APPENDIX 1

Position Paper Title

DUPONT™ PUNCH™ (ACTIVE INGREDIENT: FLUSILAZOLE) AND DUPONT™ CHARISMA™ (ACTIVE INGREDIENTS: FLUSILAZOLE AND FAMOXADONE): SUMMARY OF DATA COMPILED IN SUPPORT OF A SECTION 18 EMERGENCY EXEMPTION REQUEST FOR CONTROL OF ASIAN SOYBEAN RUST ON SOYBEANS

Authors of Original Report and Revision 1

T. Cosgrove, L. Czochor, A. Dinter,
K. Jemberg, A. Klemens, A. Marçon,
B. McInnes, L. Mullin, M. Russell,
D. Ryan, S. Singles, V. Vanderbroeck

Data Requirement

None

Date

Original Report: December 16,2004

Revision No. 1: February 2, 2005

Author Locations

E. I. du Pont de Nemours and Company
DuPont Crop Protection
Stine-Haskell Research Center
Newark, DE 19714-0030
U.S.A.

and

DuPont de Nemours (Deutschland) GmbH
DuPont Str. 1
61352 Bad Homburg v.d.H.
Germany

DuPont Project Identification

DuPont-16101

Revision No. 1

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A), (B), or (C).

Company: E. I. du Pont de Nemours and Company

Company Agent: Lesley Palmer Czochor, Ph.D.

Senior Registration Product Manager
(Title)

Lesley Palmer Czochor
(Signature)

2/2/05
(Date)

GOOD LABORATORY PRACTICE STATEMENT

The requirements of 40 CFR Part 160 are not applicable to this report because no new experimental data are being presented.

Applicant/Sponsor

E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Applicant/Submitter

Lesley Palmer Czochor

Lesley Palmer Czochor, Ph.D.

2/2/05

Date

TABLE OF CONTENTS

TABLES

FIGURES

APPENDICES

ATTACHMENT

REASON FOR REVISION

The reason for revision of this Position Paper is to correct NOELs which were incorrectly cited for a two-year chronicloncogenicity study in rats and an 18-month chronicloncogenicity study in mice. The correct NOELs have been entered into the text on pages 18, 19, 29, and 31. Expanded product use rate ranges were also entered on pages 14 and 15.

INTRODUCTION

The information in this volume is provided in support of a section 18 emergency exemption application for use of the active ingredients flusilazole, product trade name DuPont Punch™ Fungicide, and flusilazole plus famoxadone, product trade name DuPont Charisma™ Fungicide, to control Asian soybean rust on soybeans. The volume follows the general format for a tolerance petition and contains sections:

A. Product Chemistry,
B. Proposed Use Directions (including Product Labels),
C. Toxicology and Ecotoxicology,
D. Residue and Environmental Fate,
E. Efficacy, and
F. Proposed Tolerance.

Flusilazole technical, Punch™, and Charisma™ are not yet registered in the United States. Famoxadone technical is registered in the US (EPA Reg. No. 352-605) and is one of the active ingredients in DuPont™ Tanos™ Fungicide (EPA Reg. No. 352-604). The summaries herein are designed to give a very brief overview of famoxadone and a more in-depth regulatory and scientific description and risk assessment of flusilazole and the products containing it. A copy of the US EPA Fact Sheet for famoxadone is provided at the end of this document in Attachment 1. The proposed use rate of famoxadone in Charisma™ on soybeans is much lower than the approved label rate for famoxadone in Tanos™ on any crop registered in the US, with fewer applications and a longer PHI.

GLOBAL REGULATORY BACKGROUND

Flusilazole is sold in about 40 countries around the world for use on such crops as grapes, stone fruit, pome fruit, cereals, oilseed rape, table and sugar beets, bananas, and soybeans. The major market is in Europe but there are important sales in Asia, Africa and South America. In particular, products containing flusilazole or flusilazole plus other fungicidal active ingredients, including famoxadone, have demonstrated efficacy against Asian soybean rust in South Africa, Brazil, and Argentina. Flusilazole is registered for use on soybeans in South Africa and Argentina, and registration is pending in Brazil. A Codex Maximum Residue Limit (MRL) for flusilazole on soybeans is not expected since residues are usually <0.01 ppm.

Flusilazole is currently being reviewed under the European Union (EU) re-registration process. The Rapporteur Member State (Ireland) and the technical experts from all EU Member States have agreed that all technical questions on flusilazole have been addressed and there is sufficient

information for the environmental and human risk assessments according to Directive 911414 EC. A decision on inclusion in Annex I is expected during 2005. In the meantime, Germany recently re-registered the major flusilazole product (Harvesan®) for 10 years after a very thorough review of data on flusilazole and a complete EU dossier on the product. New registrations continue to be granted globally in a broad range of markets demonstrating the continuing usefulness of flusilazole in agriculture.

Flusilazole technical and the Nustar® formulation were registered on apples in Canada in 1998 The following MRLs have been established in Canada for flusilazole; the MRLs for bananas, grapes, and raisins are for imported crops.

Raisins	1 ppm
Grapes	0.5 ppm
Apples	0.2 ppm
Bananas	0.1 ppm
Meat and meat byproducts of cattle, milk	0.01 ppm *

*expression includes flusilazole + bis(4-fluorophenyl)(methyl)silanol + 1*H*-1,2,4-triazole

Famoxadone is registered in more than 60 countries on such crops as grapes, cucurbits, tomatoes, potatoes, head lettuce, oilseed rape and cereals. The major market is in Europe, but it is also sold in North and South America, and Asia. A registration application is pending in Brazil for Charisma™ on soybeans. The default MRL in the EU for famoxadone on soybeans is set at 0.02 ppm.

US REGULATORY BACKGROUND - FLUSILAZOLE

In the US, registration activity on flusilazole (Pc Code 128835) began in the mid-1980s with applications for and approval of several Experimental Use Permits on products containing flusilazole, including Nustar® (20% Dry Flowable) and Punch™ 25 and 40 EC.

Year	Crop	Product	Reg. No.	Petition No(s).	Comments
1984	Peanut	40 EC*	352-EUP-118	4G3064, 5H5477	withdrawn
1984-1989	Apples	Nustar® DF	352-EUP-123	5G3165 and 5H5449	
1985-1987	Apples	40 EC*	352-EUP-126	NA	crop destruct
1984-1989	Table grapes	40 EC* & Nustar® DF	352-EUP-125	5G3196 and 8H5556	
1985	Table grapes	40 EC*	352-EUP-127	NA	crop destruct
1990	Wheat, barley	Punch™ 25 EC	352-EUP-155	0G3886	

(* Not the same 40EC formulation as the Punch™ product proposed herein.)

The following temporary tolerances were established under those EUPs:

Apples	0.2 ppm
Apple Pomace	1.5 pprn
Table Grapes	0.05 pprn
Wheat	0.05 pprn
Barley	0.05 pprn
Straw, wheat and barley	1.0 pprn
Meat/Meat Byproducts	0.01 pprn
Milk	0.01 ppm
Liver	0.1 ppm

The following temporary tolerances were proposed by DuPont, and reviewed and accepted by EPA, but not established because the EUP was withdrawn.

Peanuts	0.3 pprn (not established)
Peanut hulls	1.0 pprn (not established)
Peanut oil	1.5 pprn (not established)
Poultry	0.01 pprn (not established)
Eggs	0.01 pprn (not established)

In 1986, a registration application was submitted for Nustar® (File Symbol 352-LNU) on apples and grapes (PP Nos. 7F3491 and 7H5530). In 1987, an application was submitted for an import tolerance for flusilazole on bananas (PP No. 7E3515). Those applications are pending at US EPA.

DuPont's interest in pursuing a section 3 registration in the US for flusilazole products on soybeans is a direct result of their recent outstanding performance against Asian soybean rust in several countries, including South Africa, Zimbabwe, France, Brazil and Argentina. (See Section E). The Homeland Security Act of 2004 provided for the creation of the National Plant Disease Recovery System (NPDRS) with a list of target pathogens and vectors of concern. In accordance with that, USDA and EPA had contacted CropLife America earlier this year and requested that the CLA membership provide any global efficacy testing or other information on chemistries that may provide protection against the target pathogens/vectors. DuPont sent a flusilazole formulation sample (Capitan® 25EW) to USDA for testing in Illinois, and flusilazole will also be a part of USDA tests in Zimbabwe, South Africa, and Paraguay for the 2005 season (they will evaluate 125 g ai/ha). USDA has tested Punch™ formulations in Zimbabwe and demonstrated its activity. These formulations are described in the Residue and Efficacy Sections D and E.

A substantial database of supporting studies has already been submitted to and reviewed by US EPA in support of the prior registration actions, above. Additional studies have been conducted in the interim to support our global registration efforts and have also been (or will be) submitted to EPA in support of the section 3 registration application for Punch, targeted for the first quarter

2006. Several other studies have been identified as specifically required for US registration and these are either in progress or will begin in 2005. A brief list of these studies is provided below.

Product Chemistry
•Stability to elevated temperature, metals, and metal ions with technical
.Physical and chemical characteristics studies to US EPA Guidelines on Punch and Charisma (EU Guideline study results are reported herein)

Ecotoxicology
•Acute toxicity to oysters - shell deposition
•Acute toxicity to mysid shrimp
•Acute toxicity to sheepshead minnow
Chronic toxicity to mysid shrimp
•Chronic toxicity to sheepshead minnow
•A waiver will be requested for the cbironomid sediment toxicity test with *Chironomus tentans* (a *Chironomus riparius* study will be submitted in support of the waiver)
•Algal toxicity *(Anabaena, Navicula, Skeletonema)*
•Aquatic plant toxicity – *Lemna*

Metabolism/Residues
•Soybean residue and processing studies in progress
-Soybean metabolism study planned
•Some additional analytical methodology may be needed

US REGULATORY BACKGROUND - FAMOXADONE

Famoxadone technical and Tanos™ fungicide are registered in the US (EPA Reg. Nos. 352-605 and 352-604, respectively). Tanos™ is used to control various diseases such as early blight, late blight, Anthracnose, downy mildew, etc., on cucurbits, head lettuce, peppers, potatoes, and tomatoes.

The following tolerances have been established in the US for famoxadone (40CFR Part 180.587):

Commodity	Parts per million
Cattle, fat	0.02
Cattle, liver	0.05
Goat, fat	0.02
Goat, liver	0.05
Grape[1]	2.50
Grape, raisin[1]	4.0
Horse, fat	0.02
Horse, liver	0.05
Lettuce, head	10.0
Milk, fat (reflecting negligible residues in whole milk)	0.06
Potato	0.02
Sheep, fat	0.02
Sheep, liver	0.05
Tomato	1.0
Vegetable, cucurbits, group 9	0.30
Vegetable, fruiting, group 8 except tomato	4.0

[1]There are no U.S. registrations as of May 15,2003

To support a US registration for Charisma on soybeans, additional studies are planned (soybean residue and metabolism, etc.) and the application to US EPA is targeted for submission in the 2Q 2007.

A. PRODUCT CHEMISTRY

Physical Properties of DuPont Punch™ Fungicide (DPX-H6573-384)

Punch is an emulsifiable concentrate formulation containing 37.8% flusilazole as the active ingredient. A confidential statement of formula is available upon request. An analytical method for the determination of flusilazole content in the Punch formulation is also available.

Attribute	Method	Results
Flashpoint	EEC A.9	94 C
pH	CIPAC MT 75	5.29
Relative Density	Paar Mettler Density Meter	1.062 g/mL @ 20°C
Low Temperature Stability	CIPAC MT 39	No separation after 1 week @ 0°C
Shelf Life Stability	Real Time Storage Container: I-liter commercial container, white high-density polyethylene with a sealable closure. After completion of 2 years storage, there was no evidence of seepage, corrosion or degradation.	As made: 37.9% After 2 years storage: 37.7%

Physical Properties of DuPont Charisma™ Fungicide (DPX-MC444-18)

Charisma is an emulsifiable concentrate formulation containing 9.73% flusilazole and 9.12% famoxadone as the active ingredients. A confidential statement of formula is available upon request. Analytical methods for the determination of flusilazole and famoxadone contents in the Charisma formulation are also available.

Attribute	Method	Results
Flashpoint	EEC A.9	>100°C
pH	CIPAC MT 75	5.6
Relative Density	Paar Mettler Density Meter	1.097 g/mL @ 20°C
Low Temperature Stability	CIPAC MT 39	Good: <0.05 mL of sediment after 1 week @ 0°C
Shelf Life Stability	Container: I-liter commercial container, white high-density polyethylene with sealable closure. Seal was completely intact. Although the container was slightly paneled (drawn in on both sides), there was no evidence of seepage, degradation or corrosion.	As made: Famoxadone: 102.1 g/L Flusilazole: 109.8 g/L After 2 years storage: Famoxadone: 101.8 g/L Flusilazole: 108.4 g/L

B. PROPOSED USE DIRECTIONS

(PROPOSED PRODUCT LABELS PROVIDED SEPARATELY)

GENERAL INFORMATION - DUPONT™ PUNCH™

PUNCH™ is a locally systemic fungicide recommended for the control of Asian soybean rust on soybeans.

The Reentry interval for soybeans is 12 hours.

Apply as a spray with ground, air, or chemigation equipment, except as othenvise directed, using sufficient water to obtain thorough coverage of plants. Use only in commercial or farm plantings. Not for use in home plantings nor once any commercial crop is turned into U-Pick, Pick Your Own or similar operation.

CROP ROTATION RESTRICTIONS

Soybeans may be re-planted anytime after PUNCH™ applications. All other crops cannot be planted until 30 days after PUNCH™ application.

PUNCH™ rapidly penetrates into plant tissues and is rainfast within 1 hour after application.

USE RATES AND APPLICATION TIMINGS

Rate

Use PUNCH™ at 3 - 4 fl oz per acre for control of Asian soybean rust (*Phakopsora pachyrhizi*).

Application Information

Apply PUNCH™ as a broadcast foliar spray.

- Apply PUNCH™ on a 14-21 day schedule.
- Do not apply PUNCH™ within 30 days of harvest.

Apply no more than 2 applications per 12 month period.

GENERAL INFORMATION - DUPONT™ CHARISMA™

CHARISMA™ is a locally systemic fungicide recommended for the control of Asian soybean rust on soybeans.

The Reentry interval for soybeans is 12 hours.

