DP Barcode : D169687, D170813
PC Code No. : 060101
EFGWB Out : DEC 30 1992

TO: Barbara Briscoe
Product Manager PM 51
Special Review and Reregistration Division (H7508W)

FROM: Akiva D. Abramovitch, Ph.D., Head
Environmental Chemistry Review Section #3
Environmental Fate & Ground Water Branch/EFED (H7507C)

B. Conrad-Parks for ADA

THRU: Henry Jacoby, Chief
Environmental Fate & Ground Water Branch/EFED (H7507C)

Attached, please find the EFGWB review of...

Reg./File # :43410-24

Chemical Name :2-(thiazol-4-yl)benzimidazole

Common Name :Thiabendazole

Product Name :Arbotect, Mertect, TBZ, Tecto, Thibenzole

Company Name :Merck and Co., Inc.

Purpose :Waiver requests for 162-3,4, 164-2, and 165-3. Also, upgrading of 161-1, 161-2, and 163-1 studies.

Type Product :Fungicide Action Code: 603,606 EFGWB #(s): 92-0047, -0183 Review Time: 6.0 days

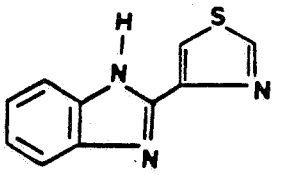
EFGWB Guideline/MRID/Status Summary Table: The review in this package contains...

161-1	MRID 41265301	Y	162-4	Waiver request	Y	164-4			166-1		
161-2	MRID 41265101	S	163-1	MRID 41170102	P	164-5			166-2		
161-3			163-2			165-1	MRID 42367801 (will be reviewed later)		166-3		
161-4			163-3			165-2			167-1		
162-1			164-1			165-3	Waiver request	Y	167-2		
162-2			164-2	Waiver request	Y	165-4	MRID 42022701 (not reviewed)		201-1		
162-3	Waiver request	Y	164-3			165-5			202-1		

Y = Acceptable (Study satisfied the Guideline)/Concur P = Partial (Study partially satisfied the Guideline, but additional information is still needed)
S = Supplemental (Study provided useful information, but Guideline was not satisfied) N = Unacceptable (Study was rejected)/Non-Concur

1. CHEMICAL:

Chemical Name: 2-(thiazol-4-yl)benzimidazole
CAS No.: 148-79-8
Common Name: Thiabendazole
Trade Name: Arbotect, Mertect, TBZ, Tecto, Thibenzole
Chemical Structure:



Molecular Formula: $C_{10}H_7N_3S$
Physical/Chemical Properties of Active Ingredient:

Molecular Weight:	201.2
Physical state:	Powder
Vapor pressure:	4×10^{-9}
Solubility (25 °C):	10 g/L in water at pH 2, <50 mg/L in water at pH 5-12, >50 g/L at pH 12, 4.2 g/L acetone, 7.9 g/L ethanol, 2.1 g/L ethyl acetate. At "room temperature," 230 mg/L benzene, 80 mg/L chloroform, 39 g/L dimethylformamide, 80 g/L dimethyl sulfoxide, 9.3 g/L methanol.
Formulations:	Soluble concentrate, flowable concentrate

2. TEST MATERIAL: PAIRA

3. STUDY/ACTION TYPE:

Waiver request for 162-3,4, 164-2, and 165-3 data requirements. Also, upgrading of 161-1, 161-2, and 163-1 studies.

4. STUDY IDENTIFICATION:

Hirsch, M.P. 1991. Bioconcentration of Thiabendazole (2-(4-thiazolyl)-1H-Benzimidazole) in Bluegill Sunfish, Lepomis macrochirus. Unpublished study performed by Eastman Kodak Company, Rochester, NY, and submitted by Merck and Co., Inc, Three Bridges, NJ. (MRID 42022701).

5. REVIEWED BY:

James A. Breithaupt
Agronomist, Review Section #3
OPP/EFED/EFGWB

Signature: James Breithaupt
Date: 12/9/92

6. APPROVED BY:

Akiva Abramovitch, Ph.D.
Chief, Review Section #3
OPP/EFED/EFGWB

Signature: Brian Conaf-Parks for ADA
Date: 12/10/92

7. CONCLUSIONS:

Hydrolysis (161-1, MRID 41265301, Acceptable)

The hydrolysis study is now acceptable and satisfies the 161-1 data requirement. The study was considered unacceptable on 2/20/90 since a good estimate of the initial concentration was not provided and one-dimensional TLC methodology was the only employed analytical technique. However, the registrant submitted an aqueous photolysis study (MRID 41265101, 161-2, reviewed on 2/20/90) that used adequate HPLC methodology. HPLC was effective for differentiating parent compound from degradates in the irradiated samples, and did not detect any degradates in the dark control samples. Therefore, it is apparent that thiabendazole is stable to hydrolysis at pH 5, 7, and 9.

Aqueous photolysis (161-2, MRID 41265101, Supplemental Data)

The aqueous photolysis study that was reviewed on 2/20/90 provides only supplemental data since the parent half-life and rate of degradate formation and decline could not be accurately established and degradate concentrations widely fluctuated in the 14-30 day sampling intervals. The registrant (this submission) argued that the study should be upgraded because the TLC method was adequate for resolving the parent compound from the photoproducts prior to 14 days. However, there was degradation at 14 days with 2 significant photoproducts, and HPLC was not used to analyze the 1, 3, and 7 day samples. Therefore, the extent or existence of degradation before 14 days could not be determined, and repeating the study is necessary.

Thiabendazole degraded with a calculated half-life of 10 days. Benzimidazole appears to be the final photolytic degradate in water. The major intermediate degradates appear to be bendizimazole-2-carboxamide which degrades to benzimidazole-2-carboxylic acid, and consequently to benzimidazole.

