Shaughnessy Number: 128997

Date out of EFGWB: APR 17 1991

To: S. Lewis/J. Fairfax
Product Manager 21
Registration Division (H7505C)

From: Akiva Abramovitch, Section Head
Environmental Fate Review Section #3
Environmental Fate and Ground Water Branch
Environmental Fate and Effects Division (H7507C)

Thru: Hank Jacoby, Chief
Environmental Fate and Ground Water Branch
Environmental Fate and Effects Division (H7507C)

Hank Jacoby

Attached, please find the EFGWB review of...

Reg./File #: 3125-GIG, -GOU, - GII, -GOE, -GOG

Chemical Name: te(r)buconazole

Type Product: fungicide

Product Name: various

Company Name: Bayer AG

Purpose: submission of additional rotational crop uptake data -- response to registration standard

Date Received: 09/02/90

Total Reviewing Time (days):

Action Code:

EFGWB#(s): 90-0869, -0870, -0871, -0872, -0873

Deferrals to:

___Ecological Effects Branch, EFED

___Dietary Exposure Branch, HED

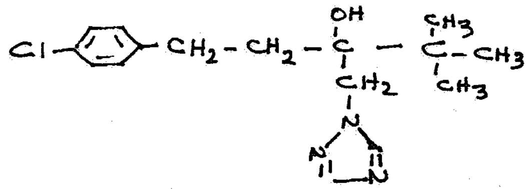
___Toxicology Branch, HED

___Non-Dietary Exposure Branch, HED

___Science Integration and Policy Staff, EFED

1. **CHEMICAL:**

chemical name: a-[2-(4-Chlorophenyl)ethyl]-a-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol
common name: te[r]buconazole, folicur
trade name: Elite
structure:



CAS #: unknown
Shaughnessy #: 128997

2. **TEST MATERIAL:**

3. **STUDY/ACTION TYPE:** submission of additional information on rotational crop study

4. **STUDY IDENTIFICATION:**

Thornton, J.S. Mobay, Inc. correspondence dated 8/15/90 regarding the study listed below

Leimkuehler, W.M.; Lenz, C.A.; Delk, J.L. **Radioactive Residues of ^{14}C - Folicur in Rotational Crops**. performed and submitted by Mobay Corp., Ag. Chem. Div., Stilwell, KS. dated 1/15/88. rec'd EPA 8/20/90 MRID # 415958-01.

5. **REVIEWED BY:**
Typed Name: E. Brinson Conerly
Title: Chemist, Review Section 3
Organization: EFGWB/EFED/OPP

E.B. Conerly 4/16/91

6. **APPROVED BY:**

Typed Name: Akiva Abramovitch
Title: Section Head, Review Section 3
Organization: EFGWB/EFED/OPP

Akiva Abramovitch
APR 17 1991

7. **CONCLUSIONS:**

1) MRID#s 407009-64 (previously reviewed) and 415958-01 (submitted with this review package) are reports of the **same** rotational crop study. MRID 415958-01 has been revised to respond to some of EFGWB's comments on the earlier version. Together with the supplemental information in the correspondence from Mr. Thornton, it is now acceptable.

2) Residues of varying nature and amount are present in all crop groups at all times sampled, although it should be noted that the application rate was approximately double the highest label rate. Samples from plantings 29 days post treatment are reported to have measurable residues of parent and/or other organosoluble compounds. Later samples (from plantings at 122 and 273 days post treatment) contain measurable amounts only of water-soluble materials, i.e. triazolyl metabolites. Toxicology Branch has determined (correspondence attached) that the triazolyl residues are of little concern. If there is a concern for the parent and other organosoluble degradates, then a 29 day post-harvest interval is insufficient, but a 4 month (120-day) replanting interval might be appropriate. Since there are no data for intervals between 29 and 122 days on which to base a recommendation, EFGWB cannot suggest an interval shorter than 120 days at this time.

3) Available data from a currently unacceptable study (DER attached) *with one exception* indicate minimal (near level-of-detection) residues in all crop groups planted 30 and 120 days post treatment. However, these crops were only analyzed for parent.

8. RECOMMENDATIONS: The remaining required data should be submitted as soon as possible.

9. BACKGROUND:

The toxicological evaluation is incomplete as of 4/2/91, but previous opinions from the TOX branch indicate that triazolyl metabolites are of little concern. A tolerance petition for barley, oats, peanuts, wheat, grapes, and grasses grown for seed is currently under review. Available data indicate persistence but low soil mobility. Some plant uptake occurs.

The status of data requirements is as follows:

hydrolysis -- fulfilled 6/9/89, stable at pH 5, 7, and 9 -- no hydrolysis after 28 days incubation

photolysis in water -- fulfilled 6/9/89 -- no photodegradation detected; extrapolated $t_{1/2}$ of 600 days

soil photodegradation -- fulfilled 6/9/89 -- slow reaction; extrapolated $t_{1/2}$ ca 191 days, producing 2 unidentified degradates (<3% of applied)

aerobic soil metabolism -- fulfilled -- additional data on product identification was required 6/9/89, but a reevaluation of available information indicates that the previously submitted study should be accepted -- resistant to metabolism -- extrapolated $t_{1/2}$ 610 days in sandy loam soil. Residues at 1 year were tebuconazole at 67.4%, unextractables at 29.1% [ca. 20% of this (3% of the total applied) was parent compound], an unidentified extractable material at 2.1%, extractable polar compounds at 1.1%, and CO_2 at less than 0.7%.

anaerobic soil metabolism -- fulfilled (see aerobic soil study) -- extrapolated $t_{1/2}$ ca 400 days

leaching/adsorption/desorption -- fulfilled as of 6/9/89 -- in column leaching studies on sand, sandy loam, silt loam, and silty clay loam, little leaching occured below 6 cm.

terrestrial field dissipation -- **study submitted, but not accepted** because of inadequate analytical methods and lack of detail in the report. **EFGWB has required a** *turf field dissipation study* because of this **compound's use pattern**

confined accumulation on rotational crops -- fulfilled by this submission taken together with the previously submitted study -- **additional data discussed in this review characterizing residues** -- The original DER is attached.

[^{14}C]Terbuconazole residues accumulated in kale, beets, and wheat planted 29, 122, and 273 days after the second of two applications of [^{14}C]terbuconazole; the first application was to wheat growing in a tub and the second application, 50 days later, was directly to the sandy loam soil surface. The concentration of [^{14}C]residues in crops from the 122-day rotation was ≈4 to 9x greater than the concentration in crops from the 29-day rotation; the concentration of [^{14}C]residues in crops from the 273-day rotation was generally ≈2-4x greater than the concentration in crops from the 29-day rotation. The 122 and 273-day interval organosoluble fractions could not be analyzed because of inadequate amounts of organosoluble [^{14}C] residues. No organosoluble [^{14}C] residue was present at >2% except in immature wheat (8%). Values below are taken from tables in the report received under MRID# 415958-01.

In crops planted at 29 days posttreatment,
total [^{14}C]residues at harvest

0.3 ppm in kale
- 15 % **terbuconazole**
- 0.4% terbuconazole-t-butyl-hydroxy
- 8.5% unidentified organosoluble (baseline and other)
- **56.2% triazolylalanine**
- 3.3% triazolylacetic acid
- 4.3% unidentified aqueous
- 12.3% unextracted

0.2 ppm in beet tops
- 7.2% terbuconazole
- 1.1% terbuconazole-t-butyl-hydroxy
- 4.3% unidentified organosoluble (baseline and other)
- **19.5% triazoylalanine**
- 6.8% triazolylacetic acid
- **20.5% triazolyl-lactic acid**
- **20.8% unidentified aqueous**
- 17.1% unextracted

0.2 ppm in beet roots
- 4.8% terbuconazole
- 0.4% terbuconazole-t-butyl-hydroxy
- 3.6% unidentified organosoluble (baseline and other)
- 6.8% triazole
- **58 % triazoylalanine**
- **13.6% unidentified aqueous**
- 12.8% unextracted

3.8 ppm in wheat grain
- in immature wheat
  - 22.9% terbuconazole
- in wheat grain
  - no detectable terbuconazole

1.1 ppm in wheat straw
- 5.4% terbuconazole
- 9.3% terbuconazole-t-butyl hydroxy

Organosoluble residues ranged from 0.4 to 22.9% of the recovered radioactivity.
Water-soluble residues ranged from 51.1 to 88.6%.
Unextractable residues ranged from 5.8 to 29.7%.
Five unknowns (0.4-1.6%) were detected.

In crops planted at 122 days posttreatment

total [^{14}C]residues at harvest

2.7 ppm in kale
- 0.64% unidentified organosoluble (diffuse/baseline)
- **56.2% triazolylalanine** (this is an apparent typo, other data indicate a more complete recovery than this shows)
- 3.3% triazolylacetic acid
- 4.3% unidentified aqueous
- 12.3% unextracted

1.3 ppm in beet tops
- 1.4% unidentified organosoluble degradates
- **21.5% triazolylalanine**
- 7.2% triazolylacetic acid
- **49.1% triazolyl-lactic acid**
- **20.8% unidentified aqueous**
- 17.1% unextracted

0.8 ppm in beet roots
- 2.2% unidentified organosoluble degradates
- **14.8% triazole**
- **54.8% triazolylalanine**
- 3.3% triazolylacetic acid
- 3.5% triazolyl-lactic acid
- 7.2% unextracted

35.4 ppm in wheat
- 8.0% unidentified organosoluble in immature wheat
- **28.5% (12.7 ppm) triazolylalanine**
- **50.8% triazolylacetic acid**
- 8.0% unidentified aqueous

- **71.0% triazolylalanine** in wheat grain
- **25.7% triazolylacetic acid** in wheat grain.
- 3.8% unidentified aqueous in wheat grain
- 1.3% unextracted

4.2 ppm in wheat straw
- 1.1% unidentified organosoluble
- **24.1% triazolylalanine**
- **25.0% triazolylacetic acid**
- **26.6% triazolyl-lactic acid**
- 9.2% unidentified aqueous
- 14.0% unextracted

15.0 ppm in wheat chaff

Organosoluble residues ranged from 0.6 to 8.1% of the recovered radioactivity, and were not further characterized.

Water-soluble residues ranged from 85.5 to 100%
- <u>Triazolylalanine</u> was the primary degradate in all crops.
- <u>Triazolylacetic acid</u> was another degradate in all crops
- <u>Triazolyl-lactic acid</u> was detected in beet tops and roots and wheat straw
- <u>Triazole</u> was detected in beet roots

unextractable residues ranged from 0 to 13%.

In crops planted at 273 days posttreatment

Total [^{14}C]residues at harvest

2.0 ppm in kale
- 0.53% unidentified organosoluble
- **85.5% triazolylalanine**
- 5.8% triazolylacetic acid
- 5.2% unidentified aqueous
- 3.0% unextracted

1.0 ppm in beet tops
- 1.7% unidentified organosoluble
- **20.6% triazolylalanine**
- 4.8% triazolylacetic acid
- **34.3% triazolyl-lactic acid**
- **11.2% unidentified aqueous**
- 27.4% unextracted

0.9 ppm in beet roots
- 1.3% unidentified organosoluble
- 16.8% triazole
- **52.2% triazolylalanine**
- 3.3% triazolylacetic acid
- 3.5% triazolyl-lactic acid
- **16.7% unidentified aqueous**
- 7.2% unextracted

7.6 ppm in wheat grain
59.0% triazolylalanine
36.2% triazolylacetic acid
4.1% unidentified aqueous
0.7% unextracted

2.6 ppm in wheat straw
15.7% triazolylalanine
16.2% triazolylacetic acid
52.0% triazolyl-lactic acid
9.1% unidentified aqueous
5.7% unextracted

6.0 ppm in wheat chaff

Organosoluble residues and unextractable residues were not further characterized.