Apply as a spray with ground, air, or chemigation equipment, except as otherwise directed, using sufficient water to obtain thorough coverage of plants. Use only in commercial or farm plantings.

Not for use in home planting nor once any commercial crop is turned into U-Pick, Pick Your Own or similar operation.

CROP ROTATION RESTRICTIONS
Soybeans may be re-planted anytime after CHARISMA™ applications. All other crops cannot be planted until 30 days after CHARISMA™ application.

CHARISMA ™ rapidly penetrates into plant tissues and is rainfast within 1 hour after application.

USE RATES AND APPLICATZON TIMINGS

Rate
Use CHARISMA™ at 8 - 10 fl oz per acre for control of Asian soybean rust (*Phakopsora pachyrhizi*).

Application Information
- Apply CHARISMA™ as a broadcast foliar spray.
- Apply CHARISMA™ on a 14-21 day schedule.
- Do not apply CHARISMA™ within 30 days of harvest.
  Apply no more than 2 applications per 12 month period.

C. TOXICOLOGY AND ECOTOXICOLOGY

C1. Toxicology

ACUTE TOXICITY STUDIES

Study	Result	Toxicity Category	Reference
	Technical material		
Acute Oral LD50 in Rats	1110 mg/kg M 674 mg/kg F	III	MRID 40042106
Acute Dermal LD50 in Rabbits	> 2000 mg/kg	III	MRID 40042107
Acute Inhalation LC50 in Rats	> 5 mg/L	IV	MRID 40042109
Eye Imtation in Rabbits	Slight	IV	MRID 40357501
Skin Imtation in Rabbits	Moderate	III	7443 TAL, 1991
Skin Imtation in Guinea Pigs	Mild		MRID 40357502
Guinea Pig Skin Sensitization	Not a sensitizer		MRID 40357502
	PUNCH™ 40EC		
Acute Oral LD50 in Rats	1696 mg/kg	III	12133 TAR, 1994
Acute Dermal LD50 in Rabbits	> 2000 mg/kg	III	12134 TAR, 1994
Acute Inhalation LC50 in Rats	> 4.9 mg/L	IV	MRID 41567606
Eye Irritation in Rabbits	Minimal	IV	11593 TAL, 1994
Skin Imtation in Rabbits	None	IV	12135 TAL, 1994
Guinea Pig Skin Sensitization	Not a sensitizer		12136 TSG, 1994
	CHARISMA™ EC		
Acute Oral LD50 in Rats	1885 mgkg	III	HLR 840-95
Acute Dermal LD50 in Rabbits	> 5000 mgkg	IV	HLR 94-96
Acute Inhalation LC50 in Rats	Not tested	(IV)	
Famoxadone tech	> 5.3 mg/L		MRID 44302410
Flusilazole tech	> 5 mg/L		MRID 40042109
Eye Irritation in Rabbits	Minimal clearing in 24 hours	IV	HLR 721-94
Skin Imtation in Rabbits	Slight	IV	HLR 90-96
Guinea Pig Skin Sensitization	Not a sensitizer		HLO 11-96

SUBCHRONIC TOXICITY STUDIES

In a 90-day study in rats fed 0, 25, 125 375 or 750 pprn flusilazole, serum cholesterol was significantly elevated in males at ≥ 375 pprn and in females at 750 ppm. There were increased liver weights in both sexes at 750 pprn (MRIDs 00072421,00161400). The only treatment-related histopathologic effect was mild liver degeneration in males at 750 ppm, and mild bladder mucosal hyperplasia in males and females at ≥375 ppm. The NOAEL was 125 pprn (9-11 mg/kg/day).

In a 90-day feeding study in mice fed 0, 25, 75, 225, 500, and 1000 ppm, the following were observed: a mild hemolytic effect at 1000 ppm; increased liver weights at ≥75 ppm; reduced kidney weights at 1000 ppm; and histopathologic changes of the liver at ≥ 75 pprn in females and of the urinary bladder at ≥ 225 pprn (MRID 40042111). The NOEL for liver effects (and for the study) was 25 pprn (4-5 mg/kg/day).

A second mouse feeding study was conducted to attain an MTD and evaluate mechanisms of effects (MRID 41514901). Mice were fed diets containing 0, 1000, 1500 or 5000 pprn flusilazole for 90 days. Compound related effects observed on the study included cardiomyopathy and increased mortality (5000 pprn males), decreased body weight and food efficiencies (all males and 5000 pprn females), alterations in hematological parameters (5000 pprn males and females), increased liver weights, liver cytoplasmic vacuolation and hypertrophy, and bladder hyperplasia and hypertrophy, in all males and females. Increased cellular proliferation was demonstrated in the bladder epithelium of males and females ≥1500 ppm and 1000 ppm males. A NOEL was established in the previous study.

Beagle dogs were fed diets containing 0, 25, 125, or 750 pprn (lowered to 500 pprn after 3 weeks) flusilazole for 90 days (MRID 00161168). Effects observed included severe weight loss, clinical chemistry and liver weight changes and evidence of cellular proliferation in the urinary bladder. A NOEL of 25 pprn (0.9 mg/kg/day) was based on bladder histology and liver effects.

Rabbits had flusilazole applied to skin at 1, 5, 25 or 200 mg/kg/day 6 hours daily for 21 days (MRID 40042119). Clinical signs of toxicity at 200 mg/kg/day included slight to mild erythema, diarrhea, and lung noise. Liver weights in females were increased at ≥5 mg/kg/day. No histopathology related to systemic effects occurred. Therefore the increased liver weight was considered an adaptive change. EPA has determined the NOAEL for systemic effects was 200 mg/kg/day, the highest dose tested.

In summary, toxicity on short-term exposure to flusilazole was investigated in feeding studies in rats, mice, and dogs and by dermal application in rabbits. The targets identified were the blood system, liver and urinary bladder. The most sensitive species was the dog, with a NOAEL of 0.9 mg/kg/day.

LONG-TERM TOXICITY AND CARCINOGENICITY

The chronic toxicity and carcinogenicity of flusilazole has been investigated in two rat, two mouse, and one dog feeding studies.

In the first feeding study, rats were fed diets containing 0, 10, 50 or 250 pprn flusilazole for 24 months (MRID 00148511). The only treatment-related effects were adaptive histopathological effects that were seen in the livers (increased liver weight and hepatocellular hypertrophy) of females at the one-year interim sacrifice. These changes either resolved (50 ppm) or progressed to diffuse fatty change and acidophilic foci (250 ppm) by the end of two years. There was no treatment-relatedincrease in tumor incidence in either sex. The NOAEL was 50 pprn (2.0-2.6 mgikglday).

A second, two-year chronic toxicity and carcinogenicity flusilazole feeding study was carried out in the rat to achieve an MTD (MRID 42613202). Rats were fed diets containing 0, 125, 375, and 750 pprn flusilazole for two years. Toxicologically significant effects of treatment with flusilazole were seen at every dose level in this study. The following were also observed: mortality (5) and induced hepatocellular hypertrophy, fatty change and mixed cell foci, testicular interstitial cell hyperplasia and interstitial cell adenomas in males; decreased mean final body weight and hepatocellular centrilobular hypertrophy in females; and increased mean absolute and relative liver weights, hepatocellular lamellar bodies, urinary bladder mucosal hyperplasia, and transitional cell neoplasms in both sexes. There was no NOEL for non-neoplastic lesions in either sex. The NOEL for neoplasms was 375 pprn (14.8 and 20.5 mg/kg/day in males and females, respectively).

In the first 18-month carcinogenicity study, mice were fed diets containing 0, 5, 25 and 200 pprn (MRID 40042114). Liver weights were significantly increased at the high dose (both sexes at interim sacrifices, males at terminal sacrifice). Increased hepatocellular fatty change occurred at the high dose and was considered sublethal and reversible in the absence of other hepatic injury. Flusilazole was not carcinogenic. The NOEL was 25 pprn (3.4-4.6 mg/kg/day).

A second 18-month feeding study was conducted to achieve an MTD (MRID 42613201). Male mice were fed diets containing 0, 100,500 or 1000 pprn flusilazole; females were fed 0, 100, 1000 or 2000 ppm. Toxicologically significant effects were seen in mice on fed flusilazole for 18 months and included decreased mean (adjusted for liver weight changes) body weights and weight gains, decreased survival, increased absolute and relative liver weight, liver pathology, liver tumors, urinary bladder hyperplasia and urinary bladder cell proliferation in both sexes. In addition, males exhibited increased clinical signs and females had urethral hyperplasia. The NOEL for oncogenicity was 500 pprn in males (73.1 mg/kg/day) and 100 pprn (19.4 mg/kg/day) in females. There was no NOEL for non-neoplastic effects due to the findings at all dose levels. The NOEL was established on the previous study.

In a one-year feeding study, dogs were given flusilazole in the diet at concentrations of 0, 5, 20, and 75 pprn (MRID 40042113). There were treatment-related effects on hematological parameters at 75 pprn including increased white blood cell count, ALP activity, and serum

cholesterol. Serum total protein and albumin levels were lower in the male high dose group. Relative liver weight was increased at 75 ppm. Treatment-related histopathological changes included liver centrilobular hepatocellular enlargement and centrilobular inflammation and hyperplasia in the lymphoid nodules of the gastric mucosa observed in the high dose. In summary, the effects of feeding flusilazole to dogs for one year were a dose-related trend towards mild to moderate hepatotoxicity and a mild leucocytosis (inflammatory) response. The effects were mainly seen in the high dose group and most pronounced in males. The liver hypertrophy was considered likely to be an adaptive response to increased metabolic demand. Based on minimal liver histology at the mid-dose, 20 ppm (0.7 mg/kg/day) is considered a NOAEL.

Summary and Conclusions of Chronic Toxicity and Carcinogenicity Studies

The dog was the most sensitive species in chronic flusilazole studies. The effects in the one-year dog study were mild to moderate hepatotoxicity and mild leucocytosis (inflammatory) response. The NOAEL was 0.7 mg/kg/day in the chronic dog study. The NOEL for chronic effects (non-neoplastic hepatotoxicity) was 2 mg/kg/day in the rat and 3.4 mg/kg/day in the mouse. Therefore the dog NOAEL of 0.7 mglkglday is the endpoint for chronic toxicity.

In the rat, target organs were consistent with the subchronic administration studies, i.e., liver and bladder. Flusilazole was oncogenic at the higher doses, causing bladder transitional cell neoplasia in both sexes and testicular Leydig cell adenomas in males. There was evidence for proliferative effect of the test substance in the bladder transitional epithelium. It can therefore be concluded that the urinary bladder tumors were caused by an epigenetic, threshold-associated mechanism. Based on subsequent mechanistic work (see mechanistic section that follows) interference of flusilazole with hypothalmic-pituitary-gonadal(HPG) axis is a possible mechanism of testicular tumor induction. Therefore, it is reasonable to conclude that a threshold exists for the induction by flusilazole of testicular adenomas. The NOEL for neoplasms was 375 pprn (14.8 and 20.5 mglkglday in males and females, respectively).

In the mouse, target organs included the liver, kidney, urinary bladder and urethra. Significant histopathological change was observed in the liver at doses below those resulting in oncogenicity. The incidence of hepatocellular adenomas was significantly increased in females from $\geq$1000 pprn and of hepatocellular carcinomas at 2000 ppm. Based on the combined results of both studies, the NOEL for oncogenicity was 200 pprn (36 mgkglday) in females and 500 pprn (73.1 mg/kg/day) for males. The increased incidences of liver tumors occurred at doses in excess of the MTD. Histopathological changes consistent with induction-related hepatotoxicity were observed at lower doses and considered to be precursors to tumor development. In the light of these observations and the lack of genotoxic potential, it is reasonable to conclude that the induction of such tumors was associated with cytotoxicity and subsequently increased cell turnover. These events suggest a threshold for flusilazole-induced mouse liver tumors.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The reproductive toxicity of flusilazole was investigated in a one-generation and two multigeneration studies in rats and ten developmental toxicity studies, six in rats (one dietary, four gavage, one dermal) and four in rabbits (one dietary and three gavage). The purpose of the multiple developmental studies was to better define the dose-response relationship and in the rats several studies were conducted with an extended dosing period to comply with guideline revisions.

Reproduction Studies in Rats

A single generation, single litter study was carried out as a continuation of a 90-day feeding study in the rat at doses of 0, 25, 125 and 375 pprn (MRIDs 00072421,00161400). Reproductive parameters were decreased in the high dose group were gestation index (all pups were born dead in 215 dams), the percentage of pups born alive per litter, the percentage of litters surviving to until weaning and the mean pup weight on day 4 post-partum. The NOEL was 125 pprn (11 mg/kg/day).

The first multigeneration study was conducted as a substudy of a two-year feeding study (MRID No. 00148511). Flusilazole was fed to rats at dietary concentrations of 0, 10, 50 and 250 pprn for 90 days after which they were mated twice to produce that F1a and F1b offspring. Selected F1b offspring were fed for 90 days to produce two F2 litters. Reproduction and lactation parameters reduced primarily in the high dose group were: the percentage of pups born alive, offspring/litter survival, and pup weights. Liver weights were increased in the F2b 250 pprn pups with no gross or histopathological lesion detected. The NOEL for the reproduction study was 50 pprn (4 mg/kg/day) based on the perinatal effects at 250 ppm.

In a second multigeneration study, flusilazole was administered to rats in diet at 0, 5, 50, and 250 pprn for a 73-day premating period and continued throughout gestation, lactation, weaning and production of the second-generation litters (MRID 41684601). One set of litters was produced in the first generation and two in the second generation. Effects in parental females were lower final body weight and minimal hepatocellular hypertrophy at 50 ppm. EPA previously determined NOEL for systemic effects was 5 pprn (0.35 mgkglday); however, 50 pprn (4.1 mg/kg/day) was considered to be an NOAEL. Reproductive effects included prolonged gestation length and decreased number of pups born alive at 250 ppm. The reproductive NOEL was 50 pprn (4.1 mgkglday). Offspring effects observed at the high dose included litter viability and survival and pup weights. There were no gross necropsy findings in parental animals or litters in either generation. The NOEL for offspring effects was 50 pprn (4.1 mg/kg/day).