Leaching-adsorption-desorption (163-1, MRID 41170102, Acceptable)

The batch equilibrium (adsorption-desorption) study is now acceptable and satisfies the unaged portion of the 163-1 data requirement. The study was previously rejected on 2/20/90 because the soils (series not specified) were sterilized with sodium azide. The registrant (this submission) argued that the sodium azide could affect the CEC of the soil, but not the organic matter, and therefore the adsorption would be unaffected. The current EFGWB reviewer calculated the extent of saturation of the soil CEC by the sodium azide and found that the CEC's of the sandy, sandy loam, and silt loam soils were exceeded. However, the Freundlich adsorption and desorption values indicate that the compound is tightly adsorbed to soil with the exception of sandy soil with very low organic carbon.

The Freundlich K_{ads} values were 2.8, 16, 22, and 269 in sandy, sandy loam, silt loam, and clay soils, respectively. Freundlich K_{des} values were 8, 19.6, 16, and 220, respectively. K_{oc} values ranged from 1,104-22,467 in the study, indicating that clay and organic carbon bind thiabendazole strongly. The 1/n values ranged from 0.67-0.87 for adsorption and 0.59-

1.41 for desorption.

Confined crop accumulation (MRID 42367801, 165-1, NOT REVIEWED)

The confined crop accumulation study will be reviewed when EFGWB reviews and evaluates the submitted aerobic soil metabolism study (MRID 41791201). The need for field crop accumulation will be addressed when the confined crop accumulation study is reviewed.

Bioaccumulation in fish (MRID 42022701, 165-4, NOT REVIEWED)

The recently-submitted bioaccumulation in fish study was not reviewed because the data requirement was previously satisfied on 2/8/91 with MRID 00416318. The bioaccumulation factors in the earlier study were 87, 20, and 747 in whole fish, edible, and viscera, respectively. Within 3 days, more than 96 % of the material in the viscera and 50 % in the edible portions were depurated. Within 14 days, 77 % of the material in the edible portions was depurated. The results in MRID 42022701 appear to be very similar to the results reported in the earlier study.

Data Waiver Requests

EFGWB agrees to waive the anaerobic aquatic metabolism (162-3), aerobic aquatic metabolism (162-4), aquatic field dissipation (164-2), and accumulation in irrigated crops (165-3) data requirements for the Merck product Fungicide 1.5T™ since the currently-registered labels do not contain aquatic uses. The registrant requested these waivers in the current submission.

ENVIRONMENTAL FATE ASSESSMENT

Thiabendazole is stable to hydrolysis, photodegradation on soil, and anaerobic soil metabolism, indicating potential persistence. The calculated aqueous photolysis half-life was 10 days, with intermediate degradates benzimidazole-2-carboxamide and benzimidazole-2-carboxylic acid forming benzimidazole as the final degradate (supplemental data). Freundlich K_{ads} values were 2.8, 16, 22, and 270 in sandy, sandy loam, silt loam, and clay soils, respectively, with K_{oc} values of 1,104-22,467. Freundlich K_{des} values were 8.2, 19.5, 16, and 219, respectively, with K_{oc} values 1,336-18,325. The mobility in soils data indicate that thiabendazole binds strongly to soil except for sandy soils with low organic carbon. Bioaccumulation factors in fish were 87, 20, and 747 in whole fish, edible, and viscera, respectively. Within 3 days, more than 96 % of the material in the viscera and 50 % in the edible portions were depurated. Within 14 days, 77 % of the material in the edible portions was depurated.

8. RECOMMENDATIONS:

(1) the hydrolysis study (MRID 41265301) that was reviewed on 2/20/90 is now acceptable.

(2) the aqueous photolysis study that was reviewed on 2/20/90 could not be upgraded with the current submission. The registrant should reconduct

the study using HPLC methodology for analysis at all sampling intervals.

(3) the batch equilibrium (adsorption-desorption) study that was reviewed on 2/20/90 is now acceptable and satisfies the unaged portion of the 163-1 data requirement. Acceptable mobility data, preferably batch equilibrium adsorption-desorption, will be required for the major degradates of thiabendazole to fully satisfy the 163-1 data requirement.

(4) the confined crop accumulation study (165-1, MRID 42367801) will be reviewed when the submitted aerobic soil metabolism (162-1) study is reviewed and evaluated by EFGWB. The need for field crop accumulation (165-2) will be addressed when the confined crop accumulation study is reviewed.

Note to PM:

Since EFGWB has no official record of the 162-1 study (MRID 41791201), the Product Manager should send a Bean Sheet for review of the 162-1 study to EFGWB.

(5) the fish accumulation study (MRID 42022701) was not reviewed because the 165-4 data requirement was previously satisfied on 2/8/91.

(6) the anaerobic and aerobic aquatic metabolism, aquatic field dissipation, and accumulation in irrigated crops data requirements are waived for the Merck product Fungicide 1.5T™ since the currently-registered label does not contain aquatic uses.

(7) field dissipation (164-1) data for thiabendazole were required on 2/20/90 and none has been received.

(8) the photodegradation on soil (161-3) and anaerobic soil metabolism (162-2) data requirements were satisfied on 2/8/91.

(9) laboratory (163-2) and field (163-3) volatility, photodegradation in air (161-4), and combination tank mixes (164-3) were waived on 12/15/88.

(10) spray drift (201-1 and 202-1) was waived on 3/16/89.

9. BACKGROUND:

Thiabendazole is a systemic fungicide registered for use on a wide variety of terrestrial food crop (citrus, bananas, apples, pears, and sweet potatoes) and terrestrial non-food crop (ornamentals, turf, and tobacco) sites. Applications may be made during the growing season to control pathogenic fungi and post-harvest to control storage diseases. Single active ingredient formulations include wettable powder, flowable concentrate, and dust. Multiple active ingredient formulations include captan, thiram, quintozene, and prochloraz. Thiabendazole is nontoxic to bees and slightly toxic to fish.

10. DISCUSSION OF INDIVIDUAL STUDIES: Not Applicable.

11. COMPLETION OF ONE-LINER: One-liner was updated.

12. CBI INDEX: Not Applicable.

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
HILLSBOROUGH ROAD, THREE BRIDGES, NEW JERSEY 08887 U.S.A.

