#043401

DATE: 7-28-78

To: Product Manager 21 (Wilson)
TS-767

Through: Dr. Gunter Zweig, Chief
Environmental Fate Branch

Through: Mr. James Conlon, Acting Director
Hazard Evaluation Division, TS-769

From: Review Section No. 1
Environmental Fate Branch

Attached please find the environmental fate review of:

Reg./File No.: 1023-50

Chemical: Cycloheximide (Acticione)

Type Product: Fungicide

Product Name: None

Company Name: The Upjohn Co,

Submission Purpose: Data submission

Date in: 9-30-77

Date out: 7-14-78

EES BRANCH REVIEW

DATE: IN _____ OUT _____ IN 9/30 OUT 7/14/78 IN _____ OUT _____

FISH & WILDLIFE ENVIRONMENTAL CHEMISTRY EFFICACY

FILE OR REG. NO. 1023-50

PETITION OR EXP. PERMIT NO. 7F1890

DATE DIV. RECEIVED 9/29/77

DATE OF SUBMISSION

DATE SUBMISSION ACCEPTED 9/29/77 3C1D - No

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

PRODUCT MGR. NO. E. Wilson (21)

PRODUCT NAME(S) none

COMPANY NAME The UpJohn Co.

SUBMISSION PURPOSE EC-data submission

CHEMICAL & FORMULATION Cycloheximide

(3-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-

Hydroxyethyl]-glutarimide)

[actidione]

1.0 Introduction

1.1 Upjohn's letter of 27 September 1977, with the current data package of 14 EC-studies, requests reassessment of the data on the basis of its scientific adequacy.

2.0 Direction for Use.

See the previous review (2/7/77)

3.0 Discussion of Data

3.1 The registrant's summary of the data indicates Ref's #1, 2 & 3 contain both hydrolysis and photolysis data.

Ref #1

Garrett, E. R. and Notari, R. E.; "Determination of Cycloheximide and its Degradation Products Alone and in Mixtures." J. Pharm. Sci 54:561-564 (1965)

The study does not include hydrolysis or photodegradation data; but does give a spectophotometric procedure for determining cycloheximide and its potential degradates.

Ref #2

Garrett, E. R. and Notari, R. E.; "Cycloheximide Transformations I; Kinetics and Mechanisms in Aqueous Acid". J. Organ. Chem. 31 425-434 (1966)

The study was done with 0.1 M cycloheximide; the hydrolysis was followed by TLC. The data at PH 1.0 (40°C) indicates a parent halflife of less than 6-hours. Two TLC-fractions were separated; amhydrocycloheximide (II) was identified as the major fraction. The minor fraction, "P", was tentatively identified as an isomer of the parent compound (I).

Acid hydrolysis:

Compound I = Compound II + "P"

Ref #3

Garrett, E. R. and R. E. Notari. "Cycloheximide Transformation II) Kinetics and Stability in a Pharmaceutically Useful pH Range" J. Pharm. Sci.; 54: 209-215 (1966)

The hydrolysis of cycloheximide (0.0006M) was followed spectophotometrically in buffered solutions. Based on calculations from experimentally determined rate constants the following times are reported for a 10% hydrolysis * of the parent.

	Solution pH			
Temp °C	4.4	7.0	9.0	11.0
30	36-day	6.8 day	1.6 hr.	1.0 min.
20	105 day	11.0 day	2.6 hr.	1.7 min.

* The hydrolysis rate decreases as hydrolysis proceeds and the approximations made apparently did not permit a halflife calculation.

Neutral-Alkalin hydrolysis

Compd I = Compd V + *[glutarimide beta-acetaldehyde]

Compd V = Compd III + Compd IV

* An unstable intermediate; see Section 4.1 for chemical names of the other hydrolysis compounds.

Conclusions

The data, References #1, #2 & #3 are summarized in sections 4.1.1 and 4.1.2.

A mixture of cycloheximide and thiram (1:1) was used to treat (1.5 oz/1,000 sq. ft) for the control of fungi. Turf plots (10' x 20') composed of Drummer soil and sand (1:1) received 16 weekly treatments each summer for 5 years and a biannual topdressing of non-sterile soil and sand (1:1). After 4 and 5 years the distribution of fungal genera were determined in both test plots and an untreated control.