In the 0- to 6-inch soil depth, total [^{14}C]residues were 1.5 ppm immediately following application of formulated [^{14}C]terbuconazole to the soil surface, 0.52 ppm at 29 days posttreatment, 0.29 ppm at 122 days posttreatment, and 0.16 ppm at 273 days posttreatment. Between 29 and 273 days posttreatment, extractable [^{14}C]residues decreased from 84 to 14% of the total radioactivity; terbuconazole was the only compound detected in extracts from the 29- and 122-day soil samples. The residue in the soil at harvest of the 273-day interval was 0.18 ppm. This was slightly higher than at planting (0.16 ppm). Although it would seem that the soil residue should have dropped between planting and harvest instead of remaining essentially the same, the uptake of [^{14}C] residues by the 273-day crops was not significant compared to the amount of total [^{14}C] residue remaining in the tub. The [^{14}C] residue in the soil prior to the surface treatment was not characterized, however, the [^{14}C] residue at the time of surface treatment was characterized [Table V, attached]...The [^{14}C] residue at this point was 93% FOLICUR. Considering a 0-time [^{14}C] concentration of 1.5 ppm, there could not have been any [^{14}C] residue other than FOLICUR present in the soil at a concentration of >0.1 ppm [at day 273]. The [^{14}C] residue in the soil at the time of harvest was not characterized, but...not enough material was extractable for characterization. This was also the case for the 273-day harvest interval [^{14}C] residue.In soil stored frozen, the amount of methanol extractable material decreases by approximately 10% relative to the amount of material present, with an equivalent increase in bound material. Total recovery has also decreased slightly, with virtually all of the material recovered in the extractable portion identified as parent tebuconazole. There has been no dramatic change during storage. The same general pattern holds true for plant materials as well.

accumulation in field rotational crops -- partially fulfilled (MRID# 409959-23) -- spinach, turnips, and wheat or sorghum were planted 30 and 120 days post-treatment in soil which had received seven applications of terbuconazole at 3.5 ppm at 10 - 25 day intervals. The original DER is attached. Except for 0.11 ppm of terbuconazole in straw from wheat planted at approximately 120 days posttreatment, terbuconazole detected in the crops from the treated plots did not significantly exceed the apparent limits of determination of terbuconazole in the various plant matrices.

Terbuconazole was ≤0.03 ppm in spinach leaves, turnip roots and tops, and wheat or sorghum grain planted approximately 30 and 120 days after 7 applications at 10- to 25-day intervals of terbuconazole to sandy loam/sandy clay loam soil and silt loam/silty clay loam soil.

In crops planted at approximately 30 days posttreatment, terbuconazole at harvest was 0.02 ppm in spinach; 0.02-0.03 and 0.01-0.03 ppm in turnip tops and roots, respectively; 0.01 and

0.03 ppm in wheat grain and straw (IN site), respectively; and 0.03 and 0.04 ppm in sorghum grain and straw (KS), respectively. In immature sorghum forage harvested at 45 days postplanting, terbuconazole was 0.01 ppm.

In crops planted at approximately 120 days posttreatment, terbuconazole was 0.02 ppm in spinach (KS site only); <0.01 ppm in turnip tops (KS site only); 0.01-0.02 ppm in turnip roots; 0.01 and 0.11 ppm in wheat grain and straw, respectively; and 0.01 and 0.02 ppm in sorghum grain and straw, respectively. In immature wheat forage harvested at 45 days postplanting, terbuconazole was 0.05 ppm.

In control crops, apparent terbuconazole was 0.01-0.02 ppm in spinach; <0.01-0.02 and 0.01-0.03 ppm in turnip tops and roots, respectively; 0.02 and 0.01 ppm in wheat forage and grain; and 0.01, 0.01, and 0.02-0.06 ppm in sorghum forage, grain, and straw, respectively.

In the 0- to 6-inch soil depth from plots treated for the 30-day plant-back, terbuconazole was 0.17-0.41 ppm immediately following the final application of terbuconazole; 0.07-0.19 ppm at 31-33 days posttreatment, and 0.04-0.12 ppm at harvest (87-308 days posttreatment). From plots treated for the 120-day plant-back, terbuconazole in the soil (0- to 6-inch depth) was 0.21-2.42 ppm immediately following the final application, 0.19-0.35 ppm at 124-126 days posttreatment, and 0.01-0.10 ppm at harvest (171-245 days posttreatment).

fish bioaccumulation -- study submitted and under review at this time

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

The applicant has provided additional data on rotational crop degradate identification to respond to EFGWB comments contained in the Registration Standard chapter. The relevant comments were as follows:

1) EFGWB comment -- ... the organosoluble and water-soluble [^{14}C] residues in all crops from all three rotations should be characterized...

Mobay response -- ... Tables VIII and IX,...[attached] contain the additional data which includes the 29 and 273-day interval samples. The 122 and 273-day interval organosoluble fractions could not be analyzed because of inadequate amounts of organosoluble [^{14}C] residues. No organosoluble [^{14}C] residue was present at >2% except in immature wheat (8%).

EFGWB reply -- The data are provided as Mobay states. This deficiency is resolved.

2) EFGWB comment -- [not verbatim] ... please provide storage stability for the materials tested.

Mobay response -- ... the storage stability data requested can be found in Tables X [soil], XI [plant matrices], and XII [plant matrices]. [All are attached.]

EFGWB reply -- In soil stored frozen, the amount of methanol extractable material decreases by approximately 10% relative to the amount of material present, with an equivalent increase in bound material. Total recovery has also decreased slightly, with virtually all of the material recovered in the extractable portion identified as parent tebuconazole. There has been no dramatic change during storage. The same general pattern holds true for plant materials as well. This deficiency is resolved.

3) EFGWB comment -- ...[^{14}C] residues in the soil prior to the soil surface treatment and at the time of harvest of the rotational crops should be quantified and [^{14}C] residues from those two intervals plus [^{14}C] residues in the soil immediately after the soil surface application should be characterized.

Mobay response -- ...Information on the concentration of [^{14}C] residues in the soil prior to the surface treatment (0.20 ppm) ... can be found in Table IV [attached]. The residue in the soil at harvest of the 273-day interval was 0.18 ppm. This was slightly higher than at planting (0.16 ppm). Although it would seem that the soil residue should have dropped between planting and harvest instead of remaining essentially the same, the uptake of [^{14}C] residues by the 273-day crops was not significant compared to the amount of total [^{14}C] residue remaining in the tub. The [^{14}C] residue in the soil prior to the surface treatment was not characterized, however, the [^{14}C] residue at the time of surface treatment was characterized [Table V, attached]...The [^{14}C] residue at this point was 93% FOLICUR. Considering a 0-time [^{14}C] concentration of 1.5 ppm, there could not have been any [^{14}C] residue other than FOLICUR present in the soil at a concentration of >0.1 ppm [at day 273]. The [^{14}C] residue in the soil at the time of harvest was not characterized, but...not enough material was extractable for characterization. This was also the case for the 273-day harvest interval [^{14}C] residue.

EFGWB reply -- The cited Tables indicate that the soil radioactivity content is back to pre-treatment level at day 273. There is a steady decrease in extractable material and a concomitant increase in bound material. Methanol-extractable material is virtually all parent tebuconazole. Reviewer calculated figures indicate that tebuconazole content in the soil is ca. 20 pp<u>b</u> at day 273. This deficiency is resolved.

4) EFGWB comment -- ...the following details about the analytical methodology should be included a) the type of TLC plate used, b) how unlabeled tebuconazole was detected following TLC, c) what compounds were being derivatized to, and d) at what stage of the methodology the plant extracts were analyzed for free triazole (which apparently required a separate derivatization step). In addition recovery efficiencies of tebuconazole and degradates from fortified soil and plant samples were not provided.

Mobay response -- This report was revised to include the following information: (a) the TLC plate was a silica gel 60 plate by Merck, 250 µm thick, (b) unlabeled standards were visualized under UV light, (c) all derivatives can be examined on page 36 (attached) of the revised report, and were performed after the ion exchange column procedure, and (d) free triazole was derivatized after being eluted off of the cation exchange column with monochloropinacolone. The derivative was then analyzed by HPLC.

Recovery efficiencies usually could not be done because [^{14}C] labeled standards of the metabolites which made up the major part of the [^{14}C] residue were not available. **<u>However, unextracted or bound material did not exceed more than approximately 10 percent on average for any component other than beet top.</u>**

EFGWB reply -- The applicant has stated that direct measurements of recovery by analysis of fortified samples was not done due to unavailability of labeled standards. This reviewer interprets the final sentence [emphasized above] in the Mobay response as stating indirectly that recovery as extractable material was ca. 90% in all materials except for beet top. If that is the case, recovery is satisfactory and this deficiency is resolved. The applicant should confirm that this interpretation is correct.

5) EFGWB comment -- requested information on plant growing conditions

Mobay response -- In response to the request for information on plant growing conditions, the following are presented: a) the crops were grown under normal greenhouse conditions and watered as needed, b) temperatures and humidities were held at the levels normally found in a greenhouse (humidity 60-70% and temperatures around $80^{0}F$), and c) day to day data were recorded on both humidity and temperature.

EFGWB reply -- this information is satisfactory, and the deficiency is resolved.

11. <u>COMPLETION OF ONE-LINER</u>: appropriate information added

12. <u>CBI APPENDIX</u>: n.a.

Mobay

A Bayer USA INC COMPANY

Agricultural Chemicals Division

Mobay Corporation
P.O. Box 4913
Hawthorn Road
Kansas City, MO 64120-0013
Phone: 816 242-2000

Document Processing Desk (PETN)
Office of Pesticide Programs - H7504C
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Attn: Ms. Susan T. Lewis
Product Manager (21)

March 18, 1991

Subject: FOLICUR® 3.6 F, EPA File Symbol 3125-GOU
ELITE® 45 DF, EPA File Symbol 3125-GII
RAXIL® 0.26 F, EPA File Symbol 3125-GOE
RAXIL 2.6 F, EPA File Symbol 3125-GOG
Pesticide Petition Nos. 9F3818, 9F3724 and 9H5575

Dear Ms. Lewis:

Mobay submitted a confined accumulation in rotational crops study (Mobay Report No. 95638; EPA MRID No. 40700964) to the Agency on 6/24/88. As a result of the Environmental Fate and Effects Division's 6/9/89 memorandum (Hank Jacoby and Emil Regelman to Susan Lewis), this study was revised in order to answer the Agency's questions. This revised study, also assigned Mobay Report No. 95638, was submitted to the Agency 8/15/90 and was assigned EPA MRID No. 41595801.

In our confined accumulation study in rotational crops, triazole (T), triazolylalanine (TA), triazolylacetic acid (TAA) and triazolyl-lactic acid (TLA) are found in significant amounts. As indicated by the enclosed copies of letters from Douglas D. Campt to P.R. Bennett, dated 3/24/88, and Lois A. Rossi to Richard L. Conn, dated 3/30/88, the Agency has decided not to express triazolylalanine as a metabolite of concern for triadimefon and propiconazole nor to require additional metabolism studies or analytical methodologies specific for triazole moieties for the following reasons:

1. Triazole alanine exhibits a relatively low toxicity to mammals based on the review of acute, subacute, metabolism/pharmacokinetics, reproductive, teratologenicity and mutagenicity studies.

2. Triazole containing compounds occur naturally in plants at high and variable levels relative to any contribution from pesticides.

3. Such levels can mask the contribution of triazole due to the application of pesticides.

Based on this decision for triadimefon and propiconazole, Mobay would like to know EPA's position on the significance of the naturally occurring triazole compounds T, TAA and TLA in rotational crops grown in soils after treatment with products containing tebuconazole? Is it necessary to include these compounds when analyzing for residues in crops?