PATRICIA A. SHEEHY
MANAGER, REGULATORY AFFAIRS
AGRICULTURAL RESEARCH & DEVELOPMENT

(908) 369-3072

September 13, 1991

Chemical Review Manager - Frank Rubis
Accelerated Reregistration Branch
Special Review & Reregistration Division (H7508w)
Office of Pesticide Programs
U.S. ENVIRONMENTAL PROTECTION AGENCY
401 M. St. S.W.
Washington, D.C. 20460

Dear Mr. Rubis:

Phase 4 Response: Thiabendazole
Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

Enclosed is our Phase 4 Reregistration Response for thiabendazole consisting of the attached completed Data Call-In Response and Requirements Status/Registrant's Response Worksheet, one volume of correspondence regarding EPA's comments on submitted studies and 3 copies of the reformatted report for the "Thiabendazole Subacute Dominant Lethal Study in the Mouse, Project ID #76-703-0" to upgrade the strutural chromosome aberration study on file, MRID #98002.

EPA's 6/12/91 Phase 4 Response referred to the enclosure of 3 Data Evaluation Records (DERs). Please send a copy of the DER for the thiabendazole photodegradation-soil study MRID #41397301 (Guideline Reference No: 61-3) to the above letterhead address. We did not receive a copy of this evaluation in the original mailing.

Should there be questions regarding this submission, please contact me at the letterhead address or telephone number.

Sincerely,

Patricia A. Sheehy

:cg

United States Environmental Protection Agency
Washington, D.C. 20460
DATA CALL-IN RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary

1. Company name and Address 000618
MERCK & CO. INC..
AGENT FOR: MERCK & CO INC
HILLSBOROUGH ROAD
THREE BRIDGES NJ 08887

2. Case # and Name
2670 Thiabendazole, and salts
Chemical # and Name 060101
Thiabendazole

3. Date and Type of DCI
GENERIC

4. EPA Product Registration	5. I wish to cancel this product registration voluntarily	6. Generic Data		7. Product Specific Data	
		6a. I am claiming a Generic Data Exemption because I obtain the active ingredient from the source EPA registration number listed below.	6b. I agree to satisfy Generic Data requirements as indicated on the attached form entitled "Requirements Status and Registrant's Response."	7a. My product is an MUP and I agree to satisfy the MUP requirements on the attached form entitled "Requirements Status and Registrant's Response."	7b. My product is an EUP and I agree to satisfy the EUP requirements on the attached form entitled "Requirements Status and Registrant's Response."
618-58					XXXXXXXX
618-67					XXXXXXXX
618-75					XXXXXXXX
618-84					XXXXXXXX
618-92					XXXXXXXX
WA86001700	XXXXXXXX This SLN was cancelled with our 1990 filing of the EPA registration fees.				

8. Certification
I certify that the statements made on this form and all attachments are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law.
Signature and Title of Company's Authorized Representative Patricia A. Sheehy Manager, Regulatory Affairs

9. Date
September 13, 1991

10. Name of Company Contact
Ms. Paticia A. Sheehy

11. Phone Number
(908) 369-3072

United States Environmental Protection Agency
Washington, D.C. 20460

REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

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AGENT FOR: MERCK & CO INC
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THREE BRIDGES NJ 08887

2. Case # and Name
2670 Thiabendazole, and salts
Chemical # and Name 060101
Thiabendazole

3. Date and Type of DCI
GENERIC

4. Guideline Requirement Number	5. Study Title	PDCI	Progress Reports 1	2	3	6. Use Pattern	7. Test Substance	8. Time Frame	9. Registrant Response
63-7	Density					ALL	TGAI	12 mos.	5 (w/comments)
63-10	Dissociation Constant					ALL	TGAI	12 mos.	5 "
63-12	pH					ALL	TGAI	12 mos.	5 "
63-13	Stability					ALL	TGAI	12 mos.	5 "
72-1(a)	Fish toxicity bluegill					ABCD	TGAI	12 mos.	1
72-3(a)	Estu/mari tox. fish					ABCD	TGAI	12 mos.	9 N/A
72-3(b)	Estu/mari tox. mollusk					ABCD	TGAI	12 mos.	9 "
72-4(a)	Early life stage fish					ABCD	TGAI	12 mos.	1
84-2(a)	Gene mutation-ames					ABCDHLM	TGAI	12 mos.	1
84-2(b)	Struct. chrom. aberration					ABCDHLM	TGAI	12 mos.	5 (reformat encl)
122-2	Aquatic plant growth					ABCD	TGAI	12 mos.	9 N/A
161-1	Hydrolysis					ABCDH	TGAI	12 mos.	5 (w/comments)
161-2	Photodegradation-water					ABCD	TGAI	12 mos.	5 "
162-3	Anaerobic aquatic metab.		Y			ABCD	TGAI	24 mos.	9 N/A
162-4	Aerobic aquatic metab.		Y			D	TGAI	24 mos.	9 "
163-1	Leach/adsorp/desorption					ABCDH	TGAI	12 mos.	5 (w/comments)
164-2	Aquatic field dissipation		Y			D	TEP	24 mos.	9 N/A

10. Certification

I certify that the statements made on this form and all attachments are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law.