Data Summary (excerpts from Table II)

	Control		Cycloheximide-Thiram	
Genera	1 cm	3-4 cm	1 cm	3-4 cm
Aspercillus	X	X	X	X
Chaetomium		X		X
Cladosperium	X			
Curvularia	X		X	
Doratomyces		X		
Fusarium	X	X	X	X
Gliocladium	X	X	X	X
Penicillium	X	X	X	X
Pyrenochaeta	X	X	X	X
Sclerotibidium	X	X	X	X
Trichoderma	X	X	X	X

Conclusion

Fungi representative of the genera found in bentgrass were not significantly affected by cycloheximide. Since fungi are usually the most susceptable organisms, the data also shows cycloheximide will not significantly effect other soil microbes.

Although the recommended protocol has not been followed the data is considered scientifically adequate.

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3.3 Since references #4 through #14 have been reviewed (2/77), and do not contain new data, they will not be reviewed at this time. We have not been validating data (reviewing) following Dr. Rogoff's memo of 12 August 1977 to Mr. Campt.

4.0 Conclusions

4.1 The current data package contains data not previously reviewed:

4.1.1 Hydrolysis

The parent compound is most stable in acid solution and has an estimated halflife of more than 30-day in neutral solution. In alkalin solution (pH 9.0) the extrapolated halflife is less than one day.

Hydrolytic products:

Acid: Anhydrocycloheximide and an isomer of the parent compound

Neutral-alkalin: 3,4-dimethylcycloheximide (V); 3-glutarimidyl acetaldehyde (III) and 3-glutarimidyl acetic acid (IV)

4.1.2 Photodegradation

Data has not been reported (Ref #1, #2, #3); nor is data presented to support the registrants statement; "...cycloheximide does not adsorb light of the wave lengths present in sunlight..

4.1.3 Effects of the pesticide on soil microbes.

Although the recommended protocols was not followed, the data (Ref #8) shows soil fungi are not significantly effected by cycloheximide. Since fungi are the soil organisms most susceptible to pesticides, the data also shows cycloheximide will not significantly effect other soil microbes.

4.2 The previous review (2/77) noted both scientific and guideline deficiencies in the referenced data. The following summary notes the scientific acceptability of the data.

4.2.1 Soil Metabolism

Not acceptable because the aerobic soil metabolites were not identified. However the degradation rate was rapid, halflife was CA 3.0 days in spiked (0.2 ppm) soils.

4.2.2. The effect of the microbes on the pesticide.

The data is considered acceptable. In view of the rapid aerobic soil degradation additional data would not be relevant to the EC-hazard assessment.

4.2.3 Leaching

The data was considered acceptable in our previous review (2/77).

4.2.4 Field Dissipation

The data was considered acceptable in our first review (8/72).

4.2.5 Fish Accumulation

Based on reviewed (8/72) data neither cycloximide nor its reported degradates bioaccumulate. A one month feeding study with quail showed no buildup of residues. Supporting the feeding study are cycloheximides solubility in water (+2%) and partitioning data with organic solvent. The reported degradates are more polar than the parent.

Our review (2/77) of the fish data, although many deficiencies were noted, showed rapid dissipation of the observed residues (0.03-0.14ppm)

Unless either photodegradation or aerobic soil data, both of which are needed, show new degradates additional fish data will not be needed.

5.0 Recommendations

P.M. Note:

If the product is registered for use on bearing cherries, the proposed use falls under Mr. Johnson's memo

5.1 Photodegradation data is needed; see the suggested protocol included in our previous review.

5.2 The following data are not scientifically adequate.

(1) Aerobic soil Metabolism (120-9760-30) our review (2/7/77) noted several deficiencies in the submitted data, of particular importance is the identity of the soil degradates.

(2) Fish Accumulation (120-9760-48)

The deficiencies in this study are detailed in our previous review.

The submitted data did not indicate accumulation. However, the data cannot be reliably assessed because of the noted deficiencies. Particularly important in determining the acceptability of the data and the need for additional studies is the identity of both soil the metabolites (aerobic) and the photodegradates in water & on soil.

5.3 All of the environmental chemistry data required by the Section 3 Regulations will be needed at the time of registration.

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7/14/78