2-27-89

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

February 27, 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Maneb (014505) Time Extension Request for Plant and Animal Metabolism studies required by the Comprehensive Data Call In Notice of 4/1/87
Progress Reports for Plant and Animal Metabolism Studies [No MRID No., RCB No. 4229]

FROM: Susan V. Hummel, Chemist
Special Registration Section II
Dietary Exposure Branch
Health Effects Division (TS-769C)

Susan V. Hummel

THRU: Richard D. Schmitt, Acting Chief
Dietary Exposure Branch
Health Effects Division (TS-769C)

Richard D. Schmitt

TO: Geri Werdig/Frank Rubis, PM#50
Data Call In Staff
Special Review and Reregistration Division (TS-767C)

Pennwalt Corporation has submitted a request for time extensions for the Plant and Animal Metabolism Studies and residue studies on apples, apple processed products, and almonds, required by the Maneb Comprehensive Data Call In Notice of 4/1/87. The due date for these studies was 10/1/88. Progress reports for both the Plant and Animal Metabolism studies currently in progress were included, along with protocols for apple and almond studies. The Pennwalt letter was dated 7/28/88. The progress reports were dated as late as 7/88 and submitted to EPA on 7/29/88. The progress reports for metabolism studies are identical to those reviewed earlier for metiram (S. Hummel, 2/6/89.

Pennwalt Corporation and the other Maneb registrants had requested a waiver from the requirement of additional metabolism studies for maneb in their 90 day response to the Data Call In Notice (Pennwalt letter of 7/6/87). The registrant stated that studies previously submitted by the registrants completely characterized the metabolism of maneb, and that the metabolism involved incorporation into natural products. RCB recommended for the denial of this waiver request in their memo of 8/7/87 (W. Hazel, RCB No. 2532). The registrants requested a time extension for residue data on almonds in their 90 day response. RCB recommended that the time extension not be granted (W. Hazel, 8/7/87, RCB no. 2532). Pennwalt later requested a time

extension for apples and apple processed fractions until 12/1/88, because Griffin (the sole maneb registrant with a registration for apples) had decided not to support apples (Pennwalt letter of 12/2/87 and subsequent telephone call to V. Bael). Pennwalt states that the letter from EPA denying the metabolism waiver request was dated 2/25/88. The Agency's letter of 2/25/88 also denied time extensions for apple and almond residue data.

Regarding metabolism, Pennwalt states that they are convinced that the EBDC's share a common metabolic pathway of degradation and incorporation into natural products; and that the metiram and maneb registrants are jointly sponsoring laboratory efforts to develop analytical methodologies to characterize EBDC metabolites and characterize the ^{14}C incorporation into natural products such as cellulose, protein, starch, amino acids, and simple carbohydrates. Xenobiotic Laboratories will be conducting studies for animal metabolism, and Hazleton Laboratories for plant metabolism.

Pennwalt states that the metabolism studies have been divided into three phases: (1) Analytical characterization of EBDC metabolites/conjugates utilizing tissues remaining from previous EBDC metabolism studies and freshly dosed tissues for method development; (2) In-life dosing of plants and animals; (3) Analysis of tissues from Phase II using methods developed in Phase I.

Synthesis of ^{14}C Maneb

Pennwalt contracted with Sigma Chemical on 3/9/89 (sic) to provide 200 mCi of ^{14}C maneb by 5/1/88. Delivery was delayed until 7/8/88. The elemental analysis of the unlabeled material was satisfactory. However, the maneb content of the ^{14}C maneb, based on CS_2 evolution was only 21%, instead of 52%. Pennwalt suggests that maneb is extremely unstable.

Progress - Animal Metabolism

Efforts to initiate animal metabolism studies appeared to have begun in late February, 1988. Phase II is reportedly on hold because of difficulties in the synthesis of ^{14}C maneb.