Signature and Title of Company's Authorized Representative Patricia A. Sheehy Manager, Regulatory Affairs

11. Date
September 13, 1991

12. Name of Company Contact
Ms. Patricia A. Sheehy

13. Phone Number
(908)369-3072

United States Environmental Protection Agency
Washington, D.C. 20460

REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary

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MERCK & CO. INC..
AGENT FOR: MERCK & CO INC
HILLSBOROUGH ROAD
THREE BRIDGES NJ 08887

2. Case # and Name
2670 Thiabendazole, and salts
Chemical # and Name 060101
Thiabendazole

3. Date and Type of DCI
GENERIC

4. Guideline Requirement Number	5. Study Title	Code	Progress Reports 1	2	3	6. Use Pattern	7. Test Substance	8. Time Frame	9. Registrant Response
164-5	Long term soil dissipation		Y	Y	Y	ABCD	TEP	48 MOS.	1
165-3	Accumulation - irrig crop		Y	Y		D	TEP	36 MOS.	9 N/A
171-4(d)	Res. analyt. method - animal		Y			ABDHL	TGAI	24 MOS.	1
171-4(e)	Storage stability		Y			ABDHL	TEP	24 MOS.	1
171-4(f)	Mag. of res. potable H2O		Y			D	TEP	24 MOS.	9 N/A
171-4(g)	Mag. of res. in fish		Y			D	TGAI	24 MOS.	9 "
171-4(h)	Mag. of res. irrigated crop		Y			D	TGAI	24 MOS.	9 "
171-4(k)	Cropfield trials								
	GRAPES								
	TERRESTRIAL FOOD CROP		Y			A	TEP	24 MOS.	9 Not supporting
	MELONS, CANTALOUPE								
	TERRESTRIAL FOOD CROP		Y			A	TEP	24 MOS.	IR-4 Project
	PEAS, FIELD								
	TERRESTRIAL FOOD CROP		Y			A	TEP	24 MOS.	9 Not supporting
	STRAWBERRY								
	TERRESTRIAL FOOD CROP		Y			A	TEP	24 MOS.	1
	TOBACCO								
	TERRESTRIAL NON-FOOD CROP		Y			C	TEP	24 MOS.	1
	AVOCADO								
	GREENHOUSE FOOD CROP		Y			H	TEP	24 MOS.	9 Not supporting
	BEANS, DRIED-TYPE								
	TERRESTRIAL FOOD CROP		Y			A	TEP	24 MOS.	9 " "

Initial to indicate certification as to information on this page (full text of certification is on page one). T.A.S

Date September 13, 1991

* Uses not being supported

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No: 060101 Case No: 2670

Company No. 618

Merck & Co., Inc.
Three Bridges, NJ 08887

Correspondence

(Re. Col. #9 of Phase 4 Requirements Status and Registrant's Response)

Table of Contents

Correspondence - Phase 4 Response

Thiabendazole

Chemical No: 060101 Case No: 2670

Introduction

This volume contains correspondence and reference material pertaining to the following Guideline Reference Numbers for which Column 9 of the Phase 4 Requirements Status and Registrant's Response Worksheet are checked.

Table of Contents (Cont'd)

PHASE 3 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No: 060101 Case No: 2670
Merck & Co., Inc. Company No. 618

A. Commitment to Do Study

Merck & Co., Inc. is committed to conduct the following studies in response to EPA's Phase 4 Response for Thiabendazole.

	72-1 (a)	Fish Toxicity - Bluegill
	72-4 (a)	Early Life Stage - Fish
	84-2 (a)	Gene Mutation - Ames
	164-5	Long Term Soil Dissipation (in progress)
	171-4 (c)	Storage Stability
**	171-4 (d)	Residue Analytical Method - Animal

**We are committing to submit the Residue Analytical Method - animal required in Phase 4, in accordance with PR Notice 88-5 "Tolerance Enforcement Methods - Independent Laboratory Confirmation By Petitioner".

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No: 2670
Merck & Co., Inc. Company No. 618

B. Not Applicable: Data Requirements/Uses Not Supported

Merck & Co., Inc. will not be conducting the following studies because the data gaps are specific to aquatic uses which are not on our currently registered labels:

122-2	**Aquatic Plant Growth**
162-3	**Anaerobic Aquatic Metabolism**
162-4	**Aerobic Aquatic Metabolism**
164-2	**Aquatic Field Dissipation**
165-3	**Accumulation - Irrigated Crop**
171-4 (f)	**Magnitude of Residue - Potable H_2O**
*** 171-4 (g)**	**Magnitude of Residue Fish**
*** 171-4 (h)**	**Magnitude of Residue Irrigated Crop**

* Waiver of data requirements were granted for each of these requirements in EPA's 9/5/89 letter as approved uses for Merck thiabendazole products do not meet the criteria for these data requirements.

Merck & Co., Inc. will not be supporting the following uses:

171-4 (k)	**Cropfield Trials - grapes, peas-field, avocado, beans - dried type, mango, soybean, sprouts, rice.**
171-4 (l)	**Processed Food - beans (cannery residue), grapes (pomace, dried), rice (polished rice), soybeans oil, crude and refined.**

IR-4 is developing 171-4 (k) data to support a domestic use on melons.

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

B.1. Request for Waiver of Data Requirement

72-3 (a) Estuarine/Marine Toxicity - Fish
MRID #41192003
72-3 (b) Estuarine/Marine Toxicity - Mollusk
MRID #41192004

A waiver of data requirements are requested for the two studies identified. In the 1988 Thiabendazole Data Call-In these studies were required because citrus and rice use create a potential for estuarine exposure.

Rice has been deleted as a use and will not be supported. We are only supporting the post-harvest treatment on citrus and request that EPA reconsider the need to conduct these studies based on the current use (citrus post-harvest) which is being supported.

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

C Merck & Co., Inc. Responses to EPA Comments on Previously Submitted Studies

EPA's Thiabendazole Phase 4 Response has identified the studies listed below as being upgradable or denied/deficient.

Merck & Co., Inc. has committed to provide the required data to support the continued registration of thiabendazole products. In Part C of our response we will be addressing EPA's comments and request reconsideration of the study evaluations for the following studies:

Study		MRID #	Tab
63-7	Density	47895	C.1
63-1	Dissociation Constant	40947302	C.2
63-12	pH	4789801	C.3
63-1	Stability	41025001	C.4
84-2(b)	Structural Aberration Chr.	98002	C.5
161-1	Hydrolysis	41265301	C.6
161-2	Photodegradation - water	41265101	C.7
163-1	Leaching/Adsorption/Desorption	41265102	C.7

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

C.4 Response to EPA Phase 4: Product Chemistry Comments

63-13 Stability: MRID #41025001

The Agency has requested information addressing stability to metal ions and sunlight. Because the product is not exposed to metal, we feel that additional information would not be applicable at this time.