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In our confined accumulation study in rotational crops (Mobay Rpt. No. 95638) only the 29-day posttreatment interval contained significant organosoluble radioactivity. The majority of the radioactivity in all posttreatment intervals was water soluble TA, TAA and TLA. Based on these data, is the need for a field rotational crop study precluded in favor of a 30-day rotational crop restriction?

If the Agency believes that a field rotational crop study is necessary, we would like to have clarification of the following points:

1. What application rate does EPA want at day 0: 1X or 1.1X?

2. Should the product be applied to bare soil or to a target crop?

3. If the Agency wants the product applied to bare soil, should a cover crop be planted after application?

4. How many test sites are necessary to obtain a tolerance for specific rotational crops? Guidelines for a generic rotational crop study using cereal, root and leafy vegetable crops require only two test sites.

From related discussions with Akiva D. Abramovitch (EF&GWB, Section III), we are aware that review of tebuconazole data are in progress now within the branch. Mr. Abramovitch advised Mobay to immediately pose our specific questions in writing with the possibility of a rapid response in conjunction with the ongoing reviews. Since the answers to the above questions impact studies for our 1991 field program, we would appreciate an early written response.

Once this letter has been received by EF&GWB, we would also like to propose a telephone conversation between the review scientist and our Mobay scientists, Dr. Val Clay and Ms. Karen Pither, to ensure that the questions are completely understood. I will follow up with Mr. Ben Chambliss in a few days to see if this can be arranged.

Yours very truly,

MOBAY CORPORATION
AGRICULTURAL CHEMICALS DIVISION

John S. Thornton

John S. Thornton, Manager
Registrations
Research and Development

JST:MKT:brh
Enclosures
(1) Copy of EPA letter, Douglas D. Campt to P.R. Bennett, dated 3/24/88.
(2) Copy of EPA letter, Lois A. Rossi to Richard L. Conn, dated 3/30/88.

cc: Mr. Ben Chambliss (Registration Division) (w/enclosures)

Akiva D. Abramovitch (w/enclosures)
EF&GWB, Section III

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

MAR 24 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

RECEIVED
CHEMICAL EVALUATION
APR 6 1988
EVALUATION CHIMIQUE
REÇU

Mr. P.R. Bennett
Bureau of Chemical Safety
Food Directorate
4th Floor East
Banting Building
Ottawa, Ontario KIA OL2

Dear Mr. Bennett:

Thank you for your letter dated December 17, 1987, requesting information on the Environmental Protection Agency's (EPA) position on triazole alanine. Uses and tolerances have been approved for the fungicide triadimefon and propiconazole on various food commodities. Triazole alanine is a plant metabolite of both of these fungicides.

In reaching a decision to establish tolerances for propiconazole and triadimefon, the Agency reviewed a substantial data base submitted by the registrants for these chemicals, including data on triazole alanine. Data published in the literature were not submitted for Agency review regarding triazole alanine. Additionally, we are not aware of any information in the literature on this issue.

The Agency based its decision not to express triazole alanine as a metabolite of concern with triadimefon and propiconazole because: triazole alanine exhibits a low potential for toxicity in mammals; the background levels of naturally occurring triazole-containing components in plants appear at high and variable levels; and such levels can mask the contribution of triazole due to the application of these pesticides.

I hope this information is useful to you. If you have any further questions, please feel free to contact me.

Sincerely,

Douglas D. Campt, Director
Office of Pesticide Programs

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RLC APR 4 1988

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MAR 30 1988

Mr. Richard L. Conn
Ciba-Geigy Corporation
Agricultural Division
P.O. Box 18300
Greensboro, NC 27419

Dear Mr. Conn:

Subject: Tilt® Fungicide
EPA Registration No. 100-617
Your Letter Dated March 3, 1988

Your letter dated March 3, 1988 requests a statement on the Agency's position concerning the residues of triazole moieties in plants in connection with the use of Tilt on various crops. That position was stated in the Toxicology Branch review of May 8, 1987 which you have received.

Specifically, the Agency has evaluated the available acute and subchronic toxicity data, as well as metabolism/pharmacokinetics, reproductive, teratogenicity, and mutagenicity studies conducted with triazole alanine, the major plant metabolite of Tilt. The Agency has also determined that background levels of naturally occurring triazole-containing components in plants appear at high and variable levels, and such levels can mask the contribution of triazoly due to treatment with Tilt.

Based primarily on the data that indicate relatively low toxicity of triazole alanine and the natural occurrence of the compound in various plants (e.g., peanuts, pecans, cereal grains), the Agency has determined the following. First, that triazole alanine exhibits a relatively low toxicity. Second, that triazole compounds occur naturally in plants at high levels relative to any contribution from the application of the

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subject pesticide. Therefore, there is no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for triazole moieties at this time.

Sincerely yours,

Lois A. Rossi

Lois A. Rossi
Product Manager (21)
Fungicide-Herbicide Branch
Registration Division (TS-767C)

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

MAY 8 1987 ~~MAY 6 1987~~

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triazole Residues in Plants: TILT® on Pecans and Small Grains

FROM: Alan Katz Toxicologist
Toxicology Branch
Hazard Evaluation Division (TS-769C) ACK 5/6/87

THRU: Marcia vanGemert, Ph.D.
Head, Toxicology Section III
Hazard Evaluation Division (TS-769C) M. vanGemert 5/6/87

and ... for WHB 5/6/87

Theodore Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

TO: Lois Rossi, PM #21
Fungicide-Herbicide Branch
Registration Division (TS-767C)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769C) (cc: S. Malak / A. Smith)

RCB has deferred to TOX in connection with PP#4F3074 on the question of the toxicological significance of residues containing the triazole moiety. TOX has evaluated the available acute and subchronic toxicity data, as well as metabolism/pharmacokinetics, reproductive, teratogenicity, and mutagenicity studies conducted with triazole alanine, the major plant metabolite of TILT®. Overall, triazole alanine exhibits a low potential for toxicity in mammals (see attached one-liners). RCB has concluded (memorandum, A. Smith to L. Rossi and Tox Branch, 12/31/86) that background levels of naturally occurring triazole-containing components in plants "appear at high and variable levels, and such levels can mask the contribution of triazoles due to treatment with propiconazole (TILT)."

Based primarily on the data base indicating relatively low toxicity of triazole alanine, and RCB's advisory that triazole compounds occur naturally in plants (e.g., peanuts, pecans, cereal grains) at high levels relative to any contribution attributable to the application of propiconazole, TOX Branch has determined that there is at this time no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for the triazole moieties contributed by propiconazole.

Tox Chem No. 862A - Triazolyl alanine File Last Updated 4/14/87 Current Date ______

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day feeding - rat; Bayer AG Institute for Toxicology; #T9015049; 9/13/83 & 2/24/84	Triazolyl alanine Batch #TLB-1207	252425 250416	Levels tested in DOR:WISW (SPF-CPB) strain- 0, 1250, 5000, & 20,000 ppm NOEL = 5,000 ppm LEL = 20,000 pppm (slight reduction in male body weight gain)		Supplementary 004101 004276 Minimum 005004 005352 005841
Mutagenic - Ames; Bayer AG Institute for Toxicology; #T-1006005 & T-900372; 1/5/83	THS 2212 Batch # E238099	256058	Negative for mutagenic effects up to 12,500 ug/plate with and without (S-9) activation.		Acceptable 004562 Acceptable 004463
13-Week feeding - dog; Bayer Ag Institute for Toxicology; #T-7-015-713 March 26, 1984 & 4/28/86	THS 2212 97.5% ai Batch # TLB 1207	256058	Levels tested beagle dogs - 0, 3200, 8000, and 20,000 ppm. NOEL = 8000 ppm LEL = 20,000 ppm(reduced body wt gain)		Supplementar 004463 Minimum 005841
Mutagenic-Cell transformation in vitro (BHK) Huntingdon; #ICI394A/ 81153; CTL/C/1085 5/15/81	R152056 (Triazolyl alanine)	072208 252132	Levels tested:0.5, 1, 2, 4, 8 mg/ml without S9; and 1,2,4,8,16 mg/ml with S9. Positive, with and without activation.		Acceptable 004562 Acceptable 004766
Dissimilation chemicals metabolite or impurity or contaminant or salt or photodegradent or etc			Caswell # 862AA #323 EE (CGA-64250)		
Acute oral LD_{50}- dog; Institute fuer Toxikologie, FRG; Report #82663; 10/14/82.	THS 2212 (Triazolylalanine) 99% purity	252132	Only 2 dogs used on study; both vomited a portion of the test material within 4 hours of dosing.		Invalid 004766
Acute oral LD_{50}- rat; Central Toxicology Laboratory, ICI Limited; #CTL/P/600; 1/18/81	R152056 (Triazolylalanine) purity unspecified	252132	LD_{50} > 2000 mg/kg (only level tested). No mortalities at 2000 mg/kg dose tested.	III	Supplementary 004766

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50}-rat; Bayer AG, Institute for Toxicology; Report #82661; 10/19/82	THS 2212 (Triazolylalanine) purity unspecified ("analytically pure")	252132	LD_{50} > 5000 mg/kg. Fasted male rats showed increased urinary output the day after dosing.	IV	Minimum 004766
Acute intraperitoneal LD_{50}-rat; Bayer AG, Toxicology Institute; Report #82661; 10/19/82	THS 2212 (Triazolylalanine) purity unspecified ("analytically pure")	252132	LD_{50} > 5000 mg/kg. At 5000 mg/kg, reversible CNS effects (spastic gait, lethargy, etc.) were observed within 1 hour of dosing. The lethal dose exceeds 5000 mg/kg.		Acceptable 004766
14-Day feeding-rat; Bayer AG, Institut fur Toxikologie; Report #82662; 10/25/82	THS 2212 (Triazolylalanine ca 100% purity	252132	Range Finding. Dose levels: 0, 3000, 10,000 ppm in drinking water. No mortalities or clinical signs of toxicity in males.		Supplementary 004766
Acute oral LD_{50}-mice; Bayer AG;#82661;10/19/82	THS 2212	252132	LD_{50} > 5000 mg/kg. No toxic signs.	IV	Minimum 004766
28-Day oral - rat;Bayer AG, Institute of Toxicology; Report #11491; Study No. T6011644;1/24/83.	THS 2212 (Triazolylalanine) "analytically pure"	252132	Dose levels: by gavage in Wistar BOR:WISW SPF/Cpb strain, 0, 25, 100, 400 mg/kg. No mortalities or clinical signs of toxicity. Some changes in hematology, clinical chemistry, organ weights. NOEL > 400 mg/kg(HDT)		Supplementary 004766
One-generation reproduction-rat; Central Toxicology Laboratory. Imperial Chemical Industries PLC; Study #RR023-0/F0; Report #CTL/L/470; 9/19/83.	Triazolylalanine Batch 1-48% Batch 2-unspecified purity	252132	Pilot Study Dose levels: 0, 150, 625, 2500, 10,000 ppm. No effects at 10,000 ppm.		Supplementary 004766