In summary, the effects of flusilazole on reproductive parameters were investigated in one single-generation and two multigeneration studies. In the single-generation study, there were effects on pup viability and weights. In the first multigeneration study, there was no parental toxicity demonstrated at doses up to 250 ppm. Offspring findings, mostly at the high dose level included reduced number of live pups at birth and reduced viability during lactation. The NOEL for this study was 50 ppm based on perinatal effects. The same dose levels were used in the

second study. Minimal signs of treatment-related effects seen in the 50 (not significant) and 250 pprn parental animals consisted of body weight effects in parental females. A significant increase in gestation length and periparturient deaths occurred in the high dose group. This finding was consistent with reduced viability of pups at birth. In addition, pups did not thrive and reduced weight gain and survival was recorded for litters of dams fed 250 pprn in all matings. The NOEL for reproductive/offspring effects was 50 ppm.

Developmental Toxicity Studies in Rats

In one feeding and three gavage studies, pregnant rats were given flusilazole on days 7-16 of gestation and sacrifice on gestation day 21. In another gavage study and a dermal study the dosing period was extended according to more recent guidance (dosed days 6-15 or 6-20 for the gavage and 6-19 dermal studies, respectively)

In the feeding study, dietary concentrations were 0, 50, 100,300 and 900 pprn (MRID 00072999). Maternal food consumption was reduced at ≥ 300 pprn during treatment and maternal body weight gains were reduced at 900 ppm. The number of resorptions was significantly increased at the two highest doses and litter size was reduced at the highest dose. There was a significant dose related increase in stunted fetuses, significant at ≥ 300 ppm. There were no dose-related incidences of malformations. The incidence of variations (supernumerary and delayed ossifications) was increased at ≥ 100 ppm. The maternal NOEL was 100 pprn (9 mg/kg/day). EPA considered the developmental NOAEL to be 100 ppm (9.0 mg/kg/day) and the NOEL for malformations to be > 900 pprn (79.2 mg/kg/day) the highest dose tested.

In the first of three rat gavage studies, flusilazole was administered by gavage (in corn oil) at concentrations of 0, 10, 50 and 250 mgikgiday (MRID 00161169). Maternal morality and clinical signs occurred at 250 mgkgiday. Weight gain and food consumption were decreased and liver weight increased at ≥ 50 mg/kg/day group during dosing. In the 250 mgkgiday group mean fetal body weight was reduced; the incidence of resorptions increased; and the number of live fetuses per litter were reduced. The number of live fetuses was also decreased in the intermediate group. There was a significant increase in malformations (cleft palate and absent renal papillae) at the maternally toxic dose, 250 mg/kg/day. There was an unusually high incidence of external hydrocephaly and distended lateral ventricles in all groups (including controls). However, this finding did not exhibit a definitive dose response and was not reproduced in another study over a similar dose range. Increased fetal variations in all dosed groups were misaligned sternebra, extra ossifications, rudimentary and extra ribs and delayed development consisting of partially ossified sternebra and vertebral arch. The maternal NOEL was 10 mg/kg/day and no fetal NOEL was established (< 10 mgikglday).

In the second gavage study, flusilazole was administered to rats at doses of 0, 0.4, 2, 10, 50, and 250 mgkglday (MRID 00161170). Maternal findings at 250 mgikgiday were reduced feed consumption and weight gain and increased liver weights. At 50 mg/kg/day, there was a significant decreased food consumption and weight for the first two days but not thereafter. Relative liver weight was increased also at 50 mgkglday. A non-statistically significant increase in stunted fetuses occurred at ≥ 10 mg/kg/day. There was a statistically significant increase in malformations (cleft palate) in the maternally toxic, high-dose group. The incidence of total

malformations (mostly absent renal papillae) and fetal variations were significantly increased at ≥ 10 mg/kg/day. The maternal NOEL 10 mg/kg was based on reduced weight gain, liver weight increases and clinical signs. The developmental NOEL was 2.0 mg/kg, based on increased incidence of skeletal variations.

The third rat developmental gavage study, was conducted to resolve the biological significance and potential reversibility of the changes to the urinary system (small or no papillae, large renal pelvi and dilated ureter) seen in the previous study (MRID 40640704). Rats were dosed with 0, 0.2, 0.4, 2, 10, and 100 mgkglday and either sacrificed at gestation day 21 or 22 to examine fetuses (Phase 1) or dams were allowed to deliver and raise their young to weaning (Phase 2). Maternal toxicity was evidenced at the high dose in both phases as decreased food consumption and reduced weight gain, clinical signs (Phase 1 only), and death (Phase 2). Minimal maternal toxicity (reduction in weight gain during Phase 2) occurred 10 mg/kg/day. Fetal effects consisted of increased incidence of resorptions and stunted fetuses (100 mg/kg/day), increased numbers of fetuses dead at birth, and lower neonatal survival. In the fetal examinations there was an increased incidence of small renal papillae, dilated ureters and subcutaneous hemorrhage at ≥ 10 mglkglday and bladder foci at 100 mg/kg/day. There were no apparent treatment-related malformations. The maternal and reproductive/developmental was NOAEL 2.0 mg/kg/day.

In the fourth rat gavage study (MRID 45042601), rats were dosed with 0, 0.5, 2, 10, or 50 mg/kg/day flusilazole on one of the following three schedules: days 6-15G (gestation) and sacrificed day 16G, days 6-15G and sacrificed day 21G, or 6-20G and sacrificed on day 21G. Results were generally similar between the three designs. Maternal weight gain was affected at ≥10 mg/kg/day. Red vaginal discharge was observed at 2 mg/kg/day. Placental weights were increased at ≥2 mg/kg/day. Fetal weights were affected at 50 mg/kg/day only in the group dosed from 6-15G and sacrificed at 21G. Fetal resorptions were increased at ≥10 mg/kg/day. Fetal variations were increased at ≥2 mg/kg/day. At 50 mgkglday there was one malformation (naris atresia). The NOEL for the study was 0.5 mg/kg/day based on minimally increased incidence of red vaginal discharge, increased placental weight and increased fetal variations at 2 mg/kg/day.

In a rat dermal developmental toxicity study (MRID 44594201), flusilazole was applied to the skin of pregnant rabbits for six hourslday on days 6 to 19 of gestation at doses of 0, 2, 10, 50, and 250 mg/kg/day. Rats were sacrificed on gestation day 20. Mean maternal weight gains were greatly reduced in the 250 mg/kg/day group. There were no abnormal clinical signs at any concentration. Microscopic examination of the dams' livers revealed minimal to mild centrilobular hepatocellular hypertrophy at ≥ 10 mg/kg/day. There were enlarged placenta observable at ≥ 10 mgkglday and microscopic placental changes at all dose levels. There were no other maternal effects at 2 mg/kg/day. Fetuses of dams treated with ≥ 10 mg/kg/day had enlarged livers and increased variations (rudimentary ribs and unossified sternebra). The lowest dose (2 mg/kg/day) was considered to approximate a NOAEL with the only effect being microscopically observable placental changes. It was not established whether the effect on placenta represent an adverse effect. Since placenta contains a large amount of cytochrome P-450 enzymes, the possibility of a metabolic/adaptive role should be considered.

Developmental Toxicity Studies in Rabbits

In a feeding study in rabbits, pregnant rabbits were fed 0,300,600 and 1200 pprn days 7-19 of gestation and sacrificed on day 29 (MRID 00154930). Because no NOEL was demonstrated, a second part was initiated in which pregnant rabbits were fed 0, 30, 100 or 300 ppm. Maternal toxicity was indicated by reduced food consumption, mean weight loss and reduced weight gain during treatment at 1200 ppm. The number of pregnant females was lower and total resorptions increased at ≥ 300 ppm. EPA previously concluded that the NOEL for this study is 600 pprn (21.2 mg/kg/day) for the dam and 100 pprn (2.8 mg/kg/day) for developmental effects based on increased resorptions at higher doses.

In three gavage studies, pregnant rabbits were dosed with flusilazole on days 7-19 of gestation and sacrificed on gestation day 29. In the initial study, doses were 0, 2, 5 or 12 mg/kg/day (MRID 00148512). There were no compound related effects at any level and the maternal and developmental NOEL was greater than the highest dose tested. In the second study, doses were 0, 12 and 35 mglkgiday (MRID 00154929). There was only one litter produced in the 35 mg/kg/day group. This doe had a net weight loss over the treatment period. The other does in this group either aborted or resorbed. There was one incidence of hydrocephaly (114 fetuses) in the high dose group. The maternal and developmental NOEL was 12 mg/kg/day.

The last rabbit developmental study was conducted to clarify tbe dose-response ielationship between 12 and 35 mgkglday (Alvarez, 216-90). Rabbits were dosed with 0, 7, 15 or 30 mg/kg/day. Maternal toxicity was demonstrated by an increase in clinical signs (vaginal staining) at ≥ 15 mg/kg and decreased food consumption in the high dose group. There was one death and only three does were pregnant in the high dose group. Total resorptions were increased in the high dose group. There were no increases in either malformations or variations at any dose level. However, the numbers of fetuses available for examination in the high dose group, and to some extent the intermediate group, were reduced by embryolfetal mortality. There was one hydrocephalic fetus in both the intermediate and high dose group. In conclusion, there was an impaired ability to maintain pregnancy at ≥ 15 mgikglday, demonstrated by increased total resorptions. The maternal NOAEL was 7 mg/kg/day and the developmental NOEL was 15 mgkglday.

Summary of Developmental Toxicity Studies

Six developmental toxicity studies have been conducted with flusilazole in rats (one feeding, four gavage, and one dermal). Four developmental toxicity studies have been conducted in rabbits (a single feeding study and three gavage studies).

In a rat developmental feeding study the NOEL for maternal and developmental effects was 100 pprn (9 mgkglday) based on reduced weight gain and increased resorptions and stunted fetuses at the next highest concentration (300 pprn). There were no increases in malformations at any concentration.

In the first rat gavage study, the matemal NOEL was 10 mgkglday based on decreased weight gain and increased fetal weights. No developmental NOEL (<10 mgikglday) was established based on increased fetal variations in every treatment group. In the second gavage study, the maternal NOEL of 10 mgikg was based on reduced weight gain and food consumption, clinical signs, and liver weight increases. The developmental NOEL was 2.0 mg/kg, based on increased incidence of skeletal variations at 10 mg/kg/day or above and malformations at 250 rngikglday. In the third rat gavage study, the maternal NOEL was 2 mg/kg/day based on minimal effects on matemal weight gain at 10 mg/kg/day. The developmental NOEL is 2.0 mgikglday based on urinary system effects at ≥ 10.0 mgikglday. In the final rat gavage study the NOEL was 0.5 mgkglday based on minimal increases in red vaginal discharge incidence, increased placental weight, and skeletal variations at 2 mgikglday.

In the rat dermal developmental study 2 mg/kg/day was near a NOAEL since the only effect observed were microscopic placental changes without accompanying adverse fetal effects. At the next highest dose, 10 mg/kg/day, maternal effects included minimal to mild centrilobular hepatocellular hypertrophy and enlarged placenta. Fetal effects at 10 mg/kg/day were enlarged livers and increased variations (rudimentary ribs and unossified stemebra). It was not established whether the effect on placenta represent an adverse effect. Since placenta contains a large amount of cytochrome P-450 enzymes, the possibility of a metabolicladaptiverole should be considered.

Taken as a whole, by the oral route the NOEL on rat oral developmental studies was 0.5 mg/kg/day. By the dermal route, 2 mgkglday is near a NOAEL.

Summary of Developmental Toxicity Studies **with Flusilazole**

Species/Route	Maternal NOEL (mg/kg/day)	Effect at LOEL	Developmental NOEL (mg/kg/day)	Effect at LOEL
Rat Dietary	9	↓Weight gain	9	Resorptions, stunted fetuses
Rat Gavage	10	↓Weight gain, food consumption, ↑liver weight	<10	Fetal variations
Rat Gavage	10	↓Weight gain, food consumption, ↑liver weight	2	Fetal variations
Rat Gavage	2	↓Weight gain	2	Small renal papillae, subcutaneous hemorrhage
Rat Gavage	0.5	Red vaginal discharge Placental effects	0.5	Fetal variations
Rat Dermal	~2	Placental effects	2	Enlarged livers, variations

Rabbit Dietary	21.2	↓Weight gain & food consumption	2.8	Increased resorptions
Rabbit Gavage	12	No effect at HDT	12	No effect at HDT
Rabbit Gavage	12	Weight loss	12	↑Total resorptions
Rabbit Gavage	7	Vaginal staining	15	↑Total resorptions

In a rabbit dietary developmental study the NOEL for the dam was 21.2 mgkgiday and the developmental NOEL was 2.8 mg/kg/day based on decreased litters and increased resorptions. In the first two rabbit gavage studies, the maternal and offspring NOELs were both 12 mg/kg/day. In the final rabbit gavage study, the maternal NOEL was 7 mg/kg/day based on increased clinical signs as 15 mgkglday. The developmental NOEL was 15 mg/kg/day based on increased resorptions at the high dose. Taken as a whole, the rabbit maternal NOEL for gavage studies is 7 mg/kg/day and the rabbit developmental NOEL is 15 mg/kg/day.