Since it was not clear exactly what additional information EPA is requesting regarding the stability of thiabendazole to sunlight, reference is being made to address EPA's comments to the following photolysis study:

> "Determination of the Photolysis Rate of ^{14}C-Thiabendazole on the Surface of Soil" MRID #41397301 & 41397302, submitted 2/27/90.

The soil photolysis study was conducted with ^{14}C-thiabendazole at 25° C $\pm$ 2.5C. The half-life was calculated to be 933 days for the exposed system, based on 12-hour exposure using a xenon arc light source to simulate natural sunlight. It was concluded from this study that thiabendazole is not subject to photodegradation on the surface of the soil.

We request that EPA reevaluate the need for any additional information to upgrade the stability data requirement (GRN: 63-13, MRID # 41025001). If further information is required, we request that EPA specifically identify the requirements necessary to support the acceptability of the stability study on file (MRID #41025001).

TRANSMITTAL DOCUMENT

Submission of "Subacute Dominant Study of
Thiabendazole in the Mouse"
A Phase 4 Response Reformat of MRID # 98002

I. Submitter Registrant - Merck & Co., Inc.
P.O. Box 2000

Rahway, New Jersey 07065

Address Correspondence To: Merck & Co., Inc.
Agricultural Research &
Development
Hillsborough Road
Three Bridges, N. J. 08887

II. Regulatory Action

The accompanying document is being submitted in an effort to upgrade the study now on file (MRID # 98002) in response to the Phase 4 Data Call-In.

III. Transmittal Date: September 13, 1991

IV. Documents in This Submission:

This study is being submitted under Guideline Reference No: 84-2(b) mutagenicity study requirements in an effort to upgrade the study currently on file (MRID # 98002)

40 CFR 158.340, Toxicology Data Requirments
Subacute Dominant Study of Thiabendazole in The Mouse, Project ID - TT# 76-703-0 (reformatted study)

Patricia A. Sheehy

Ms. Patricia A. Sheehy
Manager, Regulatory Affairs
Agricultural Research &
Development

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

C.6 Response to EPA Phase 4: Environmental Fate Comments

161-1 Hydrolysis: MRID #41265301

The Agency has indicated that this study (MRID #41265301) is denied/deficient.

No EPA comments regarding the reason for this decision were included in the Phase 4 Response nor has Merck & Co., Inc. received an Agency letter indicating a deficiency in the study.

We believe the study submitted was scientifically acceptable and in complete accordance with the requirements for an hydrolysis study.

We request that EPA provide us with a copy of the study review so that we can adequately address any outstanding issues regarding this study to fulfill our 1988 commitment to provide acceptable data to support thiabendazole registrations.

PHASE 4 REREGISTRATION RESPONSE

THIABENDAZOLE

Chemical No. 060101 Case No. 2670
Merck & Co., Inc. Company No. 618

C.7 Response to EPA Phase 4: Environmental Fate Comments

161-2 Photodegradation - water: MRID #41265101
163-1 Leaching/Adsorption/Desorption: MRID #41265102

Attached is our response to EPA's Phase 4 comments for the thiabendazole photodegradation-water (MRID #41265101) and leaching/adsorption/desorption (MRID #41170102) studies.

We believe that our response to the comments on the aqueous photolysis study should address the four issues identified in Phase 4 to upgrade the study.

We have also included an explanation for the use of sodium azide for soil sterilization in the leaching/adsorption/desorption study, and the effects the presence of this compound might have on the physical/chemical properties of the soil.

SOIL LEACHING/ADSORPTION/DESORPTION WITH THIABENDAZOLE (N-163-1)

In its comments for the soil adsorption/desorption study conducted with thiabendazole (ABC Laboratories Study Number 37635), the EPA did not accept the study due to the use of sodium azide for soil sterilization and the effects the presence of this compound might have on the physical/chemical properties of the soil. In point of fact, there was approximately as much calcium chloride (calcium ion is a N-163-1 guideline) present in the samples as sodium azide. Sterilized soil was used in the study to avoid possible complications resulting from any metabolism of the thiabendazole by soil microorganisms.

Both the cation exchange capacity and the percent organic matter affect the adsorption/desorption properties of a soil. While the addition of sodium azide to the soil could possibly affect the cation exchange capacity of the soil, it would have no effect on the percent organic material in the soil. The presence of sodium azide would, if anything, because of its potential for interaction with soil, be reflected as an increase in the mobility of thiabendazole. While repetition of the study using non-sterilized soils would allow one to evaluate binding of thiabendazole to soil in the absence of sodium azide, it should not change the overall mobility classification of thiabendazole. Based on the results of the study, thiabendazole binds tightly to soil. This conclusion would not be expected to change if the study were repeated.

DETERMINATION OF THE PHOTOLYSIS RATE OF ^{14}C-THIABENDAZOLE IN PH 5 BUFFERED SOLUTION AT 25°C (N-161-2)

The following paragraphs are in response to the four comments provided by the EPA for the aqueous photolysis study conducted with thiabendazole (ABC Laboratories Study Number 37637).

1. The initial method of analysis for all study samples was TLC. This method of analysis proved to be effective only for the initial sampling intervals (day 0 through day 7). All zones observed on the TLC scanner were effectively resolved as distinct symmetrical peaks. Analysis of the day 14 through day 30 samples using TLC demonstrated that TLC was no longer effective in resolving the parent material from the photolysis products. Peak symmetry and resolution were both poor as evidenced by the TLC scanner data. Compare, for example, the broad peak (at Rf. 0.364) possessing two shoulders (A and B) in the TLC radiochromatogram for the day 14, nonsensitized exposure II sample, with the narrow, symmetrical