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Tox Chem No. 862B

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Two-generation reproduction-rat; Central Toxicology Laboratory, Imperial Chemical Industries PLC; RRO-255/FO and RRO255/F1; 6/21/83.	Triazolyl-alanine 97.8% purity	252132	Interim report Dose levels: 0, 500, 2000, 10,000 ppm. No effects noted in the first 3 weeks of the study.		Reserved 004766
Mutagenic-Micronucleus test-mice; Imperial Chemical Industries; Report #AC83-2413;study #TCM4; 9/14/82	R152056 (Triazolyl-alanine) purity unspecified. Batch #02199/49	252132 072208	Dose levels: 2500, 5000 mg/kg. No toxicity, chromosomal damage, or erythropoietic effects; however, animals were dosed only once and only one sex tested.		Acceptable 004562 Unacceptable 004766
Teratology-rat; Central Toxicology Lab, Imperial Chemical Industries PLC; report #CTL/P/875; 10/13/83.	Triazolyl-alanine 94.8%	252132	Levels tested by gavage in Alderley Park ALpk/AP strain from day 7 to day 16 of gestation-0, 100, 300 and 1000 mg/kg. Teratogenic NOEL > 1000 mg/kg(HDT) Feto toxic NOEL = 100 mg/kg Feto toxic LEL=300 mg/kg (non-ossification of odontoid process Maternal NOEL > 1000 mg/kg(HDT)		Minimum 004766 005155
Mutagenic-DNA Damage-E. coli; Bayer AG, Institut fuer Toxikologie;Report #82738; 1/5/83	THS 2212 (Triazolyl-alanine) purity unspecified	252132	Dose levels: 62.5, 125, 250, 500, 1000 ug/plate. Nonactivated-no DNA damage. S9 activated-inadequate assay.	NA	Nonactivated assay: Acceptable; S9 Activated assay: Unacceptable 004766
Mutagenic-Micronucleus test-mice; Bayer AG, Institut fuer Toxikologie; Study#T4011615;Report# 11054 & 84005; 8/9/82	THS 2212 (Triazolyl-alanine)purity unspecified ("analytically pure")	252132	Weak positive response for 8000 mg/kg at 24-hr. Study unacceptable due to lack of critical data on positive and negative controls.	NA	Acceptable 004562 Unacceptable 004766 005352

Tox Ch. No. 862D

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic-Bacterial Point Mutations; Bayer kologie; Report #11388; 1/5/83.	THS 2212 (Triazolyl- purity unspe- cified	252132	Dose levels of 20, 100, 500, 2500, 12,500 ug/plate did not induce re- typhimurium assay. Non-activated assay not evaluated due to lack of positive control.	NA	Acceptable 004562 004459 Nonactivated assay: Unacceptable; S9 Activated assay: Acceptable 004766
Metabolism/Pharmacokine- tic-rat; Bayer AG;Report #11583;2/24/83	[14C] Tri- azolylalanine; radiochemical purity 99%	252132	Dose levels: 5 mg/kg (metabolism); 10 mg/kg (whole-body autoradiogra- phy). Rapid absorption and excre- tion in male rats:95 percent of ad- ministered dose was absorbed and 94.5 percent of the radioactivity measured in urine within 48 hours. None of the metabolites were identi- fied.	NA	Acceptable 004766
Metabolism-rat;Agricul- tural Division CIBA- GEIGY Limited;Report #CGA 131013,82/91-92/ 110; 3/2/83.	[14C]D-L- triazolyl- alanine;radio- chemical puri- ty > 99%	252132	Dose level - approx. 50 mg/kg. Al- most entirely excreted within 24 hrs; primary route-urine,secondary route-feces. Metabolites: N-acetyl, and unaltered triazolylalanine in urine.	NA	Minimum 004766

Tox Chem No. 862B

Current Date: 5/19/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade Doc. No.
Metabolism-rat; Ciba-Geigy; Study No. 131013, Report No. 11/83; Oct. 20, 1983.	^{14}C-D,L-Triazolylalanine. Purity > 99%	252132	In 24 hours, 69-86% of the dose was excreted unchanged in the urine, 8-19% was excreted as the acetyl derivative in the urine. About 3% of the dose was excreted in the urine as unknown metabolites. The total fecal radioactivity accounted for 3% of the total dose. The fecal metabolites were similar to those found in the urine except for one that could not be identified.	NA	Acceptable 004766
Mutagenic - BALB/3T3 mouse fibroblast transformation; Ciba-Geigy; Report #840324; Sept. 12, 1984	Triazolylalanine (Purity not specified)	257997	Negative with metabolic activation; inconclusive without activation. Concentrations up to 1000 ug/ml. Repeat test requested.		Unacceptable 005155 005352

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Table VIII

Percent Distribution of Total Radioactivity Recovered[1]

	Immature Wheat[2]			Wheat Grain[3]			Wheat Straw		
Posttreatment Interval (Days)	29	122	273	29	122	273	29	122	273
Component									
Organosoluble[4]	-	8.0	-	-	-	-	-	1.1	1.4
FOLICUR	-	NA[5]	-	-	-	-	4.3	NA	NA
FOLICUR-*t*-butyl-hydroxy	-	NA	-	-	-	-	7.9	NA	NA
Unknowns (1-11)[6]	-	NA	-	-	-	-	0.6	NA	NA
Baseline-Diffuse[7]	-	NA	-	-	-	-	8.0	NA	NA
Subtotal	-	8.0	-	-	-	-	20.8	1.1	1.4
Aqueous[8]									
Triazole[9]	-	ND[10]	-	ND	ND	ND	ND	ND	ND
Triazolylalanine[9]	-	28.5	-	52.9	71.0	59.0	4.9	24.1	15.7
Triazolylacetic Acid[9]	-	50.8	-	42.0	25.7	36.2	18.9	25.0	16.2
Triazolyl-lactic Acid[9]	-	ND	-	ND	ND	ND	28.4	26.6	52.0
Diffuse	-	8.0	-	3.8	3.1	4.1	5.9	9.2	9.1
Unextracted	-	4.7	-	1.3	0.2	0.7	21.1	14.0	5.7
TOTAL	-	100.0	-	100.0	100.0	100.0	100.0	100.0	100.0

[1]Normalized values.
[2]Crop samples from the 29- and 273-day intervals not available.
[3]Extracted using a 1N HCL reflux for 2 hours.
[4]Organosoluble quantitation by HPLC.
[5]NA = Not analyzed.
[6]Percent of individual peaks found in Table XII.
[7]Diffuse defined as radioactivity not associated with any specific peak.
[8]Aqueous quantitation based on elution fractions collected from the ion exchange columns, except beet root which was quantitated by HPLC.
[9]Structure in Figure 4.
[10]ND = None detected.
[11]Measured as Triazolypinacolone (Figures 28 and 29).

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TABLE VIII (cont'd)

Posttreatment Interval (Days)	Beet Top 29	Beet Top 122	Beet Top 273	Beet Root 29	Beet Root 122	Beet Root 273	Kale 29	Kale 122	Kale 273
Component									
Organosoluble[4]	-	1.4	1.7	-	2.2	1.3	-	0.64	0.53
FOLICUR	7.2	NA	NA	4.8	NA	NA	15.0	NA	NA
FOLICUR-*t*-butyl-hydroxy	1.1	NA	NA	0.4	NA	NA	0.4	NA	NA
Unknowns (1-11)[6]	4.3	NA	NA	1.5	NA	NA	4.0	NA	NA
Baseline-Diffuse[7]	2.7	NA	NA	2.1	NA	NA	4.5	NA	NA
Subtotal	15.3	1.4	1.7	8.8	2.2	1.3	23.9	0.64	0.53
Aqueous[8]									
Triazole[9]	ND	ND	ND	6.8[11]	14.8	16.8	ND	ND	ND
Triazolylalanine[9]	19.5	21.6	20.6	58.0	54.8	52.2	56.2	56.2	85.5
Triazolylacetic Acid[9]	6.8	7.2	4.8	ND	3.3	3.3	3.3	3.3	5.8
Triazolyl-lactic Acid[9]	20.5	49.1	34.3	ND	3.5	3.5	ND	ND	ND
Diffuse	20.8	6.5	11.2	13.6	16.7	16.7	4.3	4.3	5.2
Unextracted	17.1	14.2	27.4	12.8	7.2	7.2	12.3	12.3	3.0
TOTAL	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[1]Normalized values.
[2]Crop samples from the 29- and 273-day intervals not available.
[3]Extracted using a 1N HCL reflux for 2 hours.
[4]Organosoluble quantitation by HPLC.
[5]NA = Not analyzed.
[6]Percent of individual peaks found in Table XII.
[7]Diffuse defined as radioactivity not associated with any specific peak.
[8]Aqueous quantitation based on elution fractions collected from the ion exchange columns, except beet root which was quantitated by HPLC.
[9]Structure in Figure 4.
[10]ND = None detected.
[11]Measured as Triazolypinacolone (Figures 28 and 29).

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Table IX

Determination of Ppm of Triazolylalanine, Triazolylacetic Acid, Triazole and Triazolyl-lactic Acid in Rotational Crops Grown in Soil Treated with [^{14}C] FOLICUR Maintained in Frozen Storage at -10°C[1,2]

Metabolite	Triazole			Triazolylalanine			Triazolylacetic Acid			Triazolyl-lactic Acid		
Interval (Days)	29	122	273	29	122	273	29	122	273	29	122	273
Kale	ND[3]	ND	ND	0.77	0.99	1.18	0.04	0.18	0.06	ND	ND	ND
Wheat												
Immature Wheat	ND	ND	ND	ND	0.81	ND	ND	1.27	ND	ND	ND	ND
Wheat Straw	ND	ND	ND	0.10	0.38	0.34	0.33	0.5	0.28	0.61	0.7	1.11
Wheat Grain	ND	ND	ND	9.55	10.65	10.7	6.09	5.25	5.25	ND	ND	ND
Beet Tops	ND	ND	ND	0.13	0.07	0.14	0.04	0.04	0.03	0.14	0.36	0.23
Beet Roots	0.01	0.02	0.03	0.24	0.19	0.21	ND	ND	0.01	ND	ND	0.01

[1]Values were determined from those presented in Tables VI and VIII and a correction factor ratio of metabolite molecular weight vs. parent compound m.w.
[2]Intervals of frozen storage: 29-day rotational interval maintained 1155 days in frozen storage 122-day rotational interval maintained 1000 days in frozen storage 273-day rotational interval maintained 708 days in frozen storage.
[3]ND = None detected.

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Terbuconazole New Chemical Standard

To: Susan Lewis
Product Manager 21
Registration Division (H7505C)

From: Hank Jacoby, Chief
Environmental Fate and Ground Water Branch
Environmental Fate and Effects Division (H7507C)

Hank Jacoby 9/18/90

and

Henry Nelson
Acting Section Head, Review Section 3
Environmental Fate and Ground Water Branch
Environmental Fate and Effects Division (H7507C)

H Nelson 9/12/90

Attached is the EFGWB science chapter for Terbuconazole. The chapter takes into account *proposed* uses as a seed treatment on wheat, barley, and peanuts, and as a treatment for grapes, and existing uses on lawns, turf, and grass grown for seed.

ENVIRONMENTAL FATE ASSESSMENT

Based on fairly extensive data, terbuconazole is persistent and relatively immobile. It is resistant to hydrolysis, aqueous photodegradation, and soil metabolism, but slowly photodegraded on soil. Unaged terbuconazole shows little mobility (K_ds of adsorption ranged from 7 - 16 in laboratory studies on a variety of soils). Aged material was still largely parent compound, and showed little tendency to move beyond the upper 6 cm of the soil column in laboratory studies. An unsatisfactory field dissipation study with bare-ground application indicated some movement in areas of sand soil in Florida. Uptake into plants may be a significant means of dissipation. There is accumulation of the triazolyl moiety into all confined crops tested (small grain, leafy vegetable, and root crops planted 30, 120, and 273 days after treatment). Chlorophenyl-labelled material was not tested. Field data also showed accumulation in some crop materials. Accumulation into fish also occurs with rapid depuration(BCFs of 25, 229, and 99 for edible tissue, non-edible tissue, and whole fish respectively).

There are several areas of concern which have been noted. Since the compound is persistent, some *phytotoxicity* to subsequent non-target crops planted on treated soil could occur. EFGWB defers to Ecological Effects Branch on this issue. Based on the current use on turf and seed grass, and the proposed uses on grapes and for seed treatment, under most conditions terbuconazole is considered unlikely to reach *ground water*. However, like most chemicals, it does have the potential to contaminate ground water in extremely vulnerable areas (high water table, sandy soil with low organic matter). Because of its tendency to remain adsorbed to soil, terbuconazole may move off-target into adjacent *surface water* during a storm event that produces soil erosion.