GENOTOXICITY

Flusilazole was negative in the following assays:

In vitro

Bacterial gene mutation in with *Salmonella typhimurium* (MRID 00161171)
Clastogenicity: Chromosomal aberrations in cultured human lymphocytes (Vlachos, 745-86)
Mammalian gene mutation assay (CHOMGPRT) (MRID 00161172)
Unscheduled DNA Synthesis in cultured rat hepatocytes (MRID 40042117)

In vivo

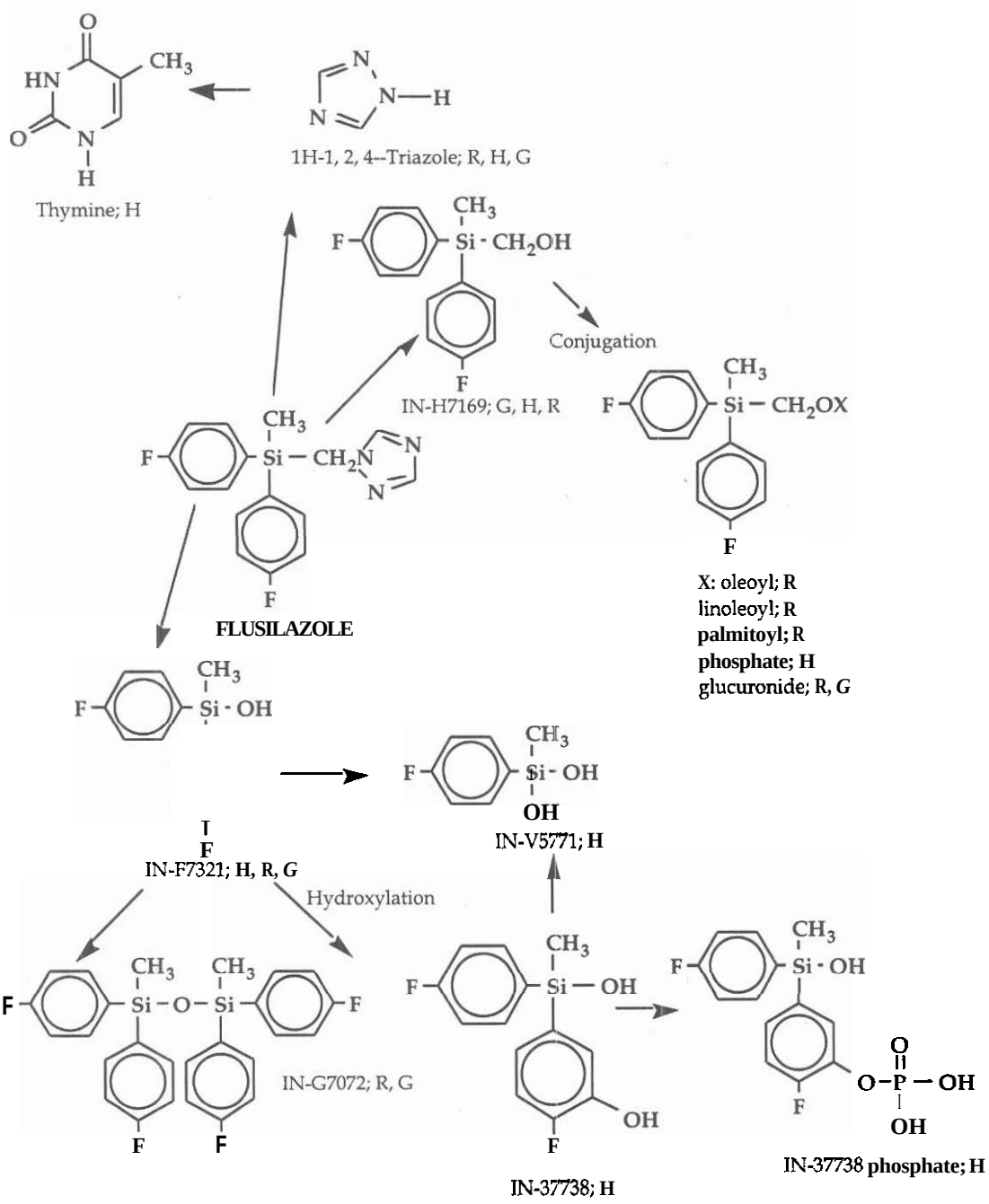
Mouse Micronucleus Test in mice dosed orally with 375 mg/kg (Vlachos 437-84)
Chromosomal Aberrations Test in the Rat Bone Marrow in rats dosed oral up to 150 mg/kg of flusilazole (MRID 00161173)

METABOLISM

The absorption and metabolism of flusilazole was investigated in rats: the molecule was labeled at either the phenyl group or at the triazole group (MRID 40042115). The tissue residues and excretion of phenyl- and triazole-labeled flusilazole were analyzed in groups of male and female rats after single doses of 8 mgikg of the labeled compound with and without preconditioning, and at 200 or 244 mgikg as a single dose. Excretion was high in all groups with 78% - 96% of the phenyl label and 93-99% of the triazole label excreted within the study period. Tissue retention was not high with between 0.1-0.7 ppm retained at 8 mgikg and 6 ppm at 200 mgkg (ranging from 1.3-3.5%). Excretion of the [phenyl(U)-^{14}C]-label was divided between feces and urine. Males excreted up to 94% and females up to 67% via the feces, while females excreted up to 27% in the urine and males only 10%. With the triazole-label excretion was primarily urinary with 72-81% recovered from the urine.

Flusilazole is extensively metabolized and excreted. **A** considerable proportion was found to be excreted from the GI tract unchanged (from 2-10%). Eight metabolites were identified. The metabolic pathway was deduced from the results of the two experiments. It was demonstrated that the cleavage and rapid excretion of the 1H-1,2,4-triazole was the primary step in the metabolism of flusilazole. The silane molecule may then be excreted or further metabolized to non-polar fatty acid metabolites (males > females), (β-D-glucopyranuronic acid conjugate (females), and may in addition further degrade to more polar molecules. The metabolites found in goats and hens indicated a similar metabolic pathway to the rat, with little evidence of potential tissue retention.

FIGURE 1 METABOLIC PATHWAYS FOR THE DEGRADATION OF FLUSILAZOLE IN ANIMALS



In the above diagram R= rats, H= poultry and G= goat.

SUPPLEMENTARY MECHANISTIC STUDIES

A 90-day study (MRID 42613204) was conducted to investigate mechanisms of toxicity (hepatotoxicity) and oncogenicity (urinary bladder transitional cell tumors and testicular Leydig cell adenomas) of flusilazole in the rat. Since genotoxicity tests were negative, a non-genotoxic mechanisms of tumor induction were investigated i.e., increased cellular proliferation rates due to irritation or chronic toxicity, and peroxisome proliferation-mediated events. Flusilazole was administered to rats in the diet at concentrations of 0, 10, 125, 375 and 750 ppm. Rats were sacrificed after 1 or 2 weeks or 1.5 or 3 months. Liver weight increases correlated well with the observed cytochrome P-450 induction. It was concluded from these results that the liver toxicity seen in this study and therefore the long-term studies also was due to the observed induction of cytochrome P-450 causing proliferation of the SER and hepatocellular hypertrophy. In the urinary bladder, there was a clear proliferative response following treatment with flusilazole. Serum hormone levels were not significantly altered in this study. It was suggested that the mechanism may lie in the ability to inhibit cytochrome P-450 activity thereby inhibiting steroidogenesis. An additional study was carried out to further investigate the possible mechanism of testicular adenoma induction. The results of this study support the proposal that the toxicity of flusilazole results from effects on cytochrome P-450, and direct toxic effects on the bladder.

In the final two-year feeding study in the rat, flusilazole was found to induce testicular adenomas in males. **A** possible non-genotoxic mechanism for such tumor induction was investigated (HLR 410-93). Flusilazole has been shown to inhibit cytochrome P-450 by the same mechanism as ketoconazole (an anti-tumor agent used in the treatment of human testicular carcinoma). In an in ***vivo*** experiment, rats were treated twice daily with either 0, 10, 25, 75 or 125 mg/kg/day of flusilazole or 0, 10, 25, 50 or 100 mg/kg/day of ketoconazole for 14 days. In an in *vitro* experiment, Leydig cells were isolated from rats and cultured with ketoconazole or flusilazole and the concentrations of steroids were measured. In the in ***vivo*** study, relative accessory sex gland weights were reduced with ketoconazole, but not flusilazole. It was concluded that either the flusilazole was less potent than ketoconazole or operated by another mechanism. Ketoconazole produced a decrease in serum testosterone and related steroids. Flusilazole caused reduction in both serum and testicular testosterone and estradiol, but was far less potent than ketoconazole. It was proposed that this data supported the theory that flusilazole could induce Leydig cell tumors by decreasing testosterone and estradiol synthesis thus disrupting the HPT axis.

SUMMARY OF MAMMALIAN TOXICOLOGY

ADME studies carried out on flusilazole indicate that the substance was rapidly absorbed and that excretion was high with 80-99% excreted with the study interval. 1.3 to 2.6% of the dose (phenyl-labeled) and 0.1 to 3.5% (triazole-label) retained in the tissues. 40-50% of the residue was excreted from the gastrointestinal tract, liver, skin and fat. Excretion of the phenyl label (silane molecule) was highest via the feces (83-94% in males and 47-67% in females) with the remaining portion excreted via the urine (7-10% in males and 20-27% in females). Urinary excretion was the primary route of excretion of the triazole moiety (72-80.6%).

Flusilazole was found to be extensively metabolized. A considerable proportion was found to be excreted from the GIT unchanged (from 2-10%). Eight metabolites were identified. The metabolic pathway was deduced from the results of the two experiments. It was demonstrated that the cleavage and rapid excretion of the 1H-1,2,4 triazole was the primary step in the metabolism of flusilazole. The silane molecule may then be excreted or further metabolized to non-polar fatty acid metabolites (males>females), β-D-glucopyranuronic acid conjugate (females), and may in addition further degrade to more polar molecules. The metabolites found in goats and hens indicated a similar metabolic pathway to the rat, with little evidence of potential tissue retention.

Flusilazole was found to be of a moderate order of toxicity by the oral route with an LD50 value of 674 mg/kg for males and 1110 mgikg for females. The potential for dermal toxicity appeared to be low (>2000 mg/kg). The inhalation ALD was 2.7 mg/l (males) and 3.7 mg/l (females). It was mild eye irritant. Potential for acute skin irritation is low and it is not a dermal sensitizer.

Short-term exposure toxicity of flusilazole was investigated in rats (gavage and dietary), mice (dietary), dogs (dietary) and in rabbits (dermal application). The targets identified were the blood system, liver and urinary bladder. The dog was found to be the most sensitive species to the hepatotoxicity and bladder toxicity of flusilazole. Degenerative liver disorder and evidence of cellular proliferation (hyperplasia) in the urinary bladder were seen at 125 ppm (4.3 mg/kg/day) in the dog. The NOAEL was 0.9 mg/kg/day.

There was no evidence of genotoxic potential in the battery of tests performed both in *vitro* and ***in vivo.***

The chronic toxicity/carcinogenicity studies in the rat, the target organs identified were consistent with the sub-chronic administration studies, i.e., liver and bladder. Flusilazole was found to be oncogenic at the higher doses, causing bladder transitional cell neoplasia in both sexes and testicular Leydig cell adenoma in males. There is evidence of a proliferative effect of flusilazole in the bladder transitional epithelium, which is likely the mechanism of tumorigenesis. Therefore, the urinary bladder tumors are considered to be caused by an epigenetic, threshold-associated mechanism. Interference of flusilazole with hypothalmic-pituitary-gonadal (HPG) axis is suggested as a possible mechanism of testicular tumor induction. Evidence in support of this theory was provided by a comparative study with the aromatase inhibitor, ketoconazole. Flusilazole did cause a slight reduction in both serum and testicular testosterone and a dose-dependent decrease in serum estradiol, but was far less potent than ketoconazole. It would appear reasonable to conclude that a threshold exists for the induction by flusilazole of testicular adenomas. The NOEL for neoplasms was 375 ppm (14.8 and 20.5 mg/kg/day in males and females, respectively).

In mouse chronic studies, the target organs were the liver, kidney, urinary bladder and urethra. The incidence of hepatocellular adenomas was increased at $\geq$ 1000 ppm. Based on the combined results of two studies, the NOEL for oncogenicity in mice is 200 ppm (36 mg/kg/day) in females and 500 ppm (73.1 mg/kg/day) for males. Since tumors occurred in excess of the MTD, and were preceded at lower doses by histopathological change consistent with induction-related

hepatotoxicity, it is reasonable to conclude that the induction of such tumors is related to cytotoxicity, which demonstrates a clear threshold.

The effect of feeding flusilazole to dogs for one year was mild hepatotoxicity and leucocytosis (inflammatory) response. These were primarily observed in the high dose group and were most pronounced in males. The dog was found to be the most sensitive species (to flusilazole hepatotoxicity). The NOAEL from the chronic dog study of 0.7 mg/kg/day is the overall flusilazole chronic toxicity endpoint.

In reproduction studies, increased gestation length, dystocia, decreased pup viability and decrease weight gain was observed. The NOEL for reproductive effects was 50 ppm (4.1 mg/kg/day).

Ten developmental toxicity studies were carried out with flusilazole, six in the rat (one dietary, four gavage, and one dermal) and four in the rabbit (one dietary and four gavage). In rats, maternal toxicity included decreased weight gain and food consumption, increased clinical signs, and increased liver weights. Fetal toxicity was evidenced by increased incidences of resorptions, fetal mortality, stunted fetuses, and skeletal variations (delayed ossifications, supernumerary ribs, and renal pelvis variations) and decreased fetal weight. Absent renal papillae occurred at 10 mg/kg/day and above and cleft palate occurred at 250 mg/kg/day. Taken as a whole, the NOEL in rats was 0.5 mg/kg/day by the oral route. By the dermal route 2 mg/kg/day was near a NOAEL based on only placental, but no fetal effects at this dose.

In a rabbit dietary developmental study the NOEL for the dam was 21.2 mg/kg/day and the developmental NOEL was 2.8 mg/kg/day based on decreased litters and increased resorptions. In the first two rabbit gavage studies, the maternal and offspring NOELs were both 12 mg/kg/day. In the second there were increased total resorptions and one malformation (hydrocephaly) at 35 mg/kg/day. In the final rabbit gavage study, the maternal NOEL was 7 mgkglday based on increased clinical signs as 15 mg/kg/day. The developmental NOEL was 15 mgkglday based on increased resorptions at the high dose. Taken as a whole, the rabbit maternal NOEL via the gavage route is 7 mg/kg/day and the developmental NOEL is 15 mgikglday.

ORAL ENDPOINTS / DIETARY EXPOSURE

In studies with pregnant animals, flusilazole produced decreased maternal weight gain, enlarged placenta, and increased fetal variations. The lowest NOEL was 0.5 mg/kg/day on a rat oral developmental toxicity study.

Flusilazole was found to exert a clear systemic toxicity on sub-chronic and chronic administration to rats, mice and dogs. A similar pattern of effects was apparent across the three species, with the liver, urinary system and blood system targeted to varying degrees. It was found to be oncogenic at high dose levels in both mice and rats, inducing bladder transitional cell neoplasia in rats and testicular adenoma in male rats and hepatocellular adenomas and carcinomas in mice. NOAELs in chronic studies were:

Rat: 2-Year Oncogenicity and Chronic Toxicitv Study (2 studies)

- The NOEL for neoplasms was 375 ppm (14.8 and 20.5 mg/kg/day in males and females, respectively).
- The NOAEL for other effects was 50 pprn (2.0 and 2.6 mgikglday in males and females, respectively).