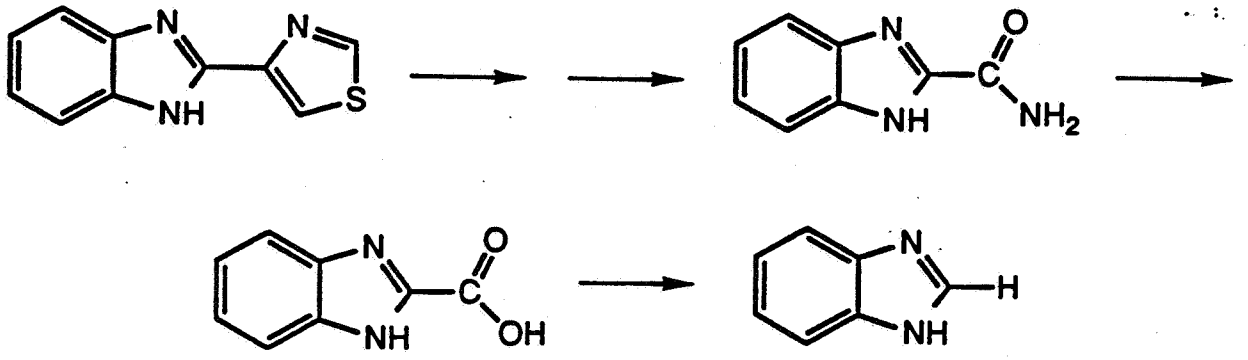
peak (Rf. 0.33) for the day 14, sensitized dark II ^{14}C-thiabendazole sample. This comparison demonstrates the inability of the TLC system to achieve useful analysis of mixtures of ^{14}C-thiabendazole and its degradates resulting from photolysis. Because of this lack of separation of degradates from thiabendazole by TLC, the "% As Parent As Determined By RTLC" values for sample days 14 and following include contributions from degradates not resolved by TLC from thiabendazole. Therefore, the " % Parent" values are too high. Illustrative figures referred to in 161-2 responses can be found in the submitted Analytical Biochemistry Laboratories Report Study Number 37637 (161-2).

In order to effectively resolve the photolysis products for the later samples an HPLC method was developed and used with these samples. A comparison of the thiabendazole peak (retention time ~25 minutes) resulting from HPLC gradient elution radiochromatographic analysis of the day 7 nonsensitized dark II sample with the peak from the day 14 nonsensitized exposure II sample indicates very little deterioration in HPLC performance. Further, this latter HPLC radiochromatogram clearly shows the presence of radioactive components with the retention times of benzimidazole-2-carboxylic acid, benzimidazole and benzimidazole 2-carboxamide. As the thiabendazole peak is well separated from those of the degradates, the "% As Parent As Determined By HPLC/TLC" values (HPLC for the sample days 14 and following) are less than those obtained for these samples by RTLC. There was no attempt made to analyze the prior samples by HPLC, other than the day 0 samples, since the initial resolution obtained through TLC analysis was effective in resolving parent material from photolysis products.

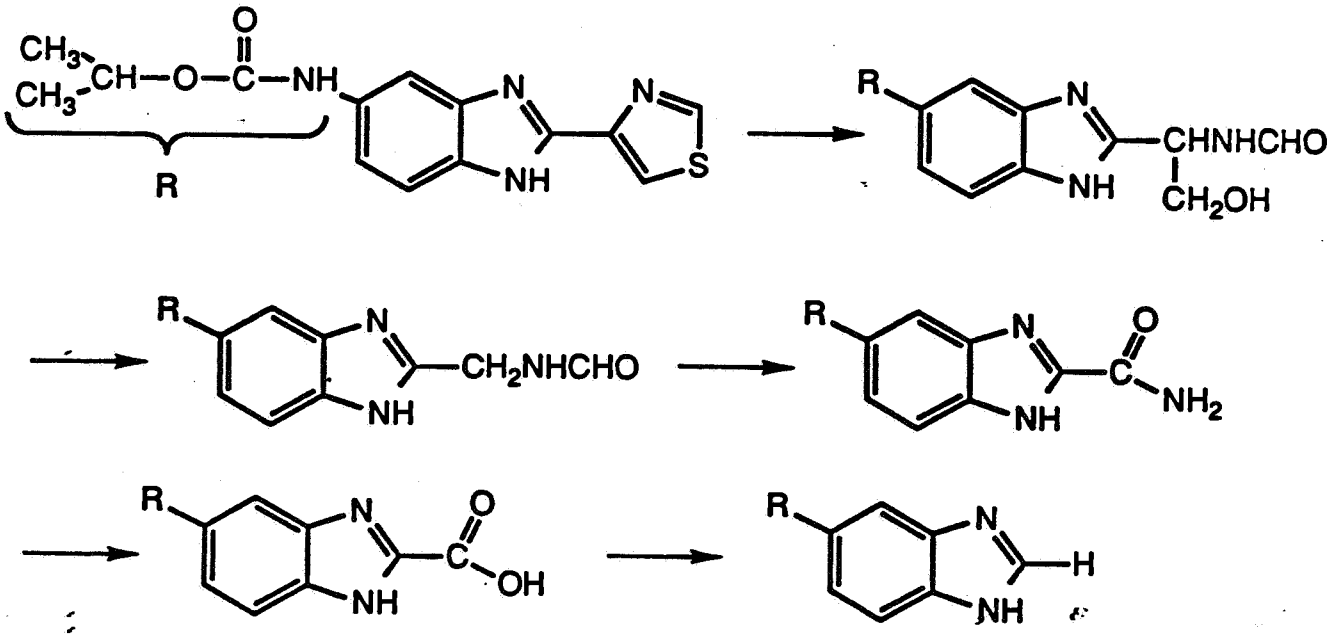
The identity of thiabendazole and degradates (benzimidazole-2-carboxamide and thiabendazole-2-carboxylic acid, and benzimidazole) was confirmed by chromatographic comparison with authentic reference standards.

2. The second question was related to the radioactivity not accounted for as identifiable compounds in both the sensitized and non-sensitized samples. In both cases, the remaining activity was spread throughout the HPLC chromatographic run as multiple components. No single component comprised more than 10 percent of the initial material. See, for example, the attached HPLC gradient elution radiochromatogram (day 14, nonsensitized exposure II sample).