GROUND WATER ASSESSMENT

It should be noted, in considering the following environmental fate characteristics, that terbuconazole is a relatively low-dosage pesticide, used at a seasonal limit of 1.35 lb a.i.[1.35 *ppm for a 3" soil layer*]/A for turf and seed grass. 0.9 lb a.i.[*0.9 ppm*]/A is proposed for use on grapes. Proposed seed treatments are ca. 0. 03 lb/100 lb seed, and expected planting rates are 35 - 150 lb of seed/A. Therefore a maximum of 0.045 lb a.i./A would result from use of treated seed.

According to available information, terbuconazole is highly stable to environmental degradation, both chemical and biological, with half-lives up to several years.

It is relatively immobile ($K_{d\ ads}$ 7 - 16) in batch equilibrium studies on unaged compound.

After 30 days aging, the radiolabelled material is still more than 80% parent terbuconazole. In column leaching studies on "aged" compound, 35 - 60% eluted out of the treated layer into the first 6 cm of the column, and as much as 15% eluted into the second 6 cm. Mobility is greatest in soils of low organic content.

Based on these criteria, terbuconazole has little potential to reach ground water, except possibly in the most vulnerable areas, in soils which are high in sand and have little organic matter. Once there, however, it could persist for a considerable length of time.

SURFACE WATER ASSESSMENT

Terbuconazole is stable to most environmental degradative processes and is relatively immobile. Based on these data, in a runoff event, terbuconazole would probably remain adsorbed to suspended soil particles, and the compound could move into adjacent bodies of surface water. Since it would be likely to stay associated with the sediment, it would be resistant to the known routes of dissipation. Although not investigated in existing data, sensitized photolysis is a potential route for environmental dissipation. Even if it is rapid, it would probably not be much of a factor under these conditions. Therefore, terbuconazole in sediment could persist long enough to affect resident biota, particularly bottom feeders.

DATA BASE ASSESSMENT

The following data are **REQUIRED**:

Terrestrial field dissipation studies:

- A turf field dissipation study must be done to support that use.
- A vineyard study must be done to support the ***proposed*** use on ***grapes***.

The following data requirements are **PARTIALLY FULFILLED**:

Aerobic soil metabolism: characterization of the unidentified degradates in *Lee and Hanna-Bey*, MRID # 407009-50 could fulfill this requirement. Otherwise a new study will be necessary.

Anaerobic soil metabolism: a requirement of the ***proposed*** use on grapes. Characterization of the unidentified degradates in *Lee and Hanna-Bey*, MRID

TERBUCONAZOLE

Table of Contents

DATA EVALUATION RECORD

STUDY 7

CHEM 128997	Terbuconazole	165-1

FORMULATION--12--EMULSIFIABLE CONCENTRATE (EC)

STUDY ID 40700964
Leimkuehler, W., C. Lenz, and J. Delk. 1988. Radioactive residues of ^{14}C-Folicur in rotational crops. Laboratory Project ID 95638. Unpublished study performed and submitted by Mobay Corporation, Stilwell, KS.

DIRECT REVIEW TIME = 10

REVIEWED BY: L. Binari TITLE: Staff Scientist

EDITED BY: K. Patten TITLE: Task Leader

APPROVED BY: W. Spangler TITLE: Project Manager

ORG: Dynamac Corporation
Rockville, MD
TEL: 468-2500

APPROVED BY: B. Conerly
TITLE: Chemist
ORG: EFGWB/EFED/OPP
TEL: 557-5456

SIGNATURE: E.B. Conerly 8/6/90

CONCLUSIONS:

Confined Accumulation - Rotational Crops

1. This study cannot be used to fulfill data requirements. Because of the deficiencies listed below, it is uncertain whether it provides enough information to allow development of a suitable protocol for a field study.

    1) [^{14}C]residues in the crops were not adequately characterized (the investigator assumed that day 120 samples represented all time periods);
    2) storage stability data were not provided for the plant and soil substrates;
    3) total radioactivity in the soil was not determined prior to the soil surface treatment and at the time of harvest of the rotational crops;

4) $[^{14}C]$residues in the soil were quantified but not identified immediately posttreatment; the test substance was not analytical grade or purer;

5) the analytical methodology was not adequately described.

2. For this study to fulfill the accumulation in confined rotational crops data requirement, the registrant must do the following: characterize organosoluble and water-soluble $[^{14}C]$residues in all crops from all three rotations; provide storage stability data for the plant and soil substrates; if samples are still available, quantify $[^{14}C]$residues in the soil prior to the soil surface treatment and at the time of harvest of the rotational crops and characterize $[^{14}C]$residues from those two intervals plus $[^{14}C]$residues in the soil immediately after the soil surface application; and provide additional details about the analytical methodology and the plant growing conditions (refer to Comments 6 and 8).

3. $[^{14}C]$Terbuconazole residues accumulated in kale, beets, and wheat planted 29, 122, and 273 days after sandy loam soil was treated with terbuconazole at 500 g ai/ha. In general, accumulation was greatest in crops from the 122-day rotation and least in the crops from the 29-day rotation. Residues in the kale ranged from 0.3 to 2.7 ppm; in beets from 0.2 to 1.3 ppm (tops and roots); and in wheat from 3.8 to 35.4 ppm (grain) and 1.1 to 4.2 ppm (straw). $[^{14}C]$Residues extracted from the crops included terbuconazole, terbuconazole-t-butyl-hydroxy, triazole, triazolylalanine, triazolylacetic acid, and triazolyl-lactic acid. In the soil, terbuconazole (the only extractable $[^{14}C]$compound) decreased from 0.43 to 0.02 ppm between the 29- and 273-day posttreatment plantings; total residues decreased from 0.52 to 0.16 ppm during the same period.

METHODOLOGY:

Triazole ring-labeled $[^{14}C]$terbuconazole (radiochemical purity 98.8%, specific activity 17.42 mCi/mMol, Mobay) was mixed with unlabeled terbuconazole (Folicur, 22.5% dry flowable), "22.5% dry flowable formulation blank", and water; the formulated test substance contained 3.1% radioactive ai. The formulated test substance was applied as a foliar spray at 500 g ai/ha (equivalent to ≈1.1 lb ai/A) to wheat (boot stage) growing on sandy loam soil (70% sand, 26% silt, 4% clay, 2.8% organic matter, pH 5.2, CEC 21 meq/100 g) contained in one galvanized tub (8 x 2.5 x 2.5 feet) in a greenhouse. At 50 days posttreatment, the wheat was harvested and the formulated test substance was applied again at 500 g ai/ha directly to the soil surface. The soil was cultivated to a depth of 1 inch and allowed to age for 29 days.

At 29 days following the application of terbuconazole to the soil surface, the soil was planted to kale, beets and wheat; each crop covered one-third of the soil (Table II). Kale and beets were harvested at maturity (58 days postplanting); wheat was harvested when immature (41 days postplanting) and at maturity (93 days postplanting). At 122 days posttreatment, the soil used for the 29-day rotation was again planted to kale, beets, and wheat. Kale and beets were harvested at maturity (85 days post-

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planting); wheat was harvested when immature (43 days postplanting) and at maturity (85 days postplanting). At 273 days posttreatment, the soil used for the 29- and 122-day rotations was again planted to kale, beets, and wheat. Kale and beets were harvested at maturity (60 and 107 days postplanting, respectively); wheat was harvested when immature (30 days postplanting) and at maturity (99 days postplanting).
Crops were separated into their various parts, homogenized with dry ice (except for wheat grain), and stored frozen (-10 C) until analysis; wheat grain was stored intact. Soil samples (6-inch cores) were taken immediately following the application of terbuconazole to the soil surface (second application) and at each planting interval; storage conditions for the soil samples were not described.

Plant samples, except for wheat grain, were extracted twice with methanol:water (1:1) (Figure 2). Extracts were filtered, combined, concentrated, and partitioned twice with methylene chloride:acetonitrile (2:1). For the 29-day plant samples, the organic phase was analyzed by reverse-phase radio-HPLC with UV detection and GC/MS; the aqueous phase was not analyzed. For the 122-day plant samples, the organic phase was not analyzed and the aqueous phase was applied to a cation exchange column; radioactivity that was not initially retained on the column was collected. Radioactivity remaining on the column was eluted with a 100 mM to 1 M linear gradient of sodium chloride; fractions containing radioactivity were pooled, concentrated, then derivatized with 3 N hydrochloric acid in n-butanol and heptafluorobutyric anhydride. Following the derivatization, the sample was evaporated to dryness, dissolved in acetonitrile, and analyzed by HPLC and GC/MS as described above. Radioactivity that was not initially retained by the cation exchange column was adjusted to pH 4-7, applied to an anion exchange column, eluted with the sodium chloride gradient, derivatized with n-butanolic hydrochloric acid, then analyzed by HPLC and GC/MS.

Wheat grain was ground to a fine powder, then extracted with methanol followed by a 2-hour reflux with 1 N hydrochloric acid (Figure 3). Extracts were filtered, combined, concentrated, applied to a cation exchange column, eluted with the linear sodium chloride gradient, derivatized, and analyzed by HPLC and GC/MS as described above.

Soil samples were analyzed for total radioactivity by LSC following combustion. Additional samples of the soil were extracted for 2 hours with methanol. The extract was filtered, concentrated, and analyzed by TLC (type of plates unspecified) using acetonitrile:methanol:acetic acid (90:10:1). Unlabeled terbuconazole was cochromatographed with the samples. Following development, radioactive areas were located using autoradiography.

DATA SUMMARY:

[^{14}C]Terbuconazole residues accumulated in kale, beets, and wheat planted 29, 122, and 273 days after the second of two 500 g ai/ha applications of formulated triazole ring-labeled [^{14}C]terbuconazole (radiochemical purity

98.8%); the first application was to wheat growing in a tub of sandy loam soil and the second application, 50 days later, was directly to the sandy loam soil surface. The concentration of [^{14}C]residues in crops from the 122-day rotation was ≈4 to 9x greater than the concentration in crops from the 29-day rotation; the concentration of [^{14}C]residues in crops from the 273-day rotation was generally ≈2-4x greater than the concentration in crops from the 29-day rotation.

In crops planted at 29 days posttreatment, [^{14}C]residues at harvest were 0.3 ppm in kale, 0.2 ppm in beet tops and roots, and 3.8 and 1.1 ppm in wheat grain and straw. Organosoluble residues ranged from 0.4 to 22.9% of the recovered radioactivity, water-soluble residues ranged from 51.1 to 88.6%, and unextractable residues ranged from 5.8 to 29.7%. In the organosoluble fraction,

terbuconazole -- comprised 20.7% of the total radioactivity in kale; 15.2 and 5.6% in beet tops and roots, 22.9% in immature wheat, and 5.4% in mature wheat straw; terbuconazole was not detected in the wheat grain. In addition, in the mature wheat straw,

terbuconazole-t-butyl hydroxy -- comprised 9.3% of the recovered radioactivity.

Five unknowns (0.4-1.6%) were detected. Water-soluble [^{14}C]residues were not characterized.

In crops planted at 122 days posttreatment, [^{14}C]residues at harvest were 2.7 ppm in kale; 1.3 and 0.8 ppm in beet tops and roots; and 35.4, 4.2, and 15.0 ppm in wheat grain, straw, and chaff. Organosoluble residues ranged from 0.6 to 8.1% of the recovered radioactivity, water-soluble residues ranged from 85.5 to 100%, and unextractable residues ranged from 0 to 13%. In the water-soluble fraction, the primary degradate in all crops was

triazolylalanine -- detected at 1.1 ppm in kale, 0.16 and 0.3 ppm in beet tops and roots, 0.7 ppm in immature wheat, and 0.51 and 12.7 ppm in mature wheat straw and grain. Another degradate found in all crops was

triazolylacetic acid -- detected at 0.04 ppm in kale, 0.05 and 0.03 ppm in beet tops and roots, 1.5 ppm in immature wheat, and 0.4 and 3.1 ppm in mature wheat straw and grain.