Xenobiotic Laboratories have been using tissues from a goat recently dosed with ^{14}C metiram and remaining tissues from the maneb goat and poultry metabolism studies. They have attempted solvent fractionation using the Blight-Dyer multiphasic solvent extraction procedure, yielding non-polar, polar, and insoluble fractions. Two-dimensional TLC has been used to separate known and suspected organosoluble metabolites. Some results were included in a more detailed progress report.

Milk and egg samples from newly treated goats and from the earlier animal metabolism studies were fractionated into lipids, ethyl acetate solution, methanol solution, lactose solution, and protein precipitate. Goat muscle, liver, kidney, and fat samples were fractionated into methanol/water, methylene chloride, and post extraction solids (PES) fractions. The total radioactivity in each fraction was reported. PES fractions from egg, muscle, liver, kidney, and fat were digested with protease enzyme and fractionated further. The report stated that most of the PES fraction appeared to be proteins. However, no justification for this statement was made. A number of TLC solvent systems were investigated. Some of the fractions were analyzed by 2D TLC. Some compounds were labeled in the 2D TLC's. Some tentative identifications were reported. No confirmatory analyses were reported. One method for analyzing amino acids was investigated. The amino acids will be derivatized with phenylthiocyanate (PTH) and analyzed by HPLC.

Phase II (in-life dosing) is scheduled to start on 12/1/88 for goats and 1/1/89 for poultry because the laboratory must handle studies serially (after the metiram studies); and due to difficulties in the synthesis of ^{14}C maneb.

Progress - Plant Metabolism

Efforts to initiate plant metabolism studies appeared to have started in April-May, 1988. These studies are now on hold because of difficulties in the synthesis of ^{14}C maneb.

Hazleton is currently developing an analytical method to strip surface residues of EBDC parent from apples, to prevent the presence of EBDC parent from degrading during subsequent extraction and analysis, thus confounding the metabolite picture. After stripping of surface residues, the Blight-Dyer procedure will be used to fractionate tissue ^{14}C. the peel and flesh of apples an potatoes will be analyzed separately. Hazleton is also developing methodologies for characterizing the incorporation of ^{14}C into plant polymeric materials (lignin, cellulose, starch, etc.) using tissues from the earlier maneb plant metabolism studies. The organic extract of tomatoes has been analyzed by 2D-TLC. The methanol/water fraction (35% TRR) will be analyzed by ion-exchange chromatography. The solid portion (13% TRR) will be treated with enzymes and the liberated activity analyzed.

Hazleton has worked on amino acid analysis by HPLC using an HP-Photodiode Array detector. Two HPLC systems (Bondapak C18 using tetrahydrofuran in water, and Waters Radial Pack C18 with phosphate buffer) were investigated for the separation of ETU, EU, EDA, acetylethylene diamine and N-formyl glycine. ETU was partially separated, but the other analytes were eluted at the unretained volume of the column. Solvent systems for two

dimensional TLC were investigated for the analytes listed above and amino acids.

The degradation of ETU to EDA was investigated. EDA was analyzed by derivatization with m-toluoyl chloride. The parent compounds (maneb and metiram) rapidly break down when washed off the surface with EDTA Solution, therefore, analysis must be rapid (within 15-30 minutes). Several solid phase extraction systems were investigated.

Phase II is on hold because of difficulty in the synthesis of ^{14}C maneb. Pennwalt proposes to schedule treatment of lettuce, potatoes, and tomatoes in a greenhouse in December, 1989(?) with sampling of the mature crops in March, 1989(?). No mention was made of scheduling for apple metabolism studies.

DEB Comments on Metabolism Progress Reports

We note the presence of HPLC chromatograms from fraction collecting. We question whether HPLC with fraction collecting has sufficient resolution to adequately separate the radioactive components of the residue (including natural products). Very little mention was made of plans for confirmatory analyses such as mass spectrometry. Confirmatory analyses are required.

Rationale for time extensions for Metabolism Studies

BASF states that they expect the characterization of ^{14}C residue incorporated into biopolymers to require difficult, extensive, time-consuming laboratory analysis. Dosing is underway or scheduled. The plant treatment schedule is dictated by the growing season. Plants cannot be harvested before fall.

