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(5-12-78)

EEE BRANCH REVIEW

DATE: IN 12/14 OUT 5/12/78 IN _____ OUT _____ IN _____ OUT _____

FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. 618-88

PETITION OR EXP. PERMIT NO. _____

DATE DIV. RECEIVED _____

DATE OF SUBMISSION _____

DATE SUBMISSION ACCEPTED _____

TYPE PRODUCT(S): I, D, H,(F) N, R, S Fungicide

DATA ACCESSION NO. 232421

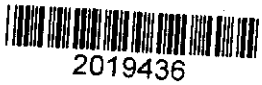
PRODUCT MGR. NO. E.M. Wilson (21)

PRODUCT NAME(S) Arbotect 20-S

COMPANY NAME Merck & Company, Inc.

SUBMISSION PURPOSE Data Submission

CHEMICAL & FORMULATION 2-(4-Thiazolyl) Benzimidazole, HYPOPHOSPHITE SALT OF



100.0 Pesticidal Use

For the control of Dutch Elm Disease

100.1 Application Method/Directions:

ARBOTECT 20-S is to be injected into the base of trees.

100.2 Application rates:

Preventive Treatment: for each 5 inches of trunk diameter inject 1 fl.oz ARBOTECT 20-S in 40 fl oz. of water to 2 fl. oz ARBOTECT 20-S in 80 fl oz. of water. Use the higher levels of ARBOTECT 20-S under high disease pressure situations.

Therapeutic Treatment: For each 5 inches of trunk diameter inject 2 fl. oz. of ARBOTECT 20-S in 80 fl oz. of water to 4 fl. oz of ARBOTECT 20-S in 160 fl. oz. of water. Use the higher levels of ARBOTECT 20-S under high disease pressure situations.

100.3 Precautionary Labeling

Keep out of lakes, streams, and ponds. Do not contaminate water by cleaning of equipment or disposal of wastes.

101.0 Chemical and physical properties

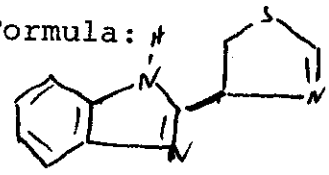
101.1 Chemical Name

2-(4-Thiazolyl) Benzimidazole

101.2 Common Name

Thiabendazole
Arbotect 20-S and Metasol TK-100 are synonymous
Both are 20% formulation of the same active ingredient

101.3 Structural Formula:



Empirical Formula $C_{10}H_7N_3S$

2

101.4 Molecular Weight:

201.26

101.5 Physical State

White to tan, odorless powder

101.6 Solubility

Soluble in a number of solvents, essentially insoluble in water. The solubility in water at 25° C varies depending on the pH 5-12 it is less than 0.05 mg/ml. Below pH 5 the solubility increases. At pH 2.0 it is approximately 10 mg/ml

Solvent	Solubility-room temp (mg/ml)
Acetone	2.8
Methanol	9.3
MEK	12.5

102.0 Behavior in the Environment

Environmental Chemistry Data is summarized as follows: (From the review of T. F. O'Brien 6/28/77)

102.1 Soil

Aerobic degredation of TBZ in soil is slow with a half life of 274-278 days. TBZ dissipates in soil so that the parent compound is gone after 4-6 weeks.

102.2 Water

Half-life in water of 23.9 minutes. Photylysis of TBZ in water is rapid.

102.3 Plant

Photodegredation on plant surface is slow.

102.4 Animal

TBZ does not appear to bioaccumulate in fish.

102.4 Behavior

Other data on leaching--plant persistence etc. is not available at this time.

103.0 Toxicological Properties

103.1.1 Mammal

Test: Acute Mamal LD_{50}
Special: Mice
Results: LD_{50} = 3.81 gm/kg

Species: Rat
Results: LD_{50} = 3.33gm/kg

Species: Rabbit
Results: LD_{50} = 3.85 gm/kg

Information from Petition #4F1518

103.1.2 Birds

Test: Avian acute oral LD_{50}
Species: Bobwhite quail
Results: $LD_{50} > 4640$ mg/kg. (Technical material)
Validation: Supplemental. See review ES-C-2

Test: Avian Acute oral LD_{50}
Species: Bobwhite quail
Results: $LD_{50} > 4640$ mg/kg. (Formulated product)
Validation: Supplemental. See review ES-C-1.