Triazolyl-lactic acid -- detected in beet tops (0.37 ppm) and roots (0.01 ppm) and wheat straw (0.8 ppm), and

triazole -- detected in beet roots (0.02 ppm).

Organosoluble [^{14}C]residues were not characterized.

In crops planted at 273 days posttreatment, [^{14}C]residues at harvest were 2.0 ppm in kale; 1.0 and 0.9 ppm in beet tops and roots; and 7.6, 2.6, and 6.0 ppm in wheat grain, straw, and chaff. Organosoluble residues ranged from 0.2 to 2.8% of the recovered radioactivity, water-soluble residues ranged from 79.0 to 96.4%, and unextractable residues ranged from 2.7 to 20.0%. Organosoluble and water-soluble [^{14}C]residues were not characterized.

In the 0- to 6-inch soil depth, total [^{14}C]residues were 1.5 ppm immediately following application of formulated [^{14}C]terbuconazole to the soil surface, 0.52 ppm at 29 days posttreatment, 0.29 ppm at 122 days posttreatment, and 0.16 ppm at 273 days posttreatment. Between 29 and 273 days posttreatment, extractable [^{14}C]residues decreased from 84 to 14% of the total radioactivity; terbuconazole was the only compound detected in extracts from the 29- and 122-day soil samples (quantitative data were not provided).

COMMENTS:

1. [^{14}C]Residues in the crops were not adequately characterized. Although the relative amounts of organosoluble, water-soluble, and unextractable residues in all plant parts was determined, only the organosoluble fraction from the 29-day rotational crops and the water-soluble fraction from the 120-day rotational crops were analyzed for specific [^{14}C]compounds. The study author assumed that the composition of the organosoluble and water-soluble fractions were identical for the three rotational intervals.

2. Freezer storage stability data were not provided for the plant substrates; it was also not specified how long samples were stored frozen prior to analysis. Storage conditions for the soil samples were not described. The freezer storage data for soil supplied in Study 6 (MRID 40700962) was unacceptable.

3. Although it was stated that the soil was sampled when the rotational crops were harvested, no data were provided. For the 29- and 122-day rotations, the date of final harvest is near to the date of planting for the next rotation, so the planting date concentrations should be valid; however, data for the 273-day rotation harvest are needed.

   Also, no soil samples were collected after the wheat treatment or before the application to the soil surface. The contribution of the first application to the "time 0" concentration in the soil (the sampling immediately after the soil surface was treated) could not be determined. The concentration in the 0- to 6-inch soil depth at time 0, 1.5 ppm, was much higher than the expected 0.55 ppm (assuming an application of 1.1 lb ai/A and 1 acre containing 2 million pounds of soil).

4. It was reported that only terbuconazole was detected following TLC of the 29- and 122-day soil extracts; however, quantitative data were not

provided. [^{14}C]Residues in the 0- and 273-day soil sample were not characterized. Time 0 should have been analyzed because [^{14}C]residues may have remained from the application to the wheat. The study author stated that insufficient extractable material from the 273-day interval was available for analysis.

5. The test substance was formulated (final purity unspecified) and, therefore, was not analytical grade or purer.

6. The analytical methodology was not adequately described; a) the type of TLC plate used was not specified, b) it was not specified how unlabeled terbuconazole was detected following TLC, c) it was not always clear what compounds were being derivatized to, and d) it was not clear at what stage of the methodology the plant extracts were analyzed for free triazole (which apparently required a separate derivatization step). Recovery efficiencies of terbuconazole and degradates from fortified soil and plant samples were not provided.

7. Immature kale and beets were not analyzed.

8. A description of the growing conditions, such as watering schedule, air temperatures, and relative humidity, was not reported.

9. The experimental design was not typical. It could not be determined why terbuconazole was applied first to a growing crop, then to the soil surface. Also, the same tubs of soil are generally not used for all three rotation intervals, rather soil that has been unvegetated for the entire rotation interval is used.

10. A confined accumulation rotational crop study using phenyl ring-labeled [^{14}C]terbuconazole may be required.

11. The study author refers to 30-, 120-, and 270-day rotations in the text and tables. In fact, the rotations were 29, 122, and 273 days.

Page_____ is not included in this copy.

Pages 33 through 50 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

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X FIFRA registration data.

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DATA EVALUATION RECORD

STUDY 8

CHEM 128997	Terbuconazole	165-2

FORMULATION--12--EMULSIFIABLE CONCENTRATE (EC)

STUDY ID 40995923
Leslie, W.L. 1988. Folicur residues in field rotational crops. Laboratory Project ID 122-003/Mobay Project ID Folicur objective No. 8500. Unpublished study performed by EPL Bio-Analytical Services, Inc., Decatur, IL, and submitted by Mobay Corporation, Stilwell, KS.

DIRECT REVIEW TIME = 14

REVIEWED BY: L. Binari TITLE: Staff Scientist

EDITED BY: K. Patten TITLE: Task Leader

APPROVED BY: W. Spangler TITLE: Project Manager

ORG: Dynamac Corporation
Rockville, MD
TEL: 468-2500

APPROVED BY: B. Conerly
TITLE: Chemist
ORG: EFGWB/EFED/OPP
TEL: 557-5456

SIGNATURE:
E.B. Conerly 8/6/90

CONCLUSIONS:

Field Accumulation - Rotational Crops

1. This study cannot be used to fulfill data requirements at this time. It is scientifically sound, but does not meet Subdivision N guidelines for the following reasons:

crop samples were only analyzed for parent terbuconazole;

storage stability data were not provided for the plant and soil substrates;

crop residue data were incomplete; and

field test data were incomplete.

2. In order for this study to fulfill the accumulation in field rotational crops data requirement, the registrant must submit the following information: degradates (as identified in the confined accumulation rotational crop study) in all crops from both rotations should be quantified; storage stability data should be provided for the plant and soil substrates; if available, residue data for the crops specified (refer to Comment 6) should be provided; and details concerning the experimental procedures and field test data (refer to Comments 7-12) should be provided.

3. Terbuconazole did not appear to accumulate in spinach, turnips, and wheat or sorghum planted approximately 30 and 120 days after sandy loam/sandy clay loam and silt loam/silty clay loam soil received seven applications at 10- to 25-day intervals of terbuconazole at 3.5 oz ai/A. At harvest, terbuconazole was detected in the spinach at 0.02 ppm; in the turnips at <0.01-0.03 ppm (tops and roots); in the wheat at 0.01 ppm (grain), 0.03-0.11 ppm (straw), and 0.05 ppm (forage); and in the sorghum at 0.01-0.03 ppm (grain), 0.02-0.04 ppm (straw), and 0.01 ppm (forage).

<u>METHODOLOGY</u>:

Terbuconazole (Folicur, 1.2 lb/gallon EC) was broadcast surface sprayed at 3.5 oz ai/A (250 g ai/ha) seven times at 10- to 25-day intervals to field plots of:

> sandy loam/sandy clay loam soil (plot size 12 x 120 feet) planted to spring rye located in Howe, Indiana, during April 14-July 7, 1986 (for 31-day plant-back of spinach and turnips), June 3-August 25, 1986 (for 32-day plant-back of wheat), and September 12-December 8, 1986 (for 126-day plant-back; all crops); and
>
> silt loam/silty clay loam soil (plot size 18 x 50 feet) located in Stilwell, Kansas, during December 12, 1986-March 12, 1987 (for 124-day plant-back), and January 8-April 23, 1987 (for 33-day plant-back).

The soil characteristics are presented in Table 1. At approximately 30 and 120 days posttreatment, spinach, turnips, and either wheat (IN) or sorghum (KS) were planted in the treated plots. Crops were harvested at maturity: 45-119 days postplanting for spinach, 56-73 days for turnips, 87-276 days for wheat, and 121-140 days for sorghum. In addition, wheat and sorghum forage were harvested at 45 days postplanting. Soil cores (diameter unspecified, 0- to 6-inch depth) were taken following the final (seventh) application, when the crops were planted (approximately 30 and 120 days posttreatment), and at mature crop harvests (87-308 days posttreatment). Samples were stored frozen for an "average of 456 days" until analysis.

Plant samples were extracted with acetone:water (3:1). The extracts were filtered, then each was partitioned with methylene chloride and sodium chloride (ratios not reported). The organic phase was evaporated to dryness, and the resulting residue was redissolved in ethyl acetate and fractionated by gel permeation chromatography. The eluate was evaporated to dryness, redissolved in toluene, and applied to a silica gel column. The column was eluted with hexane:ethyl acetate (1:1), and the eluate was evaporated to dryness. The residues were redissolved in methanol:water (1:9) and applied to a Sep-Pak C-18 column. The column was eluted with methanol:water (7:3), and the eluate was evaporated to dryness. The residues were redissolved in ethyl acetate and analyzed for terbuconazole by GC with nitrogen-phosphorous detection. The detection limit was 0.01 ppm. Recovery efficiencies from plant samples fortified with terbuconazole at 0.01 to 0.05 ppm were 68.5-117% of the applied in spinach; 55.6-125 and 70.3-111% in turnip tops and roots, respectively; and 83-168, 65.3-98.3, and 55.4-160% in sorghum forage, grain, and straw, respectively. Recovery efficiencies were not reported for wheat.

Soil samples were extracted with methanol:water (7:3), then the extract was partitioned with methylene chloride. The organic phase was evaporated to dryness, redissolved in ethyl acetate:cyclohexane (1:1), and fractionated by gel permeation chromatography. The eluate was evaporated to dryness, and the resulting residues were redissolved in methanol:water (1:9) and applied to a Sep-Pak C-18 column. The eluate was evaporated to dryness, redissolved in ethyl acetate, and analyzed by GC as described above. The detection limit was 0.01 ppm. Recovery efficiencies from soil samples fortified with terbuconazole at 0.01 to 0.05 ppm ranged from 63.1 to 160% of the applied.

DATA SUMMARY:

Terbuconazole was $\leq$0.03 ppm in spinach leaves, turnip roots and tops, and wheat or sorghum grain planted approximately 30 and 120 days after seven applications at 10- to 25-day intervals of terbuconazole (Folicur, 1.2 lb/gallon EC) at 3.5 oz ai/A (250 g ai/ha) to sandy loam/sandy clay loam soil located in Indiana and silt loam/silty clay loam soil located in Kansas. Except for 0.11 ppm of terbuconazole in straw from wheat planted at approximately 120 days posttreatment, terbuconazole detected in the crops from the treated plots did not significantly exceed the apparent limits of determination of terbuconazole in the various plant matrices.

In crops planted at approximately 30 days posttreatment, terbuconazole at harvest was 0.02 ppm in spinach; 0.02-0.03 and 0.01-0.03 ppm in turnip tops and roots, respectively; 0.01 and 0.03 ppm in wheat grain and straw (IN site), respectively; and 0.03 and 0.04 ppm in sorghum grain and straw (KS), respectively. In immature sorghum forage harvested at 45 days postplanting, terbuconazole was 0.01 ppm.

In crops planted at approximately 120 days posttreatment, terbuconazole was 0.02 ppm in spinach (KS site only); <0.01 ppm in turnip tops (KS site only); 0.01-0.02 ppm in turnip roots; 0.01 and 0.11 ppm in wheat grain and straw, respectively; and 0.01 and 0.02 ppm in sorghum grain and straw, respectively. In immature wheat forage harvested at 45 days postplanting, terbuconazole was 0.05 ppm.