Mouse: 18-Month Oncogenicitv Study (2 studies)

- The NOEL for oncogenicity was 500 pprn in males (73.1 mgikglday) and 200 pprn (36 mgikglday) in females
- NOAEL = 25 pprn (3.4 and 4.6 mg/kg/day in males and females, respectively). The NOAEL was determined in the first 18-month study. The lowest effect level (100 ppm) was determined in the second 18-month mouse study.

Dog: I-Year Chronic Toxicitv Studv

- The NOAEL was 20 ppm (0.7 mgikglday) based on mild liver toxicity at the 75 pprn dose level.

The lowest NOAEL on chronic studies was 0.7 mg/kg/day (20 ppm) in the 1-year dog feeding study. This value was considered the most appropriate for determination of chronic reference dose.

Application of flusilazole to soybeans resulted in no measurable residues. A short-term and chronic risk assessment for dietary exposure to soybeans was conducted using an oral short-term NOEL of 0.5 mgikglday from the rat oral developmental study and a chronic NOEL of 0.7 mg/kg/day from the dog chronic study. A residue of 0.01 pprn was used for all soybean residues. The results of the short-term and chronic dietary risk assessments are summarized below. The most highly exposed population group was infants with only 1.4% of the acute RfD used. These results indicate a very small percentage of the reference dose was used and that there would be a reasonable certainty of no harm from use of flusilazole on soybeans.

A separate dietary risk assessment was not conducted for famoxadone on soybeans but is not expected to be of concern. The proposed use rate of famoxadone in Charisma™ on soybeans is much lower than the approved label rate for famoxadone in Tanos™ on any crop registered in the US with fewer applications and a longer PHI.

TABLE 1 SUMMARY OF DIETARY RISK ASSESSMENT OF FLUSILAZOLE ON SOYBEANS

	PERCENT OF RFD	
POPULATION	ACUTE (at 95%ile)	CHRONIC
US Population	0.24	0.1
Infants	1.4	0.3
Females 13-49	0.2	0.0
Males 13-19	0.24	0.1
Males 20+	0.2	0.1
Seniors 55+	0.1	0.0
Children 1-2	0.5	0.1
Children 3-5	0.4	0.1
Children 6-12	0.3	0.1
Youth 13-19	0.2	0.1
Adults 20-49	0.2	0.1
Adults 50+	0.14	0.0

OCCUPATIONAL EXPOSURE

Handler Exposure

For occupational exposure, a risk estimate was conducted for the use of Punch™ and Charisma™ on soybeans applied by ground (open system) or aerial application (employing a closed system). EPA default values were used. Mixer/loaders were assumed to be wearing gloves and coveralls for open system mixing and single layer plus gloves for closed system. Ground applicators were assumed to be wearing gloves and coveralls for open cab use; aerial applicators (closed cockpit) were assumed to be wearing baseline single layer without gloves, and flaggers were assumed to be wearing gloves and coveralls. Although the EPA default of 50% clothing penetration was used in the calculations for a second layer of clothing, flusilazole-specific field data shows that this value is highly conservative. A passive dosimetry exposure study was conducted in the United Kingdom where handlers were monitored for dermal exposure while mixing/ loading and applying a liquid formulation of flusilazole using tractor mounted or drawn boom sprayers for application in barley. Data from the study show that on average (n = 12) 1.3% of the total intercepted residue (inner plus outer whole body dosimeters) was present on the inner dosimeters. Therefore, the PHED exposure estimates incorporate a 38-fold higher clothing penetration compared to the compound–specific data.

In selecting endpoints for occupational exposure, the lowest endpoint for flusilazole dermal exposure was on the rat dermal developmental study. In that study 2 mg/kg/day may be considered a NOAEL, since although there were microscopic placental changes, there was no

overt toxicity in either maternal animals or fetuses. For an inhalation endpoint for flusilazole, the oral developmental NOEL of 0.5 mg/kg/day was used.

For famoxadone, a dermal endpoint of 28 mg/kg/day was used based on an oral NOEL of 1.4 mg/kg/day from a 13-week dog study and an adjustment for 5% dermal absorption. For inhalation, the oral endpoint of 1.4 mg/kg/day without an adjustment factor was used. In the registration documents for famoxadone, EPA had determined the acceptable MOE for famoxadone was 300 for intermediate term exposure and 1000 for chronic exposure.

Flusilazole application rate was 0.11 lb./A for PUNCH™ and 0.067 lb./A for CHARISMA™. The results of the occupational risk assessment are given in Tables 2-4. Margins of exposure were all greater than 100.

TABLE 2 SHORT-TERM OCCUPATIONAL RISK ASSESSMENT FOR PUNCH™ (FLUSILAZOLE) ON SOYBEANS

Exposure Scenario	Mitigation Level	Use Pattern	Application Rate	Area Treated	Head & Neck Exposure	Upper & Lower Body	Body + Coveralls Exposure	Hands Unit Exposure	Dermal Unit Exposure	Inhalation Unit Exposure	Dermal Exposure	Inhalation Exposure	Dermal MOE	Inhalation MOE	Combined MOE
Units			lb/Acre	A/day	mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	Mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	mg/kg/day	mg/kg/day			
Data source			Label	Policy 9.1	PHED	PHED	a	PHED	b	PHED	c	d	e	f	g
Mixer/Loader															
Liquid open mix & load for ground boom application (PHED Scenario 3)	Gloves, coveralls	Soybean	0.11	200	0.00527	NA	0.0055	0.00671	0.017	0.0012	0.0055	0.00038	364	1,326	286
Liquid closed mix & load for aerial application (PHED Scenario 6)	Baseline + Gloves	Soybean	0.11	1200	0.00126	0.00564	NA	0.00168	0.0086	0.000083	0.0162	0.00016	124	3,195	119
Applicator															
Aerial Closed Cockpit (PHED Scenario 7)	Baseline	Soybean	0.11	1200	0.000156	0.00174	NA	0.00311	0.0050	0.000068	0.0094	0.00013	212	3,899	201
Ground boom Open Cab (PHED Scenario 13)	Gloves, coveralls	Soybean	0.11	200	0.00161	NA	0.00306	0.00629	0.011	0.00074	0.0034	0.00023	581	2,150	457
Flagger - liquid (PHED Scenario 25)	Gloves, coveralls	Soybean	0.11	350	0.00663	NA	0.00087	0.00313	0.011	0.00035	0.0058	0.00019	342	2,597	302

a Coverall reduction = Upper and lower body mg/lb a.i. From PHED x 0.5

b Total dermal exposure = Head and Neck + Body w coverall reduction (no coverall reduction for closed system mixer or aerial applicator) +Hands w gloves

c Dermal exposure = (lb ai/A x A/day x dermal unit exposure mg/lb ai)/70 kg

d Inhalation exposure = (lb ai/A x A/day x inhalation unit exposure mg/lb ai)/70 kg

e Dermal MOE =dermal NOAEL/dermal exposure

f Inhalation MOE = inhalation NOEL/inhalation exposure g Combined MOE = 1 (1/dermal MOE + 1/inhalation MOE)

TABLE 3 SHORT-TERM OCCUPATIONAL RISK ASSESSMENT FOR CHARISMA™ (FLUSILAZOLE) ON SOYBEANS

Exposure Scenario	Mitigation Level	Use Pattern	Application Rate	Area Treated	Head & Neck Exposure	Upper & Lower Body	Body + Coveralls Exposure	Hands Unit Exposure	Dermal Unit Exposure	Inhalation Unit Exposure	Dermal Exposure	Inhalation Exposure	Dermal MOE	Inhalation MOE	Combined MOE
Units			lb/Acre	A/day	mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	Mg/lb a.i.	mg/lb a.i.	Mg/lb a.i.	mg/kg/day	mg/kg/day			
Data source			Label	Policy 9.1	PHED	PHED	a	PHED	b	PHED	c	d	e	f	g
Mixer/Loader															
Liquid open mix & load for ground boom application (PHED Scenario 3)	Gloves, coveralls	Soybean	0.067	200	0.00527	NA	0.0055	0.00671	0.017	0.0012	0.0033	0.00023	598	2,177	469
Liquid closed mix & load for aerial application (PHED Scenario 6)	Baseline + Gloves	Soybean	0.067	1200	0.00126	0.00564	NA	0.00168	0.0086	0.000083	0.0099	0.00010	203	5,245	195
Applicator															
Aerial Closed Cockpit (PHED Scenario 7)	Baseline	Soybean	0.067	1200	0.000156	0.00174	NA	0.00311	0.0050	0.000068	0.0057	0.00008	348	6,402	330
Ground boom Open Cab (PHED Scenario 13)	Gloves, coveralls	Soybean	0.067	200	0.00161	NA	0.00306	0.00629	0.011	0.00074	0.0021	0.00014	953	3,530	751
Flagger - liquid (PHED Scenario 25)	Gloves, coveralls	Soybean	0.067	350	0.00663	NA	0.00087	0.00313	0.011	0.00035	0.0036	0.00012	562	4,264	496

a Coverall reduction = Upper and lower body mg/lb a.i. From PHED x 0.5
b Total dermal exposure = Head and Neck + Body w coverall reduction (no coverall reduction for closed system mixer or aerial applicator) + Hands w gloves
c Dermal exposure = (lb ai/A x A/day x dermal unit exposure mg/lb ai)/70 kg
d Inhalalion exposure = (lb ai/A x A/day x inhalation unit exposure mg/lb ai)/70 kg
e Dermal MOE = dermal NOAEL/dermal exposure
f Inhalation MOE = inhalation NOEL/inhalation exposure
g Combined MOE = 1 (1 dermal MOE + 1/inhalation MOE)

TABLE 4 SHORT-TERM OCCUPATIONAL RISK ASSESSMENT FOR CHARISMA™ (FAMOXADONE) ON SOYBEANS

Exposure Scenario	Mitigation Level	Use Pattern	Application Rate	Area Treated	Head & Neck Exposure	Upper & Lower Body	Body + Coveralls Exposure	Hands Unit Exposure	Dermal Unit Exposure	Inhalation Unit Exposure	Dermal Exposure	Inhalation Exposure	Dermal MOE	Inhalation MOE	Combined MOE
Units			lb/Acre	A/day	mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	mg/lb a.i.	Mg/lb a.i.	mg/kg/day	mg/kg/day			
Data source			Label	Policy 9.1	PHED	PHED	a	PHED	b	PHED	c	d	e	f	g
Mixer/Loader															
Liquid open mix & load for ground boom application (PHED Scenario 3)	Gloves, coveralls	Soybean	0.062	200	0.00527	NA	0.0055	0.00671	0.017	0.0012	0.0031	0.00021	9043	6,586	3,811
Liquid closed mix & load for aerial application (PHED Scenario 6)	Baseline + Gloves	Soybean	0.062	1200	0.00126	0.00564	NA	0.00168	0.0086	0.000083	0.0091	0.00009	3070	15,870	2,573
Applicator															
Aerial Closed Cockpit (PHED Scenario 7)	Baseline	Soybean	0.062	1200	0.000156	0.00174	NA	0.00311	0.0050	0.000068	0.0053	0.00007	5263	19,371	4,138
Ground boom Open Cab (PHED Scenario 13)	Gloves, coveralls	Soybean	0.062	200	0.00161	NA	0.00306	0.00629	0.011	0.00074	0.0019	0.00013	14422	10,680	6,136
Flagger - liquid (PHED Scenario 25)	Gloves, coveralls	Soybean	0.062	350	0.00663	NA	0.00087	0.00313	0.011	0.00035	0.0033	0.00011	8497	12,903	5,123

a Coverall reduction = Upper and lower body mg/lb a.i. From PHED x 0.5
b Total dermal exposure = Head and Neck + Body w coverall reduction (no coverall reduction for closed system mixer or aerial applicator) + Hands w gloves
c Dermal exposure = (lb ai/A x A/day x dermal unit exposure mg/lb ai)/70 kg
d Inhalation exposure = (lb ai/A x A/day x inhalation unit exposure mg/lb ai)/70 kg
e Dermal MOE = dermal NOEL/dermal exposure
f Inhalation MOE = inhalation NOEL/inhalation exposure g Combined MOE = 1 (1/dermal MOE + 1/inhalation MOE)

Flusilazole Post-Application Exposure

Occupational post-application exposure risk was estimated for workers reentering soybean fields treated with flusilazole. EPA Exposure Policy number 3.1: Agricultural Transfer Coefficients (August 2001) identifies only three reentry tasks for soybeans: hand weeding/hoeing (a low contact activity, transfer coefficient 100), scouting (a low or medium contact activity, TC 100 or 1500) and irrigating (a medium contact activity, TC 1500). No dislodgeable foliar residue (DFR) study is available for flusilazole; a dislodgeable residue was estimated using the EPA default assumption of 20% of the application rate is available as dislodgeable residue. EPA also assumes a default pesticide dissipation rate of 10% per day in the absence of chemical specific data. A dissipation study with flusilazole in wheat forage supports the default dissipation assumption (AMR 1855-90, to be submitted in the section 3 registration application). Wheat was treated with 6.5 oz/A (0.4 lb/A), which is four-fold the current rate for soybeans. The %-life for flusilazole on forage was 4 days and 6 days in two sites (IL and ID) with equations for decay of 0.1886*X +4.548 and -0.1 18*X+3.31 in IL and ID sites, respectively.

The following equation was used to estimate dislodgeable residue:

DFR = (AR) x (I-D) x (4.54 x 10^8 µg /lb) x (24.7 x 10^{-9} A/cm^2) x % transferable
DDD = (DFR (µg/cm^2) x (0.001 mg/µg) x TC (cm^2/hr) x 8 hr/day)/ BW

Where:

AR = Application rate in lb a.i./A
BW = Body Weight
D = Daily dissipation rate – assumed to be 10% per day
DDD = Daily dermal dose in mg/kg/day
DFR = DFR Dislodgeable foliar residue in µg/cm^2
TC = Transfer coefficient in cm^2/hr

Assumptions

DuPont™ Sanction Fungicide Application Rate = 0.11 lb/A
DuPont™ Charisma Fungicide Application Rate = 0.0616 lb/A
Dermal NOAEL = 2 mg/kg/day
Body weight = 60 kg

The MOE was determined by comparing the daily dermal dose to the dermal NOAEL of 2 mg/kg/day for flusilazole. The MOEs on the day of application for low contact reentry activity such as hoeing was 600 and 1200 with Punch™ and Charisma™ formulations, respectively. For medium contact activities such as scouting or irrigating, the MOE for Punch® was 100 at 9 days post application. For Charisma™ the MOE was at 99.4 by day 3 post application.

