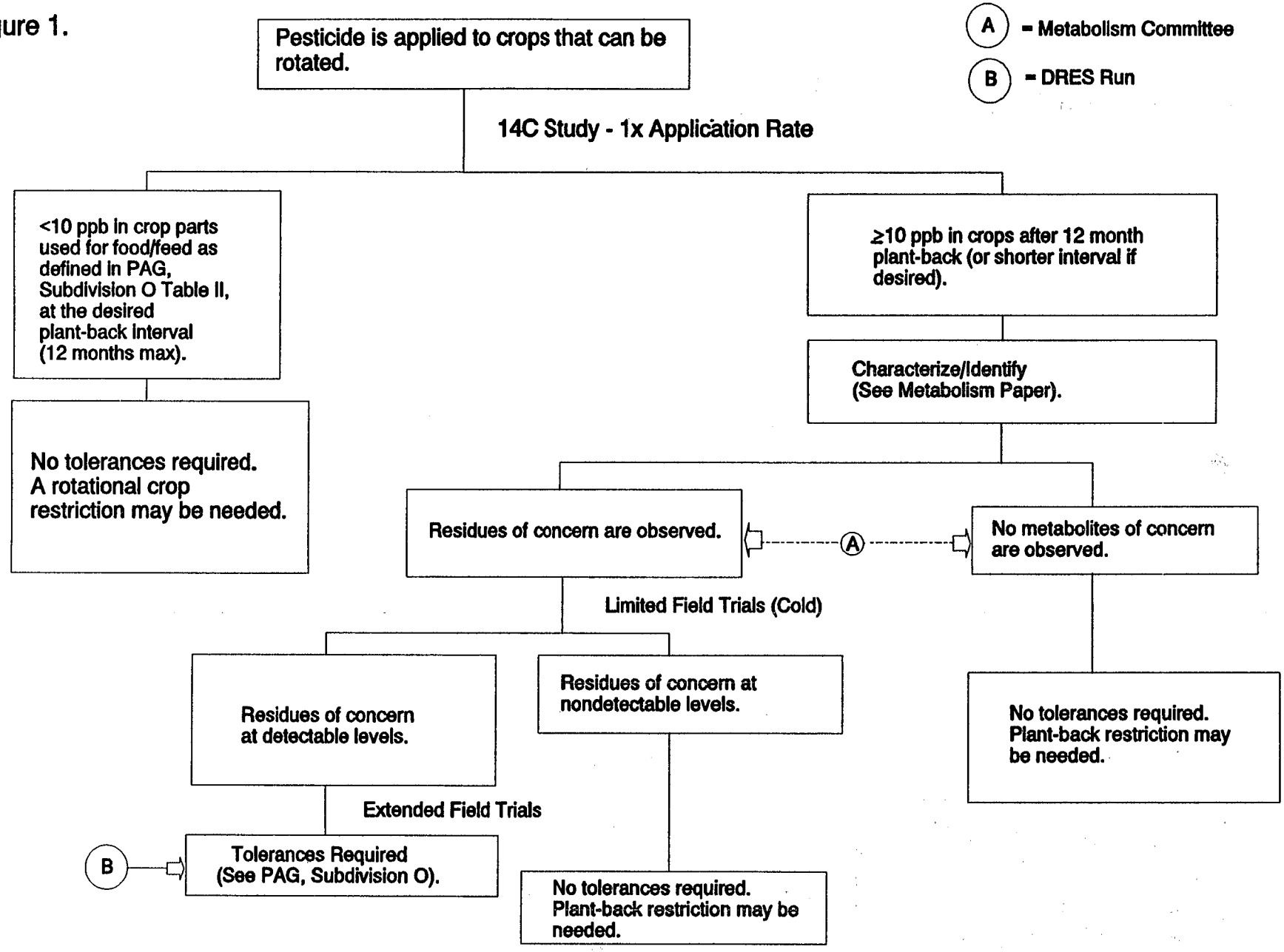
that to establish primary tolerances on all crops (or crop groups) which the Registrant intends to have as rotational crops on the label. If the Registrant desires to allow the "universe" of crops to be rotated, then magnitude of the residue data is required on representative crops (see 40 CFR 180.34 (f)) for all crop groups which could be planted in a typical crop rotation sequence. With respect to treatment, these trials should be conducted in the same manner as discussed above for the limited trials. If the Registrant believes that a lesser number of crops would be rotated because of the nature of the pesticide or due to the way it is used, then guidance should be obtained from the Agency regarding specific data requirements in that case. If tolerances exist on the crops to be rotated as a result of a primary use, then rotational data on these crops would be required only if residues in rotated crops are significant in comparison to those in the primary crop.

Regulatory Considerations

It is the Agency's position that data waivers or agreements concerning rotational crop requirements granted previously by EFGWB/EFED should continue to be effective under this new guidance and therefore HED will not reactivate rotational crop data requirements in these cases.

In the future, under revised Guidelines, the limited field rotational crop requirement may be altered so that an increased number of limited field trials will be required. This requirement will not be applied retroactively.

Figure 1.


A = Metabolism Committee
B = DRES Run
Pesticide is applied to crops that can be rotated.
14C Study - 1x Application Rate
<10 ppb in crop parts used for food/feed as defined in PAG, Subdivision O Table II, at the desired plant-back interval (12 months max).
No tolerances required. A rotational crop restriction may be needed.
≥10 ppb in crops after 12 month plant-back (or shorter interval if desired).
Characterize/Identify (See Metabolism Paper).
Residues of concern are observed.
A
No metabolites of concern are observed.
Limited Field Trials (Cold)
Residues of concern at detectable levels.
Residues of concern at nondetectable levels.
No tolerances required. Plant-back restriction may be needed.
Extended Field Trials
B
Tolerances Required (See PAG, Subdivision O).
No tolerances required. Plant-back restriction may be needed.