Test: Avian Acute Oral LD_{50}
Species: Mallard duck
Results: $LD_{50} > 4640$ mg/kg. (Technical material)
Validation: Supplemental. See review ES-C-3.

Test: Avian Subacute dietary LC_{50}
Species: Bobwhite Quail
Results: LC_{50} = 10,000 ppm. (Technical)
Validation: Core. See validation ES-D-2.

Test: Avian subacute dietary LC_{50}
Species: Bobwhite quail
Results: LC_{50} = > 6819 ~~mg/kg~~ ppm (formulated product)
Validation: Supplemental. See validation ES-D-1

Test: Avian subacute dietary LC_{50}
Species: Mallard Duck
Results: LC_{50} = > 10,000 ppm. (formulated product)
Validation: Supplemental. See validation ES-E-1

103.1.3 Fish:

Test: Acute 96-hr. LC_{50}
Species: Rainbow trout
Results: Matasal TK-100, LC_{50} = 2.46 ppm
Technical LC_{50} = 1.80 ppm.
Validation: Core, Core - See Review ES-G-1

Test: Acute 96-hr. LC_{50}
Species: Bluegill sunfish
Results: Matasal TK-100, LC_{50} = > 56.0 ppm
Technical LC_{50} = 22 ppm
Validation: Core, ~~Core~~ - See Review ES-F-1

103.1.4 Aquatic Invertebrates:

Test: Aquatic invertebrate acute toxicity
Species: Daphnia magna
Results: 48 hr. LC_{50} = 2.6 mg/l (technical
Validation: Core - See validation ES-H-1

104.0 Hazard Assessment

104.1 Discussion

Exposure to fish and wildlife should be minimal to non-existant. ARBOTECT 20-S is injected into the trunk of trees. Exposure is limited to eating plant parts (twigs-buds-seeds) which may contain small amounts of the chemical or by accidental exposure, spills.

104.1.3 Adequacy of toxicity data

In a letter dated 6 July 1977, the product manager (21) requested the 6 basic studies. Nine studies (accession No. 232421) were submitted as a result of the letter. The following listed studies have been reviewed and will support registration:

Eight-day Dietary LC_{50} - Bobwhite Quail, Thiabendazole, Final Report. Wildlife International Ltd., Easton, Md, dated November 15, 1977.

Metasol TK-100, 20% Solution, and 2-(4'Thiazolyl)-Benzimidazole - Safety Tests in Rainbow Trout. Woodard Research Corporation, Herndon, VA, dated August 27, 1971.

Metasol TK-100, 20% solution and 2-(4'Thiazolyl) Benzimidazole - Safety Test in Bluegill Sunfish Woodard Research Corporation, Herndon, VA, Dated July 6, 1971.

The Acute Toxicity of ARBOTECT 20-S to the Water Flea Daphnia Magna Straus

The following studies were validated and found to be supplemental studies. Protocol dictates that avian acute oral and dietary studies be conducted using the technical material. These studies used the formulated product. The studies may be upgraded to core if the toxicity values of the formulated product are needed.

Acute Oral LD_{50} - Bobwhite Quail, ARBOTECT 20-S, Final Report. Wildlife International LTD., Easton, MD, dated August 8, 1977.

Eight-day Dietary LC_{50} - Mallard Duck, ARBOTECT 20-S, Final Report. Wildlife International Ltd., Easton, MD, dated November 14, 1977.

Eight-day Dietary LC_{50} - Bobwhite Quail, ARBOTECT 20-S, Final Report Wildlife International Ltd., Easton, MD, dated August 12, 1977.

The following studies have been evaluated and found to contain useful information, however, they do not and cannot meet protocol requirements and thus cannot be used to support registration.

Acute Oral LD_{50} - Bobwhite Quail, Thiabendazole, Final Report. Wildlife International Ltd., Easton, MD, dated August 12, 1977.

Acute Oral LD_{50} - Mallard Duck, Thiabendazole, Final Report. Wildlife International Ltd., Easton, MD, dated November 8, 1977.

104.1.4 Additional Data Required

The following studies must be submitted or referenced to comply with registration standards.