TABLE 5 PUNCH™ SOYBEAN REENTRY

Low Contact Activity – Scouting								
Days (after last application)	0	1	2	3	4	5	6	7
Application Rate lb/A	0.11							
Estimated DFR (ug/cm ^{2})^{a,b}	0.246	0.222	0.200	0.180	0.162	0.145	0.131	0.118
Transfer Coefficient (cm^2/hr)	100	100	100	100	100	100	100	100
Average Daily Exposure (ADE) (mg ai/day) =	0.19712	0.177408	0.159667	0.1437	0.12933	0.116397	0.104758	0.094282
Body Weight (kg)	60	60	60	60	60	60	60	60
Daily dose (mg/kg/day) =	0.0033	0.0030	0.0027	0.0024	0.0022	0.0019	0.0017	0.0016
Dermal NOEL (mg/kg/day)	2	2	2	2	2	2	2	2
Margin Of Exposure =	608.77	676.41	751.56	835.07	927.86	1030.95	1145.50	1272.78

Medium Contact Activity – Irrigating										
Days	0	1	2	3	4	5	6	7	8	9
Application Rate lb/A	0.11									
Estimated DFR (ug/cm ^{2})^{a,b}	0.246	0.222	0.200	0.180	0.162	0.145	0.131	0.118	0.106	0.095
Transfer Coefficient (cm^2/hr)	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Average Daily Exposure (ADE) (mg ai/day) =	2.9568	2.66112	2.395008	2.155507	1.939956	1.745961	1.571365	1.414228	1.272805	1.145525
Body Weight (kg)	60	60	60	60	60	60	60	60	60	60
Daily dose (mg/kg/day) =	0.0493	0.0444	0.0399	0.0359	0.0323	0.0291	0.0262	0.0236	0.0212	0.0191
Dermal NOEL (mg/kg/day)	2	2	2	2	2	2	2	2	2	2
Margin Of Exposure =	40.58	45.09	50.10	55.67	61.86	68.73	76.37	84.85	94.28	104.76

a Conversion factor = µg to lb at 4.54 x 10^8 µg /lb x A to cm^2 at 24.7 x 10^{-9} A/cm2 x 0.20 assumed dislodgeable = 2.24

b Assumed 10% dissipation per day

TABLE 6 CHARISMA™ SOYBEAN REENTRY

Low Contact Activity – Scouting								
Days (after last application)	0	1	2	3	4	5	6	7
Application Rate lb/A	0.0616							
Estimated DFR (ug/cm ^{2})^{a,b}	0.138	0.124	0.112	0.101	0.091	0.081	0.073	0.066
Transfer Coefficient (cm^2/hr)	100	100	100	100	100	100	100	100
Average Daily Exposure (ADE) (mg ai/day) =	0.1103872	0.09934848	0.089414	0.080472	0.072425	0.065183	0.058664	0.052798
Body Weight (kg)	60	60	60	60	60	60	60	60
Daily dose (mg/kg/day) =	0.0018	0.0017	0.0015	0.0013	0.0012	0.0011	0.0010	0.0009
Dermal NOEL (mg/kg/day)	2	2	2	2	2	2	2	2
Margin Of Exposure =	1087.08	1207.87	1342.08	1491.20	1656.89	1840.98	2045.54	2272.82

Medium Contact Activity - Irrigating								
Days	0	1	2	3	4	5	6	7
Application Rate lb/A	0.0616							
Estimated DFR (ug/cm ^{2})^{a,b}	0.138	0.124	0.112	0.101	0.091	0.081	0.073	0.066
Transfer Coefficient (cm^2/hr)	1500	1500	1500	1500	1500	1500	1500	1500
Average Daily Exposure (ADE) (mg ai/day) =	1.655808	1.4902272	1.341204	1.207084	1.086376	0.977738	0.879964	0.791968
Body Weight (kg)	60	60	60	60	60	60	60	60
Daily dose (mg/kg/day) =	0.0276	0.0248	0.0224	0.0201	0.0181	0.0163	0.0147	0.0132
Dermal NOEL (mg/kg/day)	2	2	2	2	2	2	2	2
Margin Of Exposure =	72.47	80.52	89.47	99.41	110.46	122.73	136.37	151.52

a Conversion factor= µg to lb at 4.54 x 10^8 µg /lb x A to cm^2 at 24.7 x 10^{-9} A/cm2 x 0.20 assumed dislodgeable = 2.24

b Assumed 10% dissipation per day

TOXICOLOGY REFERENCES

ACUTE TOXICITY

Flusilazole Technical

MRID 40042106. Wylie, C. (1984) Median Lethal Dose (LD50) in Rats. DuPont Haskell Laboratory Report HLR 433-83.

MRID 40042107 Gargus, J. and J. Sutherland (1983) Acute Skin Absorption LD50 Test on Rabbits. Haskell Laboratory Report HLO 288-83.

MRID 40042109. Turner, R. (1985) Inhalation Median Lethal Concentration (LC50) of INH-6573. DuPont Haskell Laboratory Report HLR 1-85.

MRID 40357501 Dashiell, O. (1982) INH-6573 Eye Irritation Test in Rabbits. DuPont Haskell Laboratory Report HLR 582-82.

To be submitted with registration application. Clouzeau, J. (1991) Acute Dermal Imtation in the Rabbit. 7443 TAL.

MRID 40357502 Dashiell, O. (1982) IN H6573 Primary Skin Irritation and Sensitization Test on Guinea Pigs. DuPont Haskell Laboratory Report HLR 626-82.

Punch™ 40EC

To be submitted with registration application. DeJouffrey, S. (1994) Acute Oral Toxicity in Rats. 12133 TAR.

To be submitted with registration application. DeJouffrey, S. (1994) Acute Dermal Toxicity in Rats. 12134 TAR.

MRID 41567606. Valentine, R. (1988) Acute Inhalation Toxicity Study with IN H6573-125 in Rats. DuPont Haskell Laboratory Report HLR 743-87.

To be submitted with registration application. Clouzeau, J. (1994) Acute Eye Imtation in Rabbits. 11593 TAL.

To be submitted with registration application. Clouzeau, J. (1994) Acute Dermal Irritation in Rabbits. 12135 TAL.

To be submitted with registration application. DeJouffrey, S. (1994) Skin Sensitization Test in Guinea Pigs (Maximization Method of Magnusson and Kligman) 12136 TSG.

Charisma™

To be submitted with registration application Finlay L. (1996) Acute Oral Toxicity Study with an Emulsifiable Concentrate (EC) Formulation Containing 150 g/1.5 L of DPX-JE874 and 160 g/1.5 L of Flusilazole (DPX-MC444-11) in Male and Females Rats. DuPont Haskell Laboratory Report HLR 840-95

To be submitted with registration application. Sarver, J. (1996) Acute Dermal Toxicity Study with an Emulsifiable Concentrate (EC) Formulation Containing 150g/1.5 L of DPX-JE874 and 160 g/1.5 L of Flusilazole (DPX-MC444-11) in Rabbits. DuPont Haskell Laboratory Report HLR 94-96.

MRID 44302410. O'Neill, A. (1994) Inhalation Median Lethal Concentration (LC50) Study with DPX-JE874-158 in Rats. DuPont Haskell Laboratory Report HLR 791-93.

MRID 40042109. Turner, R. (1985) Inhalation Median Lethal Concentration (LC50) of INH-6573. DuPont Haskell Laboratory Report HLR 1-85.

To be submitted with registration application. Finlay, C. (1995) Acute Eye Irritation/ Corrosion Study with DPX-MC444-9 in Rabbits. DuPont Haskell Laboratory Report HLR 721-94

To be submitted with registration application. Sarver, J. (1996) Primary Dermal Irritation Study with an Emulsifiable Concentrate (EC) Formulation Containing 150g/1.5 L of DPX-JE874 and 160 g/1.5 L of Flusilazole (DPX-MC444-11) in Rabbits. DuPont Haskell Laboratory Report HLO 90-96.

To be submitted with registration application. Moore, G. (1996) Guinea Pig Dermal Sensitization – Magnusson-Kligman Maximization Test with H-21286 (DPX-MC444-11). DuPont Haskell Laboratory Report HLO 11-96.

SUBCHRONIC TOXICITY

MRIDs 00072421 and 00161400. Pastoor, T. (1983) Ninety-day Feeding and One-Generation Reproduction Study in Rats with Silane. DuPont Haskell Laboratory Report 483-83

MRID 40042111. Pastoor, T. (1983) Four-week Range Finding and Ninety-Day Feeding in Mice with Silane, [Bis(4-Fluorophenyl)](methyl) (1H-1,2,4-triazol-1-methyl) (IN H-6573). DuPont Haskell Laboratory Report HLR 341-83.

MRID 41514901. Keller, D. (1990) Subchronic Oral Toxicity: 90-Day Study with DPX-H6573-193 Feeding Study in Mice. DuPont Haskell Laboratory Report HLR 60-90.

MRID 00161168. Rickard, R. (1983) Three-month Feeding Study in Dogs with Silane (INH-6573). DuPont Haskell Laboratory Report HLR 461-83.

MRID 40042119. Sarver, J. (1986) Twenty-one Day Dose Dermal Toxicity Study with INH-6573-82 in Rabbits. DuPont Haskell Laboratory Report HLR 744-86.

LONG-TERM TOXICITY AND CARCINOGENICITY

MRID 00148511. Pastoor, T. (1984) Long-term Feeding and Two-generation, Four-litter Reproduction Study in Rats with Silane, [Bis(4-Fluorophenyl)](methyl) (1H-1,2,4-Triazol-1-ylmethyl)-(INH-6573). DuPont Haskell Laboratory Report HLR 281-84

MRID 42613202. Keller, D. (1992) Oncogenicity Study with DPX-H6573-194 (Flusilazole) 2-year Feeding in Rats. DuPont Haskell Laboratory Report HLR 527-92.

MRID 40042114. Brock, W. (1985) Long-term Feeding Study in Mice with INH-6573. DuPont Haskell Laboratory Report HLR 278-85.

MRID 42613201. Keller, D. (1992) Oncogenicity Study with DPX-H6573-193 (Flusilazole) 18-month Feeding in Mice. DuPont Haskell Laboratory Report HLR 35-92.

MRID 40042113 O'Neal, F. (1985) One-year Feeding Study in Dogs with IN H-6573. DuPont Haskell Laboratory Report HLR 461-85.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

MRIDs 00072421,00161400. Pastoor, T. (1983) Ninety-day Feeding and One-generation Reproduction Study in Rats with Silane. DuPont Haskell Laboratory Report HLR 483-83.

MRID 00148511 Pastoor, T. (1984) Long-term Feeding and Two-generation, Four-litter Reproduction Study in Rats with Silane, [Bis(4-Fluorophenyl)](methyl) (1H-1,2,4-Triazol-1-ylmethyl)-(INH-6573. DuPont Haskell Laboratory Report HLR 281-84

MRID 41684601. Mullin, L. (1990) Reproductive and Fertility Effects with Flusilazole Multigeneration Reproduction Study in Rats. DuPont Haskell Laboratory Report HLR 424-90.

MRID 00072999. Alvarez, L. (1984). Developmental Toxicity Study in Rats Given INH-6573-66 in the Diet on Days 7-16 of Gestation. DuPont Haskell Laboratory Report HLR 431-84.

MRID 00161169. Lamontia, C. (1983) Embryo-fetal Toxicity and Teratogenicity Study of INH-6573-39 by Gavage in the Rat. DuPont Haskell Laboratory Report HLR 444-83.

MRID 00161170. Lamontia, C. (1984) Embryo-Fetal Toxicity and Teratogenicity Study of INH-6573-39 by Gavage in the Rat. DuPont Haskell Laboratory Report HLR 142-84.

MRID 40640704. Alvarez, L. (1985) INH-6573: Prenatal and Postnatal Toxicity Study in Rats Dosed by Gavage on Days 7-16 of Gestation. DuPont Haskell Laboratory Report 654-85.

MRID 45042601. Munley, S. (2000) Flusilazole Technical: Developmental Toxicity Study in Rats. DuPont-2287.

MRID 44594201. Schardein, J. (1998) A Dermal Prenatal Development Toxicity Study of Flusilazole in Rats. DuPont Haskell Laboratory Report HLO-1998-01504 Revised.

MRID 00154930. Alvarez, L. (1985) INH-6573 Developmental Toxicity Study in Rabbits Treated by Diet on Days 7-19 of Gestation. DuPont Haskell Laboratory Report 337-85.

MRID 00148512. Solomon, H. (1984) Developmental Toxicity Study in Rabbits Given INH-6573 by Gavage on Days 7-19 of Gestation: DuPont Haskell Laboratory Report HLR 333-84.

MRID 00154929. Zellers, J. (1985) INH-6573. Developmental Toxicity Study (Supplemental) in Rabbits Dosed by Gavage on Days 7-19 of Gestation. DuPont Haskell Laboratory Report HLR 669-85.

To be submitted with registration application. Alvarez, L. (1990) Teratogenicity Study of DPX-H6573-66 in Rabbits. DuPont Haskell Laboratory Report HLR 216-90.

GENOTOXICITY

MRID 00161171. Donovan, S. (1982) Mutagenicity Evaluation in Salmonella typhimurium [of Silane]: MR No. 4581-047. DuPont Haskell Laboratory Report No. 611-82.

To be submitted with registration application. Vlachos, D. (1989). Evaluation of INH-6573-82 in the In Vitro Assay for Chromosome Aberrations in Human Lymphocytes. DuPont Haskell Laboratory Report HLR 745-86 Revision 1.

MRID 00161172. McCooey, K. (1983) CHO/HGPRT Assay for Gene Mutation [using Silane]. DuPont Haskell Laboratory Report HLR 449-83.

MRID 40042117. Chromey, N. (1983) Unscheduled DNA Synthesis/Rat Hepatocytes in ***vitro.*** DuPont Haskell Laboratory Report HLR 209-83

To be submitted with registration application. Vlachos, D. (1989). Mouse Bone Marrow Micronucleus Assay of INH-6573-69. DuPont Haskell Laboratory Report HLO 437-84 Revision 1.

MRID 00161173. Cortina, T. (1983) In ***vivo*** Bone Marrow Chromosome Study in Rats with H# 14,728: Final Report: HLA Project No. 201-614.

METABOLISM

MRID 40042115. Anderson, J. et al., (1986) Metabolism of [Carbon 14]-DPX-H6573 in Rats. DuPont AMR 196-128.