In control crops, apparent terbuconazole was 0.01-0.02 ppm in spinach; <0.01-0.02 and 0.01-0.03 ppm in turnip tops and roots, respectively; 0.02 and 0.01 ppm in wheat forage and grain; and 0.01, 0.01, and 0.02-0.06 ppm in sorghum forage, grain, and straw, respectively.

In the 0- to 6-inch soil depth from plots treated for the 30-day plant-back, terbuconazole was 0.17-0.41 ppm immediately following the final application of terbuconazole; 0.07-0.19 ppm at 31-33 days posttreatment, and 0.04-0.12 ppm at harvest (87-308 days posttreatment). From plots treated for the 120-day plant-back, terbuconazole in the soil (0- to 6-inch depth) was 0.21-2.42 ppm immediately following the final application, 0.19-0.35 ppm at 124-126 days posttreatment, and 0.01-0.10 ppm at harvest (171-245 days posttreatment).

COMMENTS:

1. Crop samples were only analyzed for parent terbuconazole. In a confined accumulation rotational crop study [Dynamac review dated 5/3/89, Study 7 (40700964)], terbuconazole plus the degradates terbuconazole-t-butyl-hydroxy, triazolylalanine, triazolylacetic acid, triazolyl-lactic acid, and triazole were detected in kale, beets, and wheat planted 29, 129, and 273 days after two 500-g ai/ha applications of terbuconazole were made to sandy loam soil. Soil samples were also only analyzed for terbuconazole; however, in photodegradation on soil and aerobic soil metabolism studies [Dynamac review 5/3/89, Studies 2 (40700958) and 3 (40700959)], no extractable degradates were identified; terbuconazole was shown to degrade primarily to unextractable compounds.

2. Freezer storage stability data were not provided for the plant substrates and soil. It was reported that the samples were stored for an "average" of 456 days; the actual length of time that the samples were stored must be provided. It was also reported that there was no "significant" degradation of terbuconazole in peanut vines that were stored frozen for 189 days; however; this is irrelevant because the crops used in this study were not of a similar plant matrix, the storage length exceeded 189 days, and no actual storage data were provided for the peanut vines.

3. It was reported that interference studies were conducted to determine the specificity of the method (Mobay Report No. 95680); however, this information was not provided and is necessary to verify the reported limits of determination of terbuconazole in the various plant substrates.

4. At the KS site, it appears that the test substance was not evenly applied to the test plot used for the 120-day plant-back (concentrations ranged from 0.21 to 2.42 ppm terbuconazole following final application); however, there was no apparent effect on the pattern of terbuconazole uptake by the various crops.

5. Immature spinach and turnips were not analyzed.

6. At the IN site, data for the wheat forage sample planted 30 days posttreatment and the spinach and turnip tops planted 120 days posttreatment were not provided. At the KS site, data for the sorghum forage sample planted 120 days posttreatment were not provided. No explanation was provided as to why the samples were not available for analysis.

7. It could not be determined exactly how many test plots were treated or the actual size of the plots. From the Residue Study Field Report Forms, it appears that at the IN site, a total of three plots, each 12 x 120 feet, were used. At the KS site, it appears that two plots, each 18 x 50 feet, were used.

8. Preparation of the test plots was not described. It was reported that the test substance was applied as a soil incorporated, broadcast spray, but it was not described how the test substance was "incorporated". At the IN site, the test substance was applied to spring-planted rye; vegetation cover at the KS site was not described. Field maintenance practices during the studies were not described.

9. Although data for crops and soil from control plots were provided, the size and location of the control plots in relation to the test plots were not provided.

10. The actual number of soil cores taken at each sampling interval could not readily be determined. It appears that a single core was taken for each crop at each sampling interval.

11. At the KS site, the depth to the water table was 6 feet; the depth to the water table at the IN site was not reported. For both sites, the slope of the field was not reported.

12. At the IN site, some meteorological data were provided, but were not collected on a daily basis; for the 30-day plant-back of wheat (6/3/86-6/29/86), rainfall plus irrigation totaled 40.8 inches, air temperatures ranged from -19 to 98 F, and soil temperatures (depth unspecified) ranged from 30 to 90 F; for the 30-day plant-back of spinach and turnips (4/14/86-10/2/86), rainfall plus irrigation to-

taled 26.2 inches, air temperatures ranged from 23 to 93 F, and soil temperatures ranged from 40 to 88 F; for the 120-day plant-back (9/12/86-7/9/87), rainfall plus irrigation totaled 28.4 inches, air temperatures ranged from -19 to 93 F, and soil temperatures ranged from 30 to 90 F. At the KS site for the 30-day plant-back (1/8/87-10/13/87) and the 120-day plant-back (12/11/86-11/12/87), rainfall totaled 32.1 and 33.9 inches, respectively; air and soil temperatures were not provided.

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Pages 57 through 65 are not included.

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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Triazole residues in Wheat seeds and Barley grains.

From: Alberto Protzel, Ph.D. Alberto Protzel 4/10/91
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

To: Richard D. Schmitt, Ph.D., Chief
Dietary Exposure Branch
Health Effects Division (H7509C)

Thru: James N. Rowe, Ph.D., Head James N. Rowe 4/10/91.
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Chief M van Gemert 4/10/91
Toxicology Branch II
Health Effects Division (H7509C)

In a 1/3/90 memorandum from W.J. Hazel to R.D. Schmitt, concern for triazole-derived residues from DPX-H6573 (also known as Nustar[R]) was indicated. In particular, the metabolite triazolylalanine was reported as occurring at levels of ≤ 0.05 ppm in apples, ≤ 0.09 ppm in apple juice, ≤ 0.06 ppm in grapes, and ≤ 0.9 ppm in grape juice. In addition, triazole itself (IN-H9933; 1H-1,2,4-triazole) was found to occurr at ≤0.14 ppm in milk, ≤0.03 ppm in ruminant muscle, and tentatively, at ≤0.004 ppm in poultry tissues and eggs. It was thus requested that the HED Metabolism Commitee address the issue of whether triazole-derived residues are of toxicological concern (Issue 5).

Issue 5 was addressed in a 8/21/90 memorandum from from W.J. Hazel to S. Lewis and R. Engler. Concerning Issue 5, consensus was reached that triazole-containing compounds derived from DPX-H6573 (Nustar[R]) are not of concern due to their natural occurrence and/or their low toxicity and/or their indistinguishability from background.

Likewise, in a 5/8/87 memorandum to L. Rossi, A. Katz noted that "TOX Branch has determined that there is at this time no compelling toxicological basis for requiring additional metabolism studies or analytical methodologies specific for the triazole moieties contributed by propiconazole." Levels of triazole-containing metabolites, from propiconazole were not indicated, however.

The issue of triazole-containing compounds arises again in the case of tebuconazole. As shown in Table 1, the levels of triazolylalanine that could be present jointly with tolerance levels of folicur in wheat seeds and barley grain are 6.66 and 40.0 ppm, respectively. These values are 7.4 and 44.4 times higher than the possible 0.9 ppm level for triazolylalanine in grape juice, and even higher for the other commodities listed above.

Table 1. Levels of tebuconazole and selected metabolites in various RACs.

Compound	Percent of total radioactivity	ppm possible at tolerance for RAC[1]	Reference
		----Wheat Seeds-----	
Folicur	6.0	0.5 (By defn.)	Otakie (Undated)
Triazolylalanine	80.0	6.66	
Triazolylacetic ac.	13.0	1.08	
		-----Barley Grain----	
Folicur	-	3.0 (By defn.)	Otakie (Undated)
Triazolylalanine	-	40.0	
Triazolylacetic ac.	-	6.5	

1. Triazolyalanine may occur at the following lower levels in other RACs: apples (≤ 0.05 ppm), apple juice (≤0.9 ppm), grapes (≤ 0.06 ppm), and in grape juice (≤ 0.09 ppm). It was not indicated if these values are the possible values at the tolerance for folicur.

To assess the toxicological significance of the observed levels of triazolyalanine (TA) in wheat grain and barley seeds a tentative, preliminary, RfD value was calculated based on studies selected from the triazolylalanine data base of submitted studies (Caswell No. 862B). Triazolylacetic acid was not included in the calculation but would not be anticipated to contribute materially to any toxicological concern. The selected studies are summarized in Table 2.

Table 2 shows two subchronic studies, 90-day rat and 13-week dog, with respective NOEL values of 5000 and 8000 ppm. The 13-week dog study is selected for calculation of the tentative RfD because it is the only one of the two studies classified as minimum. Due to the existence of only two subchronic studies (90-day rat and 13-week dog) and the absence of chronic studies an uncertainty factor (UF) of at least 1000 must be considered. Because one of the studies (rat) is

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supplementary this UF could range up to 3000. Thus, the tentative RfD for triazolylalanine will be calculated using a NOEL of 8000 ppm from the subchronic dog study (equiv. to 200 mg/kg/day, assuming 1 ppm = 0.025 mg/kg/day for a 10 kg. dog on dry lab chow; FDA, 1975). The NOEL value of ≥ 400 mg/kg/day reported for the 28-day gavage study in rats summarized in Table 2. is consistent with the selected NOEL of 200 mg/kg/day, and suggests that the actual NOEL may be higher than 200 mg/kg/day.

Thus, for a NOEL of 200 mg/kg/day, a tentative RfD for triazolylalanine (TA) may be estimated to be 0.2 mg/kg/day if a UF of 1000 is chosen and 0.07 mg/kg/day if a conservative UF of 3000 is chosen.

Table 2. Selected studies for tentative estimation of the RfD for triazolylalanine (From Caswell File No. 862B; see attached one-liners).

Study	Species	Dosing/Effects	Classification
90-Day feeding. Bayer AG Inst. for Tox.	Rat	0, 1250, 5000, 20000 ppm. NOEL = 5000 ppm LEL = 20000 ppm; body wt. reduction.	Supplementary
13-Week feeding. Bayer AG Inst. for Tox.	Dog	0, 3200, 8000, 20000 ppm. NOEL = 8000 ppm LEL = 20000 ppm; body wt. reduction	Minimum
28-Day oral gavage. Bayer AG Inst. for Tox.	Rat	0, 25, 100, 400 mg/kg. NOEL ≥ 400 mg/kg	Supplementary
14-Day feeding. Bayer AG Inst. for Tox.	Rat	0, 3000, 10000 ppm in drinking water. No toxic signs. NOEL not stated.	Supplementary
Two Generation Reproduction. Cent. Tox. Lab. ICI.	Rat	0, 500, 2000, 10000 ppm. Maternal NOEL ≥ 10000 ppm. Reproductive NOEL = 2000 ppm. LEL = 10000 ppm (reduced pup weights).	Supplementary

Referring to Table 1, for humans 6.66 ppm triazolylalanine in the diet would correspond to 0.08 mg TA/kg/day in a diet (assuming 1 ppm = 0.025 mg/kg/day for a 60 kg man; FDA, 1975) consisting of 50% wheat seeds. This value is below or at the estimated RfD for TA.

Likewise, referring to Table 1, for humans 40 ppm triazolylalanine in the diet

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would correspond to 1 mg TA/kg/day (assuming 1 ppm = 0.025 mg/kg/day for a 60 kg man; FDA, 1975) in a diet consisting of 100% barley seeds. This value would drop to 0.1 mg TA/kg/day in the more likely event that the diet consists of 10% barley seeds. This value is at or below the estimated RfDs for TA.

We conclude that the levels of triazolyl metabolites in the cases of wheat seeds and barley grain do not appear to present any toxicological concern at this time. It is noted that triazole is a tebuconazole metabolite in rats (EPA MRID Nos. 409959-11 and 409959-12); while triazolylalanine, triazolylacetic acid or triazolylactic acid are not listed among the identified metabolites of tebuconazole in rats, a considerable portion of the metabolites remain to be identified.