1. An avian subacute dietary LC_{50} study on a species of waterfowl (preferably mallard duck) using the technical material and,

2. An avian acute oral on either the Bobwhite quail or the species tested in (1) above.

105.0 Classification

No classification will be made since this is a data evaluation only

107.0 Conclusions

107.4 Data Adequacy

The data submitted contained an acceptable avian dietary (Bobwhite quail) study, the coldwater and warmwater acute fish toxicity tests and an acute invertebrate LC_{50} study (Daphnia).

107.5 Data Requests

The following studies must be submitted or referenced to comply with registration standards. The tests Must be conducted using the technical material and not the formulated product.

1. An avian subacute dietary LC_{50} study on a species of waterfowl (preferably Mallard duck) and,

2. An avian acute oral LC_{50}, on either the Bobwhite quail or Mallard duck (if used for the dietary study).

107.7 Recommendations.

No recommendations are necessary - data evaluation only.

J. Tice
Environmental Safety Section
EEEB-RD WH567
5/12/78

STUDY VALIDATION

DATA REVIEW NUMBER: ES-C-1

TEST: Avian acute oral LD_{50}

SPECIES: Bobwhite quail

RESULTS: Acute Oral $LD_{50} > 4640$ mg/kg

The test followed the protocol with the following exceptions: 14 day old birds and the formulated product was used. No mortality occurred at the dosage levels of 215, 464, 1000, and 2150 mg/kg. Maximum mortality (4 out of 10) occurred at 4,640 mg/kg.dosage.

CHEMICAL: ARBOTECT 20-S: A.I., 2-(4-thiazolyl) Benzimidazole hypophosphite (Formulated product)

TITLE: Final Report, Acute oral LD_{50} - Bobwhite quail. Project No. 105-115, Date of initiation, July 21, 1977.

ACCESSION NO: 232421 (Petition # 618-88)

STUDY DATE: July 21, 1977

RESEARCHER: Robert Fink, Wildlife Internatioanl Ltd.

REGISTRANT: Merck and Company

VALIDATION CATEGORY: Supplemental

CATEGORY REPAIRABILITY: Yes. Fourteen day old birds and the formulated product were used. According to the memo by J. Ackerman dated March 13, 1977, the use of young birds would not in itself make the study supplemental however the formulated product was used instead of the technical material as protocol dictates. The study may be upgraded to core if a study using the formulated product is needed.

STUDY VALIDATION

DATA REVIEW NUMBER: ES-E-1

TEST: Avian Subacute Dietary LC_{50}

SPECIES: Mallard Duck

RESULTS: 8 day dietary LC_{50} = >10,000 ppm

The test followed the protocol for minimum tests with one exception. The formulated product was used instead of the technical product. No mortality was observed at any dosage level (10,000 ppm being the highest) with only a slight reduction in weight gain at the 10,000 ppm level.

CHEMICAL ARBOTECT 20-S; a.i. 2-(4-thiazolyl) benzimidazole hypophosphite. (Formulated Product)

TITLE. Final Report, Eight-day Dietary LC_{50} - Mallard duck; Arbotect 20-S, Project No. 105-116, Dated November 14, 1977.

ACCESSION NO. 232421

STUDY DATE: July 21, 1977

RESEARCHER. Robert Fink, Wildlife International Ltd.

REGISTRANT: Merck and Company

VALIDATION CATEGORY: Supplemental

CATEGORY REPAIRABILITY: Yes. The study was classified supplemental because the formulated product was used instead of the technical material. If a study using formulated product is necessary it may be categorized as core.

STUDY VALIDATION

DATA REVIEW NO: ES-D-1

TEST: Avian Subacute Dietary LC_{50}

SPECIES: Bobwhite Quail

Results: 8 day dietary LC_{50} = 6849 ppm (5211 to 9001 ppm) Test followed the protocol for basic tests with one exception. The formulated product was used instead of the technical material. 20% mortality occurred at the 4640 ppm dose level and 80% mortality at the 10,000 ppm level.

CHEMICAL: Arbotect 20-S; a.i., 2-(4-thiazolyl) benzimidazole hypophosphite (26.6%).

TITLE: Final Report, Eight day dietary LC_{50} - Bobwhite quail. Project No. 105-114, Dated August 12, 1977

STUDY DATE: July 21, 1977

RESEARCHER: Robert Fink, Wildlife International Ltd.

REGISTRANT: Merck and Company

VALIDATION CATEGORY: Supplemental

CATEGORY REPAIRABILITY: Yes, the study was classified supplemenal because the formulated product was used instead of the technical material. If a study using formulated product is necessary it may be categorized as core.

