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

APR 1 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tebuconazole (Folicur Technical Grade) Feeding Studies Protocols.
(No MRID #, DEB No. 7704).

FROM: Freshteh Toghrol Ph.D., Chemist F. Toghrol
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THRU: Francis B. Suhre, Section Head Francis B Suhre
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TO: S. Lewis/J. Fairfax, PM-21
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In response to data gaps cited in our previous review of PP#9G3817, a temporary tolerance petition and associated EUP's for tebuconazole on peanuts and grapes (PP#9G3817, C. Olinger, 6/8/90), Mobay submits 2 protocols for tebuconazole livestock (dairy cow and laying hen) feeding studies.

In addition Mobay requests our comments on four specific questions.

In this review we will address the feeding study protocols first, then answer Mobay's questions.

Background:

Previously submitted ruminant and poultry feeding studies were determined to be inadequate (PP#9G3817, C. Olinger, 6/8/90) because:

13b). "The dairy cow and laying hen feeding studies are inadequate due to unresolved method problems and the lack of concurrent fortification and storage stability data.

13c). " The tolerance expression for all animal matrices should include the parent tebuconazole and the hydroxy metabolite, HWG 2061. Method sensitivity to tolerance proposed should be revised to the combined limits of detection for tebuconazole and HWG 2061.

Summary of the Proposed Protocols:

In response to these deficiencies the petitioner Mobay has agreed to repeat the ruminant and poultry feeding studies. Protocols entitled "Feeding Study-Dairy Cow" and "Poultry Feeding" were submitted. The objectives to these feeding studies are to determine if residues might arise in meat, milk, poultry and eggs from tebuconazole's residues in livestock feed items.

Test Substance:

For these feeding studies Folicur, technical grade with >98% purity [the active ingredient tebuconazole (α-[2-(4-chlorophenyl)-ethyl]- α-(1,1-dimethylethyl)1H-1,2,4-triazole-1-ethanol] will be used. Feeding levels of 2, 6, and 20 ppm tebuconazole will be administer to laying hens and 30, 90, and 300 ppm tebuconazole will be administer to lactating cows.

Experimental Design

Ruminant:

Ten lactating cows will be used for this feeding study. One cow will be used as a control. The remaining animals will be divided into three groups of three animals each . Each groups of animals will be fed 30 ppm (1X), 90 ppm (2X), and 300 ppm (10X) tebuconazole (in a 1.5 oz gelatin capsule bolus) once a day (after morning milking) for 28 consecutive days. Each group will be housed separately as will the control, and the animals will be handled as in normal dairy procedure. Information related to animal body weights, housing, diet composition, feeding/milking schedules during acclimation and treatment periods will be recorded. The cows will be acclimated to their test ration minus residue for at least one week prior to starting the test. The cows will be fed hay ad libitum and grain in each milking. The cows will be milked twice a day, once in the morning and once in the evening. Following each milking and milk weights determination, a 500 ml aliquot will be retained. The evening milk and the next morning milk for each cow will be pooled and designated as that day's milk. The milk will be stored frozen until analysis. The dairy cows will be sacrificed after 28 days of treatment and tissues (liver, kidney, muscle (round, flank, loin) and fat (omental, renal, subcutaneous) will be collected from the treated and control animals. Tissue

samples will be cubed, minced, or pulverized with dry ice in Hobart® cutter and stored frozen until analysis.

Poultry:

At least 48 healthy laying hens will be used in this feeding study. Four feeding levels 0, 2, 6, and 20 ppm Folicur (tebuconazole) will be mixed with poultry feed (Purina's Layena Poultry Chow) and fed to chickens for 28 successive days. Each chicken will be housed in an individual cage with its own feed. Water will be provided ad libitum. Information related to animal body weights, housing, diet composition, feeding/egg collection schedules during acclimation and treatment periods will be recorded. Treated feed will be stored in a refrigerator, to assay the storage stability. Eggs will be collected daily. Tissues will be collected at sacrifice after 28 days of treatment. The tissues sampled will include liver, gizzard, muscle (breast, leg and thigh), fat and skin. Tissues and eggs will be cut in small pieces or pulverized with dry ice in a grinder. All samples will be stored frozen until analysis. Initial extraction, if necessary, will be performed according to Folicur method of dairy tissues, milk, poultry tissues and eggs.