MECHANISTIC STUDIES

MRID 42613204. Keller, D. (1992) Mechanisms of Toxicity: 90-day Feeding Study in Rats with DPX-H6573-194 (Flusilazole): Revision No. 1. DuPont Haskell Laboratory Report HLR 628-92.

To be submitted with registration application. Cook, J. (1993) Mechanisms of Rat Leydig Cell Tumor Induction by DPX-H6573-193 (Flusilazole) (Revision 1) Supplement to Oncogenicity Study with DPX-H6573-194 (Flusilazole) Two-Year Feeding Study in Rats (HLR 527-92). DuPont Haskell Laboratory Report HLR 410-93.

WORKER EXPOSURE

To be submitted with registration application. Old, J. et al. (2002) Monitoring Exposure of Workers During Mixing, Loading, and Application Using Flusilazole 25EW Fungicide for Control of Cereal Diseases in the UK: Field Phase and Routine Analysis. Inveresk Report No. 20690 DuPont-3899.

FOLIAR DISSIPATION

To be submitted with registration application. Smyser, B. (1992) Dissipation of Flusilazole from Wheat Forage. DuPont Report AMR 1855-90.

3.0 Terrestrial Vertebrates

3.1 Terrestrial Vertebrates: Mammals

A list of the studies selected as relevant to the assessment of the toxicity of flusilazole to wild mammals is shown in Table 7. Data from the toxicity tests are primarily generated to serve consumer and operator risk assessments and contain endpoints, which may be of minor ecological importance when assessing the risk to wild mammals. For the acute assessments the lowest LD_{50} values were selected. The NOEC from the developmental rat studies is proposed as a worst case value for the long-term risk assessment.

The acute LD50 (rabbit) was 450 mg/kg bw. In a short-term toxicity test with rats and LD_{50} > 300 ppm was determined. The NOEL derived from the developmental rat studies was 10 mg/kg bwlday. The NOEL from the rat multigeneration studies is 4 mg/kg bwlday.

TABLE 7 SUMMARY OF THE RELEVANT FLUSILAZOLE ENDPOINTS FOR TERRESTRIAL VERTEBRATES - MAMMALS

Test System	Test levels	Endpoints	Reference
Oral in rabbit (technical)	0, 130, 200. 310.450. 670, 1000, 1500, 2300 mg/kg	LD_{50} (males) = 450 mglkg LD_{50} (females) = 1000 mglkg	HLR 54-85
10-Day oral in rats (technical)	0.300 ppm	LD_{50} > 300 mglkg	HLR 157-83
Development studies in rats (technical)	div.	NOEC = 10 mglkg bwlday	HLR 444-83 HLR 142-84 HLR 431-84 HLR 654-85
Rat multigeneration		NOEL = 4.0 mglkg bwlday	HLR 281-84 HLR 424-90

3.2 Terrestrial Vertebrates: Birds

In acute oral and dietary intake studies with two avian species (bobwhite quail and mallard duck), flusilazole was unpalatable with regurgitation (in oral dosing studies) and loss of body weight and reduced food intake (in dietary intake studies) particularly at the higher doses. Oral ingestion of flusilazole appears to cause anorexia or food avoidance in adult and juvenile birds. There was a strong dose-dependent linear reduction in food consumption and body mass in the first 3 days after adult mallards were given a single oral dose of flusilazole. There was a strong dose-dependent reduction in body mass in the first 5 days after 10-day old mallard ducklings and northern bobwhite quail chicks were given flusilazole in their diets. Deaths of mallard and quail chicks were likely due to starvation at doses >1000 ppm rather than direct toxic effects of

flusilazole. The mechanism for this dramatic reduction in food consumption and ensuing body mass loss is not known. The consistent observations from testing with adult and juvenile birds strongly suggest that birds would avoid consumption of flusilazole-treated foods if alternative foods were available in the wild. Mallard duck was the most sensitive species with an LD_{50} > 1,590 mgkg body weight and a LC_{50} of 1,584 mgikg feed (Table 8).

TABLE 8 SUMMARY OF THE RELEVANT FLUSILAZOLE ENDPOINTS FOR ACUTE ORAL AND SHORT-TERM TOXICITIY FOR TERRESTRIAL VERTEBRATES - BIRDS

Study	Concentrations Tested	LD_{50} or LC_{50}	Lowest Lethal Dose	NOEL	Reference
Mallard Acute oral	0, 398, 632, 1000, 1590, 2510 mg/kg bw	>1590 mg/kg bw	1590 mg/kg bw	398 mg/kg bw lethargy, body mass	HLO 424-83
Quail 5-day dietary	0, 562, 1000, 1780, 3160, 5620 ppm (0, 118, 208, 475, 602, 1441 mg/kg bw)	>5620 ppm (>1441 mg/kg bw)	1780 ppm (475 mg/kg bw)	562 ppm (118 mg/kg bw) lethargy, body mass	HLO 386-83
Mallard 5-day dietary	0, 562, 1000, 1780, 3160, 5620 ppm (0, 130, 193, 180[a], NC[b] NC[b] mg/kg bw)	1584 ppm (~180 mg/kg bw)	1780 ppm (180 mg/kg bw)	<562 ppm (<130 mg/kg bw) lethargy, body mass	HLO 385-83

a **Average ingested dose (in mgikg bw/d) is lower than expected due to starvation of chicks.**

b **NC = Not calculable due to starvation and death of birds.**

Flusilazole was tested for reproductive effects in birds (northern bobwhite quail and mallard ducks) for regulatory requirements in the United States. Results suggest that flusilazole may have reproductive effects in both species at extremely high doses administered in the diet for 20 weeks. There were no apparent treatment-related effects upon body weight or feed consumption among adults at any test concentration. In northern bobwhite quail, there were statistically significant treatment-related effects upon egg quality (22% increase in cracked eggs) and survivability of hatchlings (38% reduction in survivors/eggs set) at 625 pprn (70 mg/kg bw/d) when compared to control data. There were apparent, but not statistically significant effects on egg quality and survivability of hatchlings at 125 pprn (15 mg/kg bw). The quail NOEC was 25 ppm (3 mg/kg bwld), based upon these apparent effects. In mallards, there were statistically significant treatment-related effects upon egg quality (4% increase in cracked eggs) and eggshell thickness (15% reduction) at 625 ppm (20 mg/kg bw/d) when compared to control data. There was a statistically significant effect on eggshell thickness (8% reduction) and apparent, but not statistically significant, effects on eggshell cracks, number of hatchlings and 14-day old survivors at 125 pprn when compared to control data. The NOEC for mallards was 25 ppm

(5 mg/kg bw/d), based upon 8% reduced eggshell thickness and other apparent effects at 125 ppm (Table 9).

TABLE 9 SUMMARY OF THE RELEVANT FLUSILAZOLE ENDPOINTS FOR REPRODUCTIVE EFFECTS FOR TERRESTRIAL VERTEBRATES - BIRDS

Study	concentrations Tested	LOEC	NOEC	Reference
Quail reproduction	0, 25,125,625 ppm (0, 3, 15, 70 mg/kg bw)	125 ppm (15 mg/kg bw)	25 ppm (3 mglkg bw)	HLO 700-85
Mallard reproduction	0, 25, 125, 625 ppm (0, 5, 20, 100 mglkg bw)	125 ppm (20 mglkg bw)	25 ppm (5 mglkg bw)	HLO 701-85

4.0 Aquatic **Organisms**

4.1 **Fish**

Calculated acute LC_{50} values for flusilazole were similar between 2 fish species: 1.2 mg/L for rainbow trout, based on mortality and 1.7 mg/L for bluegill sunfish based on mortality (Table 10).

In the year 1985 DuPont conducted a 60-day early life (ELS) study with rainbow trout according the pertinent test guideline and GLP requirements that existed in 1985 (HLO 606-85). The NOEC determined in this study was 30 µg flusilazole per L based on effects on length and weight. In the year 2000, DuPont conducted another ELS study (90-day) with rainbow trout according to OECD test guideline 210. The ELS study did not meet the 66 % control hatching success requirement of OECD test guideline 210. However, it did meet the relevant US test guideline hatching success requirement of > 50 % (U.S. EPA 72-4), as well as all other test acceptance criteria in the relevant OECD and U.S. EPA test guidelines. The lower hatching rate observed was most likely due to variability in egg quality. The NOEC determined in this ELS study was 3.3 µg flusilazole per L and was based on larval abnormalities and effects on length and weight of the surviving fish (Table 10).

Based on request of the European Union a flow-through full life-cycle (FFLC) toxicity study with the fathead minnow (Pimephalespromelas) exposed to six concentrations of flusilazole was conducted to estimate the no observed effect concentration (NOEC), the lowest observed effect concentration (LOEC), and the maximum acceptable toxicant concentration (MATC). The following endpoints were measured in the FO generation: number of dead eggs, larval survival, growth, and adult reproduction (days to 1" spawn, number of spawns, number of eggs per spawn, and hatchability). In the F1 generation the following endpoints were determined: number of dead eggs, egg hatchability, larval survival, and growth. The most

sensitive endpoints during this study were the standard length in the F1 generation and the mean number of days to first spawn. Based on standard length and mean number of days to first spawn the NOEC is 25 µg flusilazole per L (nominal concentration) (Mean measured concentrations ranged between 84 and 98% of the target nominal test concentrations).

TABLE 10 SUMMARY OF FISH TOXICITY ENDPOINTS FOR FLUSILAZOLE

Test organism	Exposure period	Test design/ analysis	LC_{50} (mg/L)	NOEC (mg/L)	Reference
Oncorhynchus mykiss	96 hours	Static/nominal	1.20	0.2300	HLR 108-83
Lepomis macrochirus	96 hours	Static/nominal	1.71	0.5200	HLR 133-83
Oncorhynchus mykiss	60 days	Flow-through/ measured	-	0.0300	HLO 606-85
Oncorhynchus mykiss	90 days	Flow-through/measured	-	0.0033	DuPont-3319
Pimephales promelas	FFLC	Flow-through/nominal	-	0.0250	DuPont-5577

In a 28-day bioaccumulation study bluegill sunfish (Lepomis macrochirus) was exposed to 0.09 and 0.009 mg flusilazole/L followed by a 14-dtiy depuration period following EPA 165-3 guideline. Maximum bioconcentration occurred in liver tissue, followed by viscera (with very little muscle residue) and average whole fish BCF values were 205 (at peak) and 130 at day 28 (HLO 425-83).

4.2 Aquatic Invertebrates/Algae

The 48-hour EC_{50} and NOEC for D. magna was 3.4 mg flusilazole/L and 1.8 mg flusilazole/L. The 21-day NOEC to Daphnia magna was 0.27 mg/L, based on 58% reduced number of young at 0.57 mg/L. The 21-day NOEC to Daphnia magna was 0.27 mg/L, based on 58% reduced number of young at 0.57 mg/L. Flusilazole technical bioaccumulated in bluegill sunfish tissues. Flusilazole was algistatic to the green algae *Selenastrum* capricornutum with an EC_{50} of 6.4 mg/L (E_bC_{50}) and a NOEC of 2.0 mg/L (Table 11).

TABLE 11 SUMMARY OF INVERTEBRATE/ALGAE TOXICITY ENDPOINTS FOR FLUSILAZOLE

Test organism	Exposure period	Test design/ analysis	EC_{50} (mg/L)	NOEC (mg/L)	Reference
Daphnia magna	48 hours	Static/nominal	3.4	1.8	HLR 111-83
Daphnia magna	21 days	Flow-throughlmeasured		0.27	HLR 579-86
Selenastrum capricornutum	3 days	Staticlnominal	6.4 (E_bC_{50})	2.0	DPT 171(f)/871605

4.3 Sediment-dwelling organisms

The toxicity of [^{14}C]-flusilazole to the sediment dwelling phase of *Chironomus riparius* was assessed in a static test system in accordance with the BBA (1995) guideline for water-spiked studies (DuPont-1155). The test was started with first instar C. *riparius* hatched from egg masses. The treatments, in addition to controls, were 0.01, 0.04, 0.156, 0.625, 2.5 and 10.0 µg [^{14}C]-flusilazole added to the water 24 hours after the addition of the larvae. Exposure lasted 28 days and adult development stage and emergence rates were measured. The EC_{50} for emergence was greater than the highest treatment rate as there was no statistical evidence of reduced emergence in any treatment. Similarly, there was no evidence for a reduction in insect development. The NOEC for adult emergence and development rate is ≥ 9.96 µg flusilazole/L (based on the actual dose applied).

5.0 Honeybees

In an acute contact toxicity test flusilazole was reported to be of low toxicity to honey bees with an acute 48-hour contact LD_{50} value of 165 µg/bee. The study is in accordance with EPA 141-1 guidelines (ABM-84-6).

6.0 Terrestrial Non-Target Plants

A study to assess the effects of foliar applied flusilazole was carried out with a formulated product, DPX-N7872-205, Harvesan® (equivalent to 250 g flusilazole/L and 125 g carbendazim/L) – according to U.S. EPA-FIFRA, Subdivision J, 122-1; and Draft Guidelines Ecological Effects Test Guidelines OPPTS 850.4150 and GLP – under glasshouse conditions (DuPont-5298). The plants tested (with growth stage at application) were ***Zea mays*** (3.5 leaves), ***Avena sativa*** (3.5 leaves), *Allium cepa* (11.5 cm tall), ***Brassica napus*** (one trifoliate leaf), *Glycine max* (15 cm tall) and ***Beta***

vulgaris (4 leaves). Plants were grown in standard plastic pots (10 cm for *Avena sativa* and *Allium sepa* or 15 cm for the other crops) with three seeds per pot for Z. *mays* and *G. max* and six seeds per pot for the remaining plant species. For each plant species, ten replicates each containing one plant were sprayed with the control and test preparations. The control (water only) and the Harvesan preparation of 0.8 L/ha (equivalent to 200 g flusilazole/ha) were applied with a hydraulic sprayer in 400 L water/ha using 8002 T-jet flat fan nozzles. Following treatment, plants were arranged in a glasshouse in a randomized complete block design, by species. After 20 days the visual response ranged from -0.74 to 3.21% (A. *cepa* and *A. sativa*, respectively) (Table 12). Shoot dry weight ranged from -16.61 to 10.72% of the control shoot dry weight for *A. cepa* and A. *sativa*, respectively (Table 13).