STUDY VALIDATION

DATA REVIEW NUMBER: ES-D-2

TEST: Avian subacute dietary LC_{50}

SPECIES: Bobwhite Quail

RESULTS: LC_{50} > 10,000 ppm.

Study followed accepted protocol using 14 day old birds and 5 concentrations levels. The concentrations ranged from 464 - 10,000 ppm. Two deaths were reported in the control group. Death was attributed to "toe picking". No deaths were reported in the treatment group.

CHEMICAL: thiabendazole technical, 98.5% a.i.

TITLE: Final Report - Eight day Dietary LC_{50} - Bobwhite Quail

ACCESSION #): 232421, Reg. No. 618-88

STUDY DATE: October 3, 1977

RESEARCHER: Robert Fink, Wildlife International Ltd.

REGISTRANT: Merck Chemical Division

VALIDATION CATEGORY: CORE

STUDY VALIDATION

DATA REVIEW NUMBER: ES-G-1

TEST: Acute 96 hour LC_{50} (Coldwater)

SPECIES: Rainbow trout (Salmo gardneri)

RESULTS: Acute LC_{50} (Matasol TK-100) = 2.46 ppm (1.96-3.04 ppm)
Acute LC_{50} (Thiabendazole) = 1.80 ppm (1.39-2.22 ppm)

The studies followed acceptable protocol (Stephan) with two exceptions: Test temperatures varied from 63°F - 68°F (17.2° - 20°C) throughout the test period. Recommended temperature is 12°C + 1°. The loading factor for the test was equal to or greater than 0.8g/l. (The exact amount of water in the test chamber was not given so the container volume (15l) was used for calculations.) This factor is adequate for tests run at recommended temperature but since higher temperatures were used, loading could have been a factor causing mortality.

Seven geometeracally arranged (1.8x) concentrations between 0.56 ppm and 18.0 ppm were used. No mortality occured at 0.56 ppm and 100% at 5.6 ppm.

CHEMICAL: Metasol TK-100, 20% solution and 2-(4'thiazolyl) benzimidazole (98.5% a.i.)

TITLE: Metasol TK-100, 20% solution and 2-(4'thiazolyl) benzimidazole safety tests in rainbow trout.

RESEARCHER: Woodard Research Corp., Carter D. Johnston, Ph.D.

REGISTRANT: Merck and Company

VALIDATION CATEGORY: CORE

CATEGORY RATIONAL. The study appears to be sound with the exception of higher than normal temperatures. Descrepencies as well as missing information were evident throughout the report, however, it is felt that they were detrimental to the registrant. Information not reported is:

1. capacity of the test vessels

2. D.O.%

3. % a.i. of test material (chemestry information accession no. 227331 indicates a.i. are 20.3% and 98.5% for Arbotect 20-S and thiabendazole respectively.

4. Statistical methods used to determine LC_{50}. (Attached is calculations of LC_{50} value using Finney, D.J., Probit Analysis, 1952.

STUDY VALIDATION

DATA REVIEW NUMBER: ES-F-1

TEST: Acute 96 hour LC_{50} (Warmwater)

SPECIES: Bluegill Sunfish (Lepomis macrochirus)

RESULTS: Metasol TK-100 (20% a.i.). LC_{50} = > 56.0 ppm.
thiabenzimidazole (Technical). LC_{50} = 22 ppm (19-27 ppm)

The study followed acceptable protocol (Stephan) testing both formulated product and technical material. Eight geometeracally arranged (factor 1.8x) concentrations between 0.56 ppm and 56 ppm were used. No mortality was observed at 5.6 ppm and [illegible] 100% mortality at 56.0 ppm. for the technical material.

Statistical methods used to determine LC_{50} were not referenced. Attached is calculations determining LC_{50} using method by J.D. Finney, Probit Analysis. The results closely compares to results stated in the report.

CHEMICAL: Metasol TK-100, 20% Solution; (Arbotec 20-S)
2-(4'thiazolyl) benzimidazole (98.5% a.i.)

TITLE: Metasol TK-100, 20% Solution and 2-(4'thiazolyl) benzimidazole safety tests in rainbow trout.

RESEARCHER: Woodard Research Corp., Carter D. Johnston, Ph.D.