CBRS Comments/Recommendation Concerning Feeding Study Protocols:

Since the submitted protocol for feeding studies is very general, we are unable to provide specific/detailed comments concerning the protocols adequacies. However, we have no objections to the generic experimental design described in these protocols.

We note that the registrant did not address the specific deficiencies cited in our review of PP#9G3817, C. Olinger, 6/8/90. These deficiencies are restated below:

13b). "The dairy cow and laying hen feeding studies are inadequate due to **unresolved method problems and the lack of concurrent fortification and storage stability data.**

13c). " The tolerance expression for **all animal matrices should include the parent tebuconazole and the hydroxy metabolite, HWG 2061. Method sensitivity to tolerance proposed should be revised to the combined limits of detection for tebuconazole and HWG 2061.**

We recommend that a copy of the Standard Evaluation Procedure for Residues in Meat, Milk, Poultry, and eggs: Feeding Studies /Feed-through be provided to the petitioner (attached).

Mobay's Question #1

" Will restricting the feeding of peanut vines and hay eliminate the need for temporary tolerances of any kind in meat, milk and eggs"

CBRS's Comments to Question #1

Peanut meal, vines, hay, hulls, and soapstock are feed items. Restriction against feeding livestock peanut vines and hay does not eliminate the need for meat, milk, poultry, and eggs tolerances. Although peanut vines and hay are under the control of the grower, peanut meal, hulls, and soapstock are not.

Mobay's Question #2

"Relative to the permanent tolerance expressions for any crops, how many sites would DEB consider necessary for a minimal program to repeat the required crop field trial studies for representative analysis of metabolite residues only?"

CBRS's Comments to Question #2

If a metabolite is of toxicological concern, then it must be included in the tolerance expression. Since the purpose of the residue field trial is to quantify the total residue likely to result from the proposed use of pesticide, all components of the terminal residue, determined to be of toxicological concern, must be assayed.

Field trial data should reflect all principal growing regions (geographical representatives) with **sufficient number of sites included to determine an appropriate tolerance (maximum residue level under seasonal variations, differences in varieties of crop , cultural practices, and the importance of the crop)**.

Grapes are grown primarily in CA (90%) and NY/PA (5%). Peanuts are grown primarily in GA/AL/FL (67%), NC/VA (16%) and TX/OK (16%). Samples should be analyzed for both tebuconazole and its metabolites from the same treated samples (because there may be difference in residue levels from one year to another). Data must be provided on all parts of the crop used for food and feed. Field trial should reflect the proposed use with respect to rate of application, mode of application, number of applications, time of applications, spray volume and PHI. For more information please refer to the Agency's Acceptance Criteria for Crop Field Trials (Attached to our previous memo dated 2/7/91).

Mobay's Question #3

"For residue studies and storage stability, will DEB allow data from wheat to cover the requirements for barley, apples to cover pears, etc."

CBRS's Comments to Question #3

Storage stability data for a pesticide and its metabolites in or on a crop are required to support a tolerance. Samples used in a storage stability study should be stored exactly like the field incurred residue samples; e.g., in the same freezer, in the same type of containers, and for the same lengths of time. Translation of storage stability data from one commodity to another requires that the commodities are related (in the same crop group) and that the experimental design of the study reflects the conditions under which the field samples were stored. For further information, the petitioner should consult our Position Document on Storage Stability (attached to our memo dated 2/7/91).

Mobay's Question #4

"For any crop requiring processing data, if no metabolites are found in the RAC's in either the radioactive study or representative residue data, will the EPA require a processing study to show lack of concentration of the metabolites in the processed food items?"

CBRS's Comments to Question #4

If no residues are found on a raw agricultural commodity (RAC) after application of the pesticide at an exaggerated rate, then the Agency will consider waiving the requirement to conduct a processing study.

Attachment : DEB Standard Evaluation Procedure Residue in Meat, Milk, Poultry, and Egg: Feeding Studies/Feed-through by R. A. Loranger EPA 540/09/90-087, NTIS: PB 90-208943 (15 pages).

cc: with Attachment to PP#9G3817, Tebuconazole S.F., R.F., Circ., F. Toghrol, PMSD/ISB.
RDI: F.B.S 3/28/91): E. Zager: (3/29/91):
H7509C:DEB:F.Toghrol:F.T.:RM:802:CM#2:703-557-7887:3/29/91.