DEB Comments on Time Extensions for Metabolism Studies

The registrant did not initiate the plant and animal metabolism studies until the spring of 1988. The studies could have been completed by the due date if they had been initiated shortly after the Comprehensive Data Call In Notice of 4/1/87 was issued. The plant treatment schedule for potatoes is not dictated by the growing season since potatoes can be grown in a greenhouse. (The growing season for apples is dictated by the growing season, but the studies could have been initiated in 1987.) Animal studies are not tied to a growing season. Laboratory scheduling problems are not scientifically justifiable reasons for failure to initiate a study.

Failure to complete the required plant and animal metabolism studies by the due date of 10/1/88 means that residue data for any additional metabolites other than parent compound and ETU will not be initiated for at least another growing season.

Feeding studies will be delayed. Therefore residue data and feeding studies for other compounds of toxicological concern will not be available in a timely manner. These data could impact on the Special Review for EBDC's.

The analyses required for the identification of biopolymers (natural products) are no more difficult than those required for other pesticides which are incorporated into natural products.

Protocols for Residue Studies

Almond. Protocol 36-88 (Revised 3/4/88). Almonds will be treated four times at 6.4 lb ai/A with Maneb + Zinc F4 in four locations in CA (2 ground, 2 aerial)). The applications will be time at the popcorn stage, full bloom, petal fall, and 5 weeks after petal fall. Four replicate plots will be used in each location. Separate samples of whole almonds will be collected from each replicate plot. The spray volume will be 25-100 gal/A for ground and 10-20 gal/A for aerial applications.

Apples. Two trials will be conducted in NY, using ground application and an unspecified number of replicates. Ten applications of Maneb + Zinc F4 at 22.5 lb ai/A will be made in 25-100 gal/A. Applications will be made at 7-10 day intervals from first cover until 15 days before harvest. Residue samples will be frozen immediately after harvest. Samples for processing will be cooled and shipped immediately to the processing facility. Processing protocols were not included.

Rationale for Time Extensions

A time extension until 12/1/88 for apple and almond residue studies and apple processing studies is requested because the drought in the summer of 1988 has delayed harvest until 9/1/88.

DEB Comment

The same time extension requests were denied in the Agency letter of 2/25/88. Apple residue studies were due 3/1/88 for the Storage Stability Data Call In Notice. Apple residue studies from several states were submitted, but the apples were stored greater than 6 months. Storage Stability studies indicated that ETU was stable for less than one month. Therefore, the apple residue studies submitted in response to the Storage Stability Data Call In Notice of 3/31/87 cannot be used to satisfy the requirements of the 4/1/87 Comprehensive DCI.

We note that only one state was included in the apple protocol. Full geographic representation is needed for apples. We also note that the proposed application rate is abnormally high. Perhaps this is a typographical error, or an exaggerated rate in order to conduct processing studies.

Regarding the effect of the drought, we consulted with N. Pelletier, BEAD. Dr. Pelletier states that the drought would have little effect on the harvest dates. Additionally, we note that the requested extended due date has past, and no data have been received. The due date for the apple processing study is 4/1/89, so no time extension is needed for this study.

Since residues of ETU are not stable in frozen storage, all residue samples (and particularly apples) should be analyzed as soon as possible after harvest. If the residue samples from harvest in August were analyzed within 2 weeks of harvest, the results could be reported to EPA by 10/1/88, although we recognize that this would be a tight schedule.

Failure to receive the full data required by the Comprehensive Data Call In Notice by the stated due dates could delay the next Special Review document on EBDC's.

Conclusions/Recommendations

There are no scientifically justifiable reasons for failure to initiate the metabolism studies. However, the granting of time extensions is not a scientific decision, but rather an administrative decision of the Special Review and Reregistration Division. The requested revised due date for metabolism studies of June 1, 1989 is reasonable based on harvest in the Fall of 1988.