REGISTRANT: Merck and Company

VALIDATION CATEGORY: CORE For both formulated and Technical material.

CATEGORY RATIONAL: N/A

STUDY VALIDATION

DATA REVIEW NO: ES-H-1

TEST: Aquatic invertebrate acute toxicity

SPECISE: Daphnia magna

RESULTS: 48 hour LC_{50} = 2.6 mg/l (2.1 - 3.1 mg/l conf. limits.) The study followed established protocol (Stephan 1975) using the Spearman - Kärber Estimation (Finney, 1971) to calculate LC_{50} levels and 95% confidence limits. Results expressed as weight (toxicant) per volume of water. Four replicates were used in each concentration with 5 individuals used per jar.

Concentration mg/l	PERCENT MORTALITY					
	Control	1.0	1.8	3.2	5.6	10.0
24 hr.	5%	0	5%	25%	25%	35%
48 hr.	5%	5%	25%	60¢	100%	95%

CHEMICAL: Arbotect 20-S (77 RTS 424) 20% a.i.

TITLE: The acute toxicity of arbotect 20-S to the water flea Daphnia magna straus.

ACCESSION NO.: 232421 (Pepition #618-88)

STUDY DATE: August 30, 1977

RESEARCHER: Union Carbide Corp. Environmental Services. Curt Hutchinson

REGISTRANT: Merk and Company, Inc.

VALIDATION CATEGORY: CORE

STUDY VALIDATION

DATA REVIEW NO: ES-C-2

TEST: Avian Acute Oral LD_{50}

SPECIES: Bobwhite quail

RESULTS: Avian Acute oral LD_{50} = 4640 mg/kg

Fourteen day old birds were tested on a period of 8 days. Five dosage levels were used 215, 464, 1000, 2150 and 4640 mg/kg. Birds at the 2150 and 4640 dosage level showed symptons of toxicity. The thiabendazole treated group as a whole showed a reduction in body weight gain over the 8 day test period. No mortalities were observed during the test period with the exception of the dieldrin controls

CHEMICAL: Thiabendazole technical, 98.5% a.i.

TITLE: Final Report Acute Oral LD_{50} - Bobwhite Quail Project No. 105-119, July 28, 1977

ACCESSION NO.: 232421 Reg. No. 618-88

STUDY DATE: July 28, 1977

RESEARCHER: Robert Fink - Wildlife International Ltd.

REGISTRANT: Merck Chemical Division

VALIDATION CATEGORY: Supplemental

CATEGORY Repairability: No. The study used 14 day old birds instead of 16 week old birds and was conducted for only 8 days instead of 14 days. Since the treated group (especially the three highest dosages) showed a statistically significant reduction in body weight gain, the study should have run to its full term. (14 days).

STUDY VALIDATION

DATA REVIEW NO: ES-C-3

TEST: Avian Acute Oral LD_{50} - Mallard Duck

SPECIES: Mallard Duck

RESULTS: Acute oral LD_{50} = > 4640 mg/kg

Study deviated from accepted protocal by using 14 day old birds instead of 16 week old birds and by conducting the test over an 8 day period instead of 14 days. Five dosage levels (215, 464, 1000, 2150 and 4640 mg/kg) were used. Within 4 hours after dosing, birds at the higest level exhibited signs of lethaigy, lower limb weakness, and loss of coordination, with one duck showing depression and reduced reaction to stimuli. By day 6 surviving birds were asymptomatic. Two deaths occurred on day 4 at the 215 mg/kg level and 1 on day 2 at the 4640 mg/kg level. The treated group as a whole showed a reduction in body weight gain over the 8 day test period.

CHEMICAL: Thiabendazole Technical, 98.5% a.i.

TITLE: Final Report - Acute Oral LD_{50} - Mallard Duck Project No. 105-118.

ACCESSION NO: 232421 Reg. No. 618-88

STUDY DATE: October 4, 1977

RESEARCHER: Robert Fink, Wildlife International Ltd.

REGISTRANT: Merck Chemical Division

VALIDATION CATEGORY: Supplemental

CATEGORY REPAIRABILITY: No. The study used 14 day old birds instead of 16 week old birds and was conducted for only 8 days instead of 14 days. Since the treated group showed a statistically significant reduction in body weight gain, the study should have run to full term (14 days) to see if other deaths or problems occurred.