3. With respect to elimination of the thiazolyl group, the formation of benzimidazole-2-carboxamide and benzimidazole-2-carboxylic acid, as well as benzimidazole, from thiabendazole during exposure of the latter to photolysis in buffered solution indicates that the thiazolyl group degrades in a stepwise manner with loss of small fragments, e.g.,



Further evidence for this type of stepwise degradation was found in studies with cambendazole (shown below), an analog of thiabendazole. Cambendazole undergoes metabolism in mammals to produce a large number of metabolites, the formation of some of which involves degradation of the thiazole ring [VandenHeuvel et al., J. Agric. Food Chem., 26, 1357 (1978); reprint attached]. It is evident that a reasonable metabolic pathway involving losses of small fragments from the thiazolyl group can be formulated:



The carboxylic acid from cambendazole undergoes decarboxylation upon standing in solution; benzimidazole-2-carboxylic acid is also an unstable compound, undergoing conversion to benzimidazole. Although the above pathway involves mammalian metabolism, it suggests that similar, stepwise degradation occurs to the thiazolyl group of thiabendazole exposed to photolysis conditions in buffered solution. These mono- and diatomic fragments would be utilized in normal pathways. They would be incorporated into natural constituents and not adversely impact the environment.

4. The molar absorptivity of thiabendazole was not calculated, as it was not a requirement of the aqueous photolysis guideline. The molar absorptivity can be calculated based on a 1-cm pathlength, which is the cell size used in the spectrophotometer (Beckman Instruments Company DU-6) used for this study. The molar absorptivity for thiabendazole found using this system is 32394 (UV max 297, pH 5 acetate buffer).

THIABENDAZOLE Sh# 060101

Page_____ is not included in this copy.

Pages 26 through 29 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.

____ Information about a pending registration action.

X___ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Environmental Fate & Effects Division
PESTICIDE ENVIRONMENTAL FATE ONE LINE SUMMARY
THIABENDAZOLE
Last Update on October 19, 1992
[V] = Validated Study [S] = Supplemental Study [U] = USDA Data

LOGOUT	Reviewer: JAB	Section Head: BCP for ADA	Date:

Common Name:THIABENDAZOLE
Smiles Code:S(C=N1)C=C1C(=N-c2cc3)N-c2cc3
PC Code # : 60101 CAS #:148-79-8 Caswell #:

Chem. Name :2-(4-THIAZOLYL)BENZIMIDAZOLE

Action Type:Fungicide

Trade Names:APL-LUSTER;ARBOTECT; MERTECT
(Formul'tn):WP 60%; 45% FLOWABLE; SMOKE GENERATOR
Physical State:

Use : GREEN MOLD, BLUE MOLD, AND STEM END ROT OF CITRUS FRUITS;
Patterns :CERCOSPORA LEAF SPOT; FUSARIUM BASAL ROT AND PENICILLIUM
(% Usage) :BLUE MOLD ON ORNAMENTAL BULBS AND CORMS.
:

Empirical Form: $C_{10}H_7N_3S$
Molecular Wgt.: 201.25 Vapor Pressure: 4.00E -9 Torr
Melting Point : °C Boiling Point: °C
Log Kow : pKa: 4.70 @ °C
Henry's : E Atm. M3/Mol (Measured) 2.12E-11 (calc'd)

Solubility in ...					Comments
Water	50.00E		ppm	@20.0 °C	pH dep.
Acetone	4.20E	3	ppm	@20.0 °C	
Acetonitrile	E		ppm	@ °C	
Benzene	2.30E	2	ppm	@20.0 °C	
Chloroform	8.00E	1	ppm	@20.0 °C	
Ethanol	7.90E	3	ppm	@20.0 °C	
Methanol	9.30E	3	ppm	@20.0 °C	
Toluene	E		ppm	@ °C	
Xylene	E		ppm	@ °C	
dimethylformamide	3.90E	4	ppm	@20.0 °C	
dimethylsulfoxide	8.00E	4	ppm	@20.0 °C	

Hydrolysis (161-1)
[V] pH 5.0:STABLE 45C
[V] pH 7.0:STABLE 45C
[V] pH 9.0:STABLE 45C
[V] pH :STABLE AT pH 5, 7, AND 9.
[ ] pH :
[ ] pH :

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THIABENDAZOLE
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Photolysis (161-2, -3, -4)
[S] Water:23.9 MIN
[S] :10 DAYS AT pH 7. BENZIMIDIZOLE IS FINAL DEGRADATE AND
[ ] :THE INTERMEDIATE DEGRADATES ARE BENZIMIDIDAZOLE-2-CARBOX-
[ ] :AMIDE AND CARBOXYLIC ACID.

[V] Soil :933 DAYS
[S] Air :8 % DEG IN 30 DAYS IRRAD. WITH A XENON LAMP

Aerobic Soil Metabolism (162-1)
[S] 403 DA
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]

Anaerobic Soil Metabolism (162-2)
[V] STABLE
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]

Anaerobic Aquatic Metabolism (162-3)
[S] PARTITIONS INTO SOIL, LEAVING
[ ] NEGLIGIBLE RESIDUES IN THE
[ ] WATER.
[ ]
[ ]
[ ]
[ ]

Aerobic Aquatic Metabolism (162-4)
[S] NOT LEACHED BY WATER IN 4 SOIL
[ ] TYPES.
[ ]
[ ]
[ ]
[ ]
[ ]

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Soil Partition Coefficient (Kd) (163-1)

	SOIL	OC	CEC	Kads	Kocads	Kdes	Kocdes
[ ]	SAND	0.3	0.3	2.8	1104	16	3260
[ ]	SD LM	0.4	10	16	3992	19	4865
[ ]	SI LM	1.2	10	22	1812	16	1335
[ ]	CLAY	1.2	25.8	270	22467	220	18325

[ ] EFGWB 90-0079, 2/20/90, UPGRADED ON 10/92.