Since the drought will not affect the harvest date, the drought is not a scientifically justifiable reason to extend the due dates for apple and almond residue and processing studies. However, the granting of time extensions is not a scientific decision, but rather an administrative decision of the Special Review and Reregistration Division. The registrant should note that the apple processing studies were due 24 months after the DCI was issued, 4/1/89, so no extension is needed for apple processing studies.

Our comments on the progress reports should be sent to the registrant so that they may ensure that these comments are addressed in their final report. If this time extension is granted, we recommend that regular detailed progress reports be required.

cc: R.F., circu, S. Hummel, Metiram S.F., Metiram S.R.F. (Hummel), Metiram R.S.F. (Edwards), V. Bael (SRB/RD), S. Lewis (PM#21), PMSD/ISB
RDI:FBS:02/27/89:EZ:02/27/89
TS-769:DEB:RM810:CM#2:SVH:svh:02/27/89
File:MANB189.EXT

8/18/88 mrd

REGISTRATION DIVISION DATA REVIEW RECORD

Confidential Business Information — Does Not Contain National Security Information (E.O. 12065)

8/16/88

1. CHEMICAL NAME MANEB

48165 4Q

2. IDENTIFYING NUMBER	3. ACTION CODE	4. ACCESSION NUMBER	TO BE COMPLETED BY PM
014505	400		5. RECORD NUMBER 229,896
			6. REFERENCE NUMBER
	RCB # 4229		7. DATE RECEIVED (EPA) 8/8/88
			8. STATUTORY DUE DATE (12/6)
			9. PRODUCT MANAGER (PM) Werdig/Rubis
			10. PM TEAM NUMBER 50

14. CHECK IF APPLICABLE

- ☐ Public Health/Quarantine
- ☐ Minor Use
- ☐ Substitute Chemical
- ☐ Part of IPM
- ☐ Seasonal Concern
- ☐ Review Requires Less Than 4 Hours

AH 8-15-88

12-5-88

TO BE COMPLETED BY PCB

11. DATE SENT TO HED/TSS [redacted]

12. PRIORITY NUMBER 50

13. PROJECTED RETURN DATE [redacted]

15. INSTRUCTIONS TO REVIEWER

A. HED
- ☐ Total Assessment - 3(c)(5)
- ☐ Incremental Risk Assessment - 3(c)(7) and/or E.L. Johnson memo of May 12, 1977.

B. SPRD (Send Copy of Form to SPRD PM)
- ☐ Chemical Undergoing Active RPAR Review
- ☐ Chemical Undergoing Active Registration Standards Review

C. ☐ BFSD

D. ☐ TSS/RD

E. ☐ Other X

F. INSTRUCTIONS

Request for extension of residue studies, plant/animal metabolism studies.

PROTOCOLS ALSO ATTACHED.

Pennwalt - Maneb Comprehensive DCI dated 4/1/87

16. RELATED ACTIONS

17. 3(c)(1)(D)

☐ Use Any or All Available Information ☐ Use Only Attached Data
☐ Use Only the Attached Data for Formulation and Any or All Available Information on the Technical or Manufacturing Chemical.

18. REVIEWS SENT TO

☐ TB ☐ EEB ☐ EF ☐ PL
☐ RCB ☐ EFB ☐ CH ☐ BFSD

19.	To	TYPE OF REVIEW	NUMBER OF ACTIONS: Registration	Petition	EUP	SLN	Sec. 18	Inert	MNR. USE	Other
HED		TOXICOLOGY								
HED		ECOLOGICAL EFFECTS								
HED	X	RESIDUE CHEMISTRY								
HED	X	ENVIRONMENTAL DATE								
RD/TSS		CHEMISTRY								
RD/TSS		EFFICACY								
RD/TSS		PRECAUTIONARY LABELING								
BFSD		ECONOMIC ANALYSIS		•						

20. ☐ Label Submitted with Application Attached	21. ☐ Confidential Statement of Formula	22. ☐ Representative Labels Showing Accepted Uses Attached	23. Date Returned to RD (to be completed by HED)	24. Include an Original and 4 (four) Copies of This Completed Form for Each Branch Checked for Review