References

Otakie G.F. Undated. Memorandum. PP#9F3724/9F03818 and FAP#9H5575. Permanent Tolerance Petitions - New Chemical - Tebuconazole. Tolerance Petition Section II. Chemistry Branch I - Tolerance Support. Health Effects Division (H7509C). U.S.E.P.A.

FDA. 1975. Food and Drug Administration. Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. Third Printing. Published 1959 by the Association of Food and Drug Officials of the United States.

Attachment

HED one-liners for triazolylalanine (Caswell No. 862B).

cc: Gary F. Otakie (HED)
E. Brinson Conerly (EFED)

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

TOXCHEM NO. 862B- Triazolyl alanine FILE LAST PRINTED: 03/25/91

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-3(a) Developmental Toxicity Study Species: rat ICI Central Tox. Lab. CTL/P/875; 10/13/83	Triazolyl alanine 94.8%	252132	Levels tested by gavage in Alderly Park ALpk/AP strain from day 7 to day 16 of gestation-0, 100, 300 and 1000 mg/kg. Teratogenic NOEL > 1000 mg/kg (HDT). Fetotoxic NOEL = 100 mg/kg Fetotoxic LEL = 300 mg/kg (nonossification of odontoid process Maternal NOEL > 1000 mg/kg(HDT)		Minimum 004766 005155
83-4 Reproduction-1 generation Species: rat ICI Central Tox. Lab. RR0230/F0; 9/19/83	Triazolyl alanine 48% batch 1; batch 2 unspec. purity.	252132	Pilot Study. Dose levels: 0, 150, 625, 2500, 10,000 ppm. No effects at 10,000 ppm.		Supplementary 004766
83-4 Reproduction-2 generation Species: rat ICI Central Tox. Lab. RR0255/F0; 6/21/83	Triazolyl alanine 97.8%	252132	Interim report. Dose levels: 0, 500, 2000, 10,000 ppm. No effects noted in the first 3 weeks of the study.		Reserved 004766
83-4 Reproduction-2 generation Species: rat ICI CTL/P/1168; 8/19/86	Triazole alanine, purity 97.8%; batch TLB 1207/ 018-024 (Y01210/003/005	265205 265206 265207 413268-03	Dietary levels: 0, 500, 2000, 10,000 ppm in Alpk:AP strain. Maternal NOEL> 10,000 ppm (HDT). Developmental NOEL = 2000 ppm; LEL = 10,000 ppm (reduced pup weights (High dose) F1B & F2A.) Additional information did not allow upgrading. Study must be repeated.		Supplementary 005841 008292
Feeding-14 day Species: rat Bayer AG Instit. Fur Tox. Germ 82662; 10/25/82	THS 2212 (Triazoyl alanine 100% purity)	252132	Range Finding. Dose levels: 0, 3000, 10,000 ppm in drinking water. No mortalities or clinical signs of toxicity in males.		Supplementary 004766
Feeding- 28 day oral Species: rat Bayer AG Instit. Fur Tox. Germ T6011644; 1/24/83	THS 2212 (Triazolyl alanine "analytically pure")	252132	Dose levels: by gavage in Wistar BOR:WISW SPF/Cpb strain, 0, 25, 100, 400 mg/kg. No mortalities or clinical signs of toxicity. Some changes in hematology, clinical chemistry, organ weights. NOEL > 400 mg/kg(HDT)		Supplementary 004766
82-1(a) Feeding-3 month Species: rat Bayer AG Instit. Fur Tox. Germ T9015049; 2/24/84	Triazolyl alanine, batch TLB-1207	252425 258416	Levels tested in BOR:WISW (SPF-CPB) strain- 0, 1250, 5000, & 20,000 ppm NOEL = 5,000 ppm. LEL = 20,000 ppm (slight reduction in male body weight gain)		Supplementary 004101 004276 Minimum 005094 005352 005841

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82-1(b) Feeding-13 week Species: dog Bayer AG Instit. Fur Tox. Germ T-7-015-713; 4/28/86	THS 2212 97.5% a.i., batch TLB 1207	256058	Levels tested beagle dogs - 0, 3200, 8000, and 20,000 ppm. NOEL = 8000 ppm. LEL = 20,000 ppm (reduced body wt. gain)		Supplementary 004469 Minimum 005841
84-2(a) Mutagenic-Ames Species: salmonella Bayer AG Instit. Fur Tox. Germ T-1006005; 1/5/83	THS 2212, batch E238099	256058	Negative for mutagenic effects up to 12,500 ug/plate with and without (S-9) activation.		Acceptable 004562 Acceptable 004469
84-2(a) Mutagenic-Ames Species: salmonella Ciba-Geigy Ltd. 860187; 7/11/86	Triazole alanine; CGA 131013 Tech, 97.4% a.i.	265204	Strains tested: TA98, TA100, TA102, TA1535 and TA1537. Negative with & without activation.		Acceptable 005841
84-2(b) Mutagenic-in vitro transform. Species: BHK cells Huntingdon Res. Centre, Eng. ICI394A81153; 5/15/81	Triazolyl alanine (R152056)	072208 252132	Levels tested: 0.5, 1, 2, 4, 8 mg/ml without S9; and 1,2,4,8,16 mg/ml with S9. Positive, with and without activation		Acceptable 004562 Acceptable 004766
84-2(b) Mutagenic-DNA damage/repair Species: E. coli Bayer AG Instit. Fur Tox. Germ 82738; 1/15/83	THS 2212 (Triazolyl alanine) purity not specified	252132	Dose levels: 62.5, 125, 250, 500, 1000 ug/plate. Nonactivated-no DNA damage. S9 activated-inadequate assay.		Accep. (w S9) 004766 Unacc (no S9) 004766
84-2(b) Mutagenic-in vitro transform. Species: mice BALB/3T3 cells Ciba-Geigy Ltd. 840324; 9/12/84	Triazolyl alanine (purity not specified)	257997	Negative with metabolic activation; inconclusive without activation. Concentrations up to 1000 ug/ml. Repeat test requested.		Unacceptable 005155 005352
84-2(b) Mutagenic-DNA repair test Species: rat hepatocytes Ciba-Geigy Ltd. 860184; 7/11/86	Triazole alanine; CGA 131013 Tech 97.4% a.i.	265204	Negative.		Acceptable 005841

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84-4 Mutagenic-micronucleus assay Species: mice ICI Central Tox. Lab. TOM4; 9/14/82	R152056 (Triazolyl alanine) purity not spec batch 02199/49	252132 072208	Dose levels: 2500, 5000 mg/kg. No toxicity, chromosomal damage, or erythropoietic effects; however, animals were dosed only once and only one sex tested.		Acceptable 004562 Unacceptable 004766
84-4 Mutagenic-micronucleus assay Species: mice Bayer AG Instit. Fur Tox. Germ T4011615; 8/9/82	THS 2212 (Traizolyl alanine) puirty not spec. ("analytically pure")	252132	Weak positive response for 8000 mg/ kg at 24-hr. Study unacceptable due to lack of critical data on positive and negative controls.		Acceptable 004562 Unacceptable 004766 005352
84-4 Mutagenic-point mutation Species: salmonella Bayer AG Instit. Fur Tox. Germ 11388; 1/5/83	THS 2212 (triazolyl alanine purity unspec.)	252132	Dose levels of 20, 100, 500, 2500, 12,500 ug/plate did not induce re- typhimurium assay. Non-activated assay not evaluated due to lack of positive control.		Acceptable 004562 004469 Unacc (+ S9) 004766 Acceptable 004766
84-4 Mutagenic-point mutation Species: Ch. Hamster V9 cells Ciba-Geigy Corp. Inc. 860258; 7/11/86	Triazolyl alanine; CGA 131013 Tech 97.4% a.i.	265204 413268-01	Positive with metabolic activation; negative without activation.		Acceptable 005841 008282
84-4 Mutagenic-micronucleus assay Species: Ch. Ham. bone marrow Ciba-Geigy Ltd. 860185; 7/11/86	Triazole alanine; CGA 131013 Tech, 97.4% a.i.	265204 413268-02	Incomplete. Additional information provided. Study upgraded to Acceptable		Unacceptable 005841 Acceptable 008292
84-4 Mutagenicity-Protein syn. Species: microorganisms Ciba-Geigy Ltd. ABR-86057; 9/19/86	Triazole alanine (purity not spec.)	265208	Inconclusive. Test species: E. coli; S. cerevisiae; A. flavus. Protein synthesis inhibitory potential.		Unacceptable 005841
85-1 Pharmacokinetics Species: rat Bayer AG Instit. Fur Tox. Germ 11583; 2/24/83	C14-Triazolyl alanine, radiochemical purity 99%	252132	Dose levels: 5 mg/kg (metabolism); 10 mg/kg (whole-body autoradiography) Rapid absorption and excretion in male rats: 95 percent of administered dose was absorbed and 94.5 percent of the radioactivity measured in urine within 48 hours. None of the metabs were identified		Acceptable 004766

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85-1 Metabolism Species: rat Ciba-Geigy Ltd. CGA 131013; 3/2/83	C14-Triazolyl alanine, radiochemical purity > 99%	252132	Dose level - approx. 50 mg/kg. Almost entirely excreted within 24 hrs; primary route-urine,secondary route-feces. Metabolites: N-acetyl, and unaltered triazolylalanine in urine.		Minimum 004766
85-1 Metabolism Species: rat Ciba-Geigy Ltd. 131013; 10/20/83	C14-D,L-Triazolyl alanine purity > 99%	252132	In 24 hours, 69-86% of the dose was excreted unchanged in the urine,8-19% was excreted as the acetyl derivative in the urine. About 3% of the dose was excreted in the urine as unknown metabolites. The total fecal radioactivity accounted for 3% of the total dose. The fecal metabolites were similar to those found in the urine except for one that could not be identified.		Acceptable 004766
85-1 Metabolism Species: rat Ciba-Geigy Corp. Inc. ABR-8602-3; 3/24/86	C14-Triazolyl alanine purity > 99%	265209	Rapid absorption and elimination. 85% excretion in urine. Single oral dose: 0.56,54.4 and 993.7 mg/kg.		Minimum 005841
85-1 Metabolism Species: rat Ciba-Geigy Ltd. ABR86041; 6/3/86	C14-Triazole alanine purity > 99%	265209	Major urinary metabolites identified as unchanged triazole alanine and N-acetyl triazole alanine.		Minimum 005841
Metabolites			Caswell # 862AA. #323 EE (CGA-64250)		
81-1 Acute oral LD50 Species: dog Inst. of Tox.; Fed Rep Germany 82663; 10/14/82	Triazolyl alanine 99%	252132	Only 2 dogs used on study; both vomited a portion of the test material within 4 hours of dosing.		Invalid 004766
81-1 Acute oral LD50 Species: rat Central Toxicology Lab CTL/P/600; 1/18/81	Triazolyl alnine	252132	LD50 > 2000 mg/kg (only level tested). No mortalities at 2000 mg/kg dose tested.	3	Supplementary 004766

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1-1 cute oral LD50 pecies: rat ayer AG Instit. Fur Tox. Germ 2661; 10/19/82	Triazolyl alanine	252132	LD50 > 5000 mg/kg. Fasted male rats showed increased urinary output the day after dosing.	4	Minimum 004766
1-1 cute oral LD50 pecies: mice ayer AG Instit. Fur Tox. Germ 2661; 10/19/82	THS 2212	252132	LD50 > 5000 mg/kg. No toxic signs.	4	Minimum 004766
cute intraperitoneal LD50 pecies: rat ayer AG Instit. Fur Tox. Germ 2661; 10/19/82	Triazolyl alanine	252132	LD50 > 5000 mg/kg. At 5000 mg/kg, reversible CNS effects (spastic gait, lethargy, etc.) were observed within 1 hour of dosing. The lethal dose exceeds 5000 mg/kg.		Minimum 004766

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