Soil Rf Factors (163-1)
[S] DOES NOT LEACH; REMAINS IN
[ ] TOP 3"LAYER OF SdLm, SAND,
[ ] SiClLm, AND CLAY SOILS.
[ ]
[ ]
[ ]

Laboratory Volatility (163-2)
[ ]
[ ]

Field Volatility (163-3)
[ ]
[ ]

Terrestrial Field Dissipation (164-1)
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]

Aquatic Dissipation (164-2)
[ ]
[ ]
[ ]
[ ]
[ ]
[ ]

Forestry Dissipation (164-3)
[ ]
[ ]

Long-Term Soil Dissipation (164-5)
[ ]
[ ]

Accumulation in Rotational Crops, Confined (165-1)
[ ]
[ ]

Accumulation in Rotational Crops, Field (165-2)
[ ]
[ ]

Accumulation in Irrigated Crops (165-3)
[ ]
[ ]

Bioaccumulation in Fish (165-4)
[V] BCF'S OF 87, 20, AND 747 IN WHOLE, EDIBLE, AND VISCERA.
[ ] 96 % DEPURATION IN 3 DAYS IN VISCERA AND EDIBLE WAS SIGNIF.

Bioaccumulation in Non-Target Organisms (165-5)
[ ]
[ ]

Ground Water Monitoring, Prospective (166-1)
[ ]
[ ]
[ ]
[ ]

Ground Water Monitoring, Small Scale Retrospective (166-2)
[ ]
[ ]
[ ]
[ ]

Ground Water Monitoring, Large Scale Retrospective (166-3)
[ ]
[ ]
[ ]
[ ]

Ground Water Monitoring, Miscellaneous Data (158.75)
[ ]
[ ]
[ ]

Environmental Fate & Effects Division
PESTICIDE ENVIRONMENTAL FATE ONE LINE SUMMARY
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Field Runoff (167-1)
[ ]
[ ]
[ ]
[ ]

Surface Water Monitoring (167-2)
[ ]
[ ]
[ ]
[ ]

Spray Drift, Droplet Spectrum (201-1)
[ ]
[ ]
[ ]
[ ]

Spray Drift, Field Evaluation (202-1)
[ ]
[ ]
[ ]
[ ]

Degradation Products

Benzimidazole
Benzimidazole-2-carboxylic acid
Benzimidazole-2-carboxamide
5-hydroxythiabendazole

Environmental Fate & Effects Division
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THIABENDAZOLE
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Comments

Thiabendazole controls the same spectrum of fungi as benomyl. Under field conditions, TBZ dissipates in soil via binding and undergoes less than 10% degradation. Dissipation of TBZ residues is confined to top 3" segment during the first season, and occasionally reaches 6" depth by end of second season. Thiabendazole does not inhibit bacteria in soil. Algae either metabolize it or accumulate it.

Koc = 2500 (U)

References: EFGWB FILES, REVIEWS
Writer : PJH, JAB

DP BARCODE: D170813 REREG CASE # 2670

CASE: 807285 DATA PACKAGE RECORD DATE: 11/05/91
SUBMISSION: S380299 BEAN SHEET Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REREGISTRATION ACTION: 603 RESUBMISSION
CHEMICALS: 060101 Thiabendazole

ID#: 060101-000618
COMPANY: 000618 MERCK & CO INC
PRODUCT MANAGER: 51 BARBARA BRISCOE 703-308-8065 ROOM: CS1 3H3
PM TEAM REVIEWER: FRANKLIN RUBIS 703-308-8184 ROOM: CS1 4J6
RECEIVED DATE: 08/16/90 DUE OUT DATE: / /

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 170813 EXPEDITE: Y DATE SENT: 11/05/91 DATE RET.: / /
CHEMICAL: 060101 Thiabendazole
DP TYPE: 999 Miscellaneous Data Package
ADMIN DUE DATE: 12/05/91 CSF: N LABEL: N

ASSIGNED TO	DATE IN	DATE OUT
DIV : EFED	11/7/91	/ /
BRAN: EFGB	/ /	/ /
SECT:	/ /	/ /
REVR :	/ /	/ /
CONTR:	/ /	/ /

* * * DATA REVIEW INSTRUCTIONS * * *

COMPANY IS REQUESTING WAIVERS FOR 162-3, 4, 164-2, 165-3. DO YOU CONCUR. PLEASE PROVIDE ME WITH YOUR COMMENTS.

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL
154410	EFGB/IO	08/16/90	09/06/90	Y	N	N
154411	TB-2	08/16/90	09/06/90	Y	N	N
154412		08/16/90	09/06/90	Y	N	N
154413	OREB/IO	08/16/90	09/06/90	Y	N	N
154414	EEB/IO	08/16/90	09/06/90	Y	N	N
170812	EEB	11/05/91	12/05/91	Y	N	N

DP BARCODE: D169687 REREG CASE # 2670

CASE: 807285 DATA PACKAGE RECORD DATE: 10/15/92
SUBMISSION: S404713 BEAN SHEET Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REREGISTRATION ACTION: 606 DATA PACKAGE REVIEW
CHEMICALS: 060101 Thiabendazole 100.00 %

ID#: 060101-000618
COMPANY: 000618 MERCK & CO INC
PRODUCT MANAGER: 51 BARBARA BRISCOE 703-308-8177 ROOM: CS1 3H3
PM TEAM REVIEWER: FRANKLIN RUBIS 703-308-8184 ROOM: CS1 4J6
RECEIVED DATE: 09/19/91 DUE OUT DATE: 12/18/91

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 169687 EXPEDITE: N DATE SENT: 10/08/91 DATE RET.: / /
CHEMICAL: 060101 Thiabendazole
DP TYPE: 101 Phase IV Review
ADMIN DUE DATE: 12/17/91 CSF: N LABEL: N

ASSIGNED TO	DATE IN	DATE OUT
DIV : EFED	10/10/91	/ /
BRAN: EFGB	/ /	/ /
SECT:	/ /	/ /
REVR :	/ /	/ /
CONTR:	/ /	/ /

* * * DATA REVIEW INSTRUCTIONS * * *

PLEASE REVIEW THE ATTACHED PACKAGE.

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL