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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

AUG 6 1992

MEMORANDUM

SUBJECT: Bromacil. Protocol for Nature of the Residue in Plants-Citrus Fruit. DuPont Protocol No. AMR 2322-92. No MRID#. DP Barcode #D181056. CBRS #10318.

FROM: Steven A. Knizner, Chemist *Steven A Knizner*
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DuPont Agricultural Products submitted a protocol for determination of the nature of the residues in citrus fruit on April 24, 1992. This protocol was reviewed by J. Smith on 6/3/92. DuPont has modified their protocol in an attempt to remedy deficiencies noted in the review.

Definitive guidance as to CBRS requirements for plant metabolism studies is found in the CBRS document entitled "Additional Guidance for Conducting Plant and Livestock Metabolism Studies", dated 7/16/92, and references cited therein (copy enclosed). CBRS realizes that this guidance document was prepared after DuPont revised their original protocol, but it will to serve to emphasize and more fully explain CBRS concerns, especially relating to application of pesticides at exaggerated rates and required analyses.

You will find below a list of deficiencies noted in the J. Smith memo, changes made by the registrant to remedy the deficiencies, and an evaluation of the changes.

Deficiency 1. The proposal does not indicate where the tree is located (state, greenhouse, etc.).

The revised protocol states that the tree to be used in the field trial is located at DuPont's Madera, CA farm. If it is necessary to generate larger amounts of metabolites for identification, young orange trees grown in a greenhouse in Wilmington, DE will be used.

This deficiency is resolved.

Deficiency 2. The proposal does not discuss the age of the tree.

The revised protocol states a "young" tree will be used in the field trial and, if necessary, the greenhouse study. The age, source and pesticide history, if available, will be provided in the field study records.

This deficiency is not resolved. The age(s) of the tree(s) must be available. Is there a difference in age between a "young" tree in an orange grove and a "young" tree in a greenhouse? Label instructions for application of Hyvar X are specific for different ages of trees, so the age of the tree is a critical issue.

Deficiency 3. The proposal does not discuss sampling size.

The revised protocol indicates that approximately one pound of composite leaf samples will be randomly collected at approximately 7, 15, 30, 60 days after application, and harvest (mid-December). Similarly, approximately 0.5 pounds of immature fruit, if available, will be taken at each sampling interval. Enough fruit will be allowed to mature so that at least 50 fruit are present at harvest. A half pound of leaf and fruit samples will be taken from the control tree on the same sampling schedule as the treated plot.

This deficiency is resolved.

Deficiency 4. The final sampling interval is unclear.

The revised protocol notes that samples will be harvested in mid-December.

This deficiency is resolved.

Deficiency 5. The proposal does not discuss analyses (including separation, identification/characterization technique) of samples.

The revised protocol states "If a metabolite does not co-chromatograph with any reference standard, and represents more than 10% of the total radioactive residue or >0.01 ppm, whichever is greater, attempts will be made to further characterize the metabolite, possibly by isolation and identification of the metabolite by spectral techniques if sufficient quantities can be purified." The recent guidance document for plant and animal metabolism studies requires that any ¹⁴C extractables present at greater than 50 ppb must be both characterized and identified, if the ¹⁴C extractables are present at 10-50 ppb, the organosoluble compounds must be subjected to chromatographic analysis, and if the ¹⁴C extractables are present below 10 ppb, no work up is necessary.

The revised protocol states that characterization of unextractable residues comprising more than 10% of the total radioactive residue (TRR) will follow the tier approach suggested by M.F. Kovacs. The recent guidance document for plant and animal metabolism studies requires that if nonextractable residues are greater than 50 ppb, or 10% of the total residual radioactivity, whichever is greater, attempts must be made to release the activity by four different treatments (6N acid and/or base reflux, sonication followed by enzyme treatments, use of surfactants, and treatment with dilute acid and/or base at ambient temperature).

This deficiency is not totally resolved. The registrant is referred to the recent guidance document for plant and animal metabolism studies for detailed analytical requirements. Figure 1 (for extractable residues) and Figure 2 (for non-extractable residues) outline analytical requirements. Failure to meet these requirements could result in rejection of the study.

Deficiency 6. The proposal does not call for application of bromacil at maximal or exaggerated rates.

The revised protocol proposes using one 3.2 lb ai/A application of an aqueous solution of ¹⁴C-bromacil. The maximum application rate for bromacil *per se* is 6.4 lb ai/A/season. The registrant states that the 3.2 lb ai/A rate is maximal for "young" trees grown in CA, but "older" trees receive two applications at 3.2 lb ai/A (time interval between applications was not stated in the protocol). The distinction between "young" and "older" trees is not noted.

Failure to apply bromacil at maximal or exaggerated rates may make identification of metabolite(s) impossible. The J. Smith memo recommended using up to a 10X rate of application, phytotoxic concerns permitting. The recent guidance document concerning plant and animal metabolism studies stresses that exaggerated application rates of phytotoxic herbicides

are necessary to achieve sufficient radioactivity for characterization/identification, and if the exaggerated rate causes phytotoxicity in the plant, metabolism information on the "sick" plant is preferable to having no information because of a lack of sufficient radioactive residue.

This deficiency is not resolved.

CBRS has one other comment on the revised proposal. The revision states "To generate larger amounts of metabolites for identification, young orange trees grown in the greenhouse or fresh oranges may be treated with ^{14}C bromacil." CBRS fails to understand how treating fresh oranges with bromacil will aid in the identification of metabolites. If the registrant had in mind injecting a fresh orange with a solution containing ^{14}C bromacil, they should be advised that this is unacceptable.

CBRS would not be opposed to having a meeting to discuss how the registrant intends to conduct this study; however, we recommend that prior to such a meeting the registrant review the recent guidance document concerning plant and animal metabolism studies.

Note to PM: Please provide a complete copy of this review, including enclosure, to the registrant.

Enclosure.

cc: Bromacil S.F., R.S.File, List A File., circ., R.F., S.Knizner
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H7509C:CBRS:SAK:sak:Bromacil.rev:CM#2:8/6/92