TABLE 12 VISUAL RESPONSE OF PLANTS 20 DAYS FOLLOWING A FOLIAR SPRAY APPLICATION OF DPX-N7872-205 AT 0.8 L/HA (EQUIVALENT TO 200 G FLUSILAZOLE/HA) UNDER GLASSHOUSE CONDITIONS

Species	Treatment	Mean visual response (%)	% effect relative to the control
Zea mays (maize)	Control	0.60	
	DPX-N7872-205	1.30	0.7
Avena sativa (oat)	Control	6.60	
	DPX-N7872-205	9.60	3.21
Allium cepa (onion)	Control	5.70	
	DPX-N7872-205	5.00	-0.74[a]
Brassica napus (rape)	Control	1.20	
	DPX-N7872-205	1.20	0.00
Glycine max (soybean)	Control	0.60	
	DPX-N7872-205	0.40	4.20
Beta vulgaris (sugar beet)	Control	1.10	
	DPX-N7872-205	0.60	4.51

[a] A negative inhibition is a growth enhancement.

TABLE 13 SHOOT DRY WEIGHT OF PLANTS 20 DAYS FOLLOWING A FOLIAR SPRAY APPLICATION OF DPX-N7872-205 AT 0.8 L/HA (EQUIVALENT TO 200 G FLUSILAZOLE/HA) UNDER GLASSHOUSE CONDITIONS

Species	Treatment	Mean shoot dry weight (g)	%Effect relative to the control
Zea mays (maize)	Control	53.70	-
	DPX-N7872-205	51.85	3.44
Avena sativa (oat)	Control	6.91	-
	DPX-N7872-205	6.17	10.72
Allium cepa (onion)	Control	0.31	
	DPX-N7872.205	0.37	-16.61'
Brassica napus (rape)	Control	73.93	
	DPX-N7872-205	72.15	2.41
Glycine max (soybean)	Control	24.18	
	DPX-N7872-205	26.21	-8.40
Beta vulgaris (sugar beet)	Control	41.30	
	DPX-N7872-205	43.22	4.65

[a] A negative inhibition is a growth enhancement.

Overall the foliar application of 200 g flusilazole/ha – applied as 0.8 L DPX-N7872-205 per ha - to six plant species, representing two families of monocotyledenous and three families of dicotyledenous plants, had no effects greater than 10.72% on plant growth, relative to unheated plants indicating that the risk posed by flusilazole to non-target plants due to potential spray drift into off-field habitats next to the target crop will be very low.

7.0 Additional ecotoxicology studies planned

To complete the ecotoxicology data package for flusilazole the following additional studies are planned to be conducted following the EPA guidelines:

(1) Oyster shell deposition
(2) Acute toxicity to mysid shrimp
(3) Chronic toxicity to mysid shrimp
(4) Acute toxicity to sheepshead minnow
(5) Chronic toxicity to sheepshead minnow (ELS)

(6) Toxicity to *Lemna gibba*
(7) Toxicity to *Anabena*
(8) Toxicity to *Navicula*
(9) Toxicity to *Skeletonema*
(10) Toxicity to *Chironomus tentans* (OPPTS method) if study is not waived

These studies will be included in the registration application for flusilazole.

8.0 Conclusions

For flusilazole a complete core ecotoxicological data package is available. The low - acute and chronic - toxicity of flusilazole for terrestrial vertebrates (mammals and birds), aquatic organisms (fish, daphnids, alga and sediment dwelling organisms), honey bees and terrestrial plants indicates a low risk for the environment due to potential exposure of flusilazole following the use of flusilazole at 125 g/ha twice per year in arable crops (i.e. soybeans) according to Good Agricultural Practice.

Overall, the results of the available comprehensive ecotoxicology data package for flusilazole (DPX-H6573) allow the conduct of an ecological risk assessment and the safe use of flusilazole at even higher rates, e.g., in the European Union over two decades indicates a very low risk for the environment due the use of flusilazole in arable crops.

9.0 References

ABM-84-6: Meade, A.B. (1984) Acute Contact LD_{50} Study in Honey Bees (*Apis mellifera* L.) with INH6573-39 (DPX-H6573). *(MRID 40042142)*

DPT 171(f)/871605: Douglas, M.T. & Handley, J.W. (1987) The Algistatic Activity of DPX-H6573. (MRID *41534806)*

DuPont-1155: Forster, A. (1999) [^{14}C] Flusilazole: To assess the toxicity to the sediment dwelling phase of the midge *Chironomus riparius*.

DuPont-3319: Hoke, R.A. (2000) Flusilazole Technical: Early life-stage toxicity to Rainbow Trout, *Oncorhynchus mykiss*. (MRID *45107701)*

DuPont-5298: Heldreth, K.M. (2001) Carbendazim/flusilazole (DPX-N7872) SE (1:2): A greenhouse study to investigate the effects on the vegetative vigor of several terrestrial plants following foliar exposure.

DuPont-5577: Rhodes, J.E. (2003) Flusilazole (DPX-H6573) Technical: Full life-cycle toxicity test with the Fathead Minnow, Pimephales promelas, under flow-through test conditions.

HLO 424-83: Beavers, J. (1983) An Acute Oral Toxicity Study in the Mallard with H #14,960 (H6573-41). (MRID *137628)*

HLO 385-83: Beavers, J.B. (1983) A Dietary LC„ in the Mallard with H #14,960 (H6573-41). (MRID *137629)*

HLO 386-83: Beavers, J.B. (1983) A Dietary LC„ in the Bobwhite with H #14,960 (H6573-41). (MRID *137630)*

HLO 425-83: Hunon, D.G. (1983) Residue Studies with ^{14}C-Phenyl-labeled DPX-H6573 in Bluegill Sunfish. (MRID not available but reviewed by EPA)

HLO 606-85: Forbis, A.D. (1985) Early Life-Stage Toxicity Test of H:14875-02 to Rainbow Trout (Salmo gairdneri) in a Flow-Through System. (MRID *40042140)*

HLO 700-85: Beavers, J.B. (1985) H #15,559 Technical (H6573): A One-Generation Reproduction Study with the Bobwhite (*Colinus virginianus*). (MRID *40042136)*

HLO 701-85: Beavers, J.B. (1985) #15,559-technical (H6573): A One-Generation Reproduction Study with the Mallard (*Anas platyrhynchos*). (MRID *40042137)*

HLR 54-85: Sarver, J.W. (1985) Approximate lethal dose (ALD) of INH-6573-66 in rabbits.

HLR 108-83: Hutton, D.G. (1983) 96-Hour LC„ to Rainbow Trout. (MRID *137632)*

HLR 111-83: Hutton, D.G. (1983) 48-Hour LC„ to Daphnia magna. (MRID *137633)*

HLR 133-83: Hutton, D.G. (1983) 96-Hour LC„ to Bluegill Sunfish. (MRID *137631)*

HLR 142-84: Lamontia, C.L. (1984) Embryo-fetal toxicity and teratogenicity study of INH6573-39 by gavage in the rat. (MRID *161170)*

HLR 157-83: Burgess, B.A. (1983) Ten-Dose Oral Subacute Test in Rats.

HLR 281-84: Pastoor, T. (1984) Long-term Feeding and Two-generation, Four-litter Reproduction Study in Rats with … INH-6573. (MRID *148511)*

HLR 424-90: Mullin, L. (1990) Reproductive and Fertility Effects with Flusilazole Multigeneration Reproduction Study in Rats *(MRID 41684601)*

HLR 431-84: Alvarez, L. (1984) Developmental toxicity study in rats given INH6573-66 in the diet on days 7-16 of gestation. (MRID *148513)*

HLR 444-83: Lamontia, C.L. (1983) Embryo-fetal toxicity and teratogenicity study of INH6573-39 by gavage in the rat. (MRID *161169)*

HLR 579-86: Hunon, D.G. (1986) Chronic Toxicity of Silane, [bis(4-fluorophenyl)] (methyl) (1H-1,2,4-triazol-1-ylmethyl)- to Daphnia *magna*. (MRID *40042141)*

HLR 654-85: Alvarez, L. (1985) INH6573: Prenatal and postnatal toxicity study in rats dosed by gavage on days 7-16 of gestation. *(MRID* 154928)

D. RESIDUE AND ENVIRONMENTAL FATE

D1. Residue and Metabolism

D1.a. Residue

Summary of Famoxadone and Flusilazole Residue Data in Soybeans

Residue trials have been conducted on soybeans treated with several different flusilazole formulations (1-3 applications, 1.07-2.86 oz flusilazole/A, 14-72 day PHI) in France (2 trials with 2 applications, 22-34 day intervals), Brazil (3 trials with 2 rates, 3 applications, 14-day intervals), Argentina (2 trials, 2 rates, 1 application) and South Africa (2 trials, 2 rates, 2 applications, 16-30 day intervals) for a total of 10 sites.

Residue trials have been conducted on soybeans treated with one famoxadone formulation (3 applications, 1-2 oz famoxadone/A, 14-28 day PHI) in Brazil (3 trials with 2 rates, 3 applications, 14-day intervals) for a total of 3 sites.

A decline study was conducted in Brazil for three different flusilazole formulations. The average half-life for flusilazole residues in soybeans following 3 applications was 7 days (range 6.8-7.3 days).

A decline study was conducted in Brazil for one famoxadone formulation. The half-life for famoxadone residues in soybeans following 3 applications was 11.2 days.

The overall data has been summarized. The data is also presented by country in subsequent tables.

In all trials there were no quantifiable flusilazole residues at a 30-day PHI or later except for 1 trial in France (0.01 mg/kg, 2.86 oz flusilazole/A, 48-day PHI). From data concerning processing of soybeans to oil + cake, it was determined that any residues of flusilazole found in the soybean seed would concentrate in the resulting oil by a factor of 3X.

In all trials there were quantifiable famoxadone residues at a 14- to 28-day PHI (0.010-0.020 mg/kg for 14-day, 0.010 mg/kg for 28-day PHI).

The proposed US label for DPX-H6573 40EC, Punch™ 40EC, on soybeans includes 2 applications at 1.75 oz flusilazole ai/A/application with a 14-day interval and a 30-day PHI.

The proposed US label for Charisma™EC on soybeans includes 2 applications at 1.07 oz flusilazole ai/A/application + 1.0 oz famoxadone ai/A/application with a 14-day interval and a 30-day PHI.

Formulation	Active Ingredient 1	Active Ingredient 2
DPX-H6573 40EC	400 g flusilazole/L	---------
Charisma™ EC	107 g flusilazole/L	100 g famoxadone/L
Punch™ CS	250 g flusilazole/L	125 g MBC/L
Alert®	125 g flusilazole/L	250 g MBC/L
Fusión®	125 g flusilazole/L	250 g MBC/L
Punch-Xtra®	125 g flusilazole/L	250 g MBC/L
Capitan®	250 g flusilazole/L	---------

MBC = Carbendazim
Alert and Fusión are the same formulation.

				Flusilazole Residue (mg/kg, *ppm*)						
				PHI						
Country	Location	Test Material	Rate (oz ai/A)	0	7	14	21	28	48	72
Brazil (a)	Rondonopolis	Punch™ CS	1.07	-----	-----	0.01	-----	<0.01	-----	-----
			2.14	-----	-----	0.02	-----	<0.01	-----	-----
Brazil (a)	Ponta Grossa	Punch™ CS	1.07	-----	-----	0.01	-----	<0.01	-----	-----
			2.14	-----	-----	0.02	-----	<0.01	-----	-----
Brazil (a)	Londrina	Punch™ CS	1.07	0.06	0.02	0.01	0.01	<0.01	-----	-----
			2.14	-----	-----	0.02	-----	<0.01	-----	-----
Brazil (a)	Rondonopolis	Charisma™	1.07	-----	-----	<0.01	-----	<0.01	-----	-----
			2.14	-----	-----	<0.01	-----	<0.01	-----	-----
Brazil (a)	Ponta Grossa	Charisma™	1.07	-----	-----	0.01	-----	<0.01	-----	-----
			2.14	-----	-----	0.01	-----	<0.01	-----	-----
Brazil (a)	Londrina	Charisma™	1.07	0.05	0.01	0.01	<0.01	<0.01	-----	-----
			2.14	-----	-----	0.01	-----	<0.01	-----	-----
Brazil (a)	Rondonopolis	Alert®	1.07	-----	-----	0.01	-----	<0.01	-----	-----
			2.14	-----	-----	0.01	-----	<0.01	-----	-----
Brazil (a)	Ponta Grossa	Alert®	1.07	-----	-----	0.01	-----	<0.01	-----	-----
			2.14	-----	-----	0.02	-----	<0.01	-----	-----
Brazil (a)	Londrina	Alert®	1.07	0.06	0.01	<0.01	<0.01	<0.01	-----	-----
			2.14	-----	-----	0.01	-----	<0.01	-----	-----
France	Buzet	Punch™ CS	2.86	-----	-----	-----	-----	-----	-----	<0.01(b)
France	Fauverney	Punch™ CS	2.86	-----	-----	-----	-----	-----	0.01(c)	-----

Three applications, 14-day spray intervals.
Processed to cake and oil. Both fractions had <0.01 mgikg flusilazole residues.
Processed to cake and oil. Cake residues were 0.01 mg/kg flusilazole and oil residues were 0.03 mgikg (3X concentration factor).
Note: Highest residue at 14 day PHI or later is 0.020 mgikg.

				Famoxadone Residue (mg/kg, ppm)						
				PHI						
Country	Location	Test Material	Rate (oz ai/A)	0	7	14	21	28	48	72
Brazil (e)	Rondonopolis	Charisma™	1.0	-----	-----	0.01	-----	0.01	-----	-----
			2.0	-----	-----	0.02	-----	0.01	-----	-----
Brazil (e)	Ponta Grossa	Charisma™	1.0	-----	-----	0.01	-----	0.01	-----	-----
			2.0	-----	-----	0.01	-----	0.01	-----	-----
Brazil (e)	Londrina	Charisma™	1.0	0.05	0.03	0.02	0.01	0.01	-----	-----
			2.0	-----	-----	0.02	-----	0.01	-----	-----

(a) Three applications, 14-day spray intervals.

				Flusilazole Residue (mg/kg, ppm)				
				PHI				
Country	Location	Test Material	Rate (oz ai/A)	34	38	48	54	60
Argentina (f)	Peyrano	Fusión®	1.43	-----	-----	-----	-----	<0.01
			2.86	-----	-----	-----	-----	<0.01
Argentina (f)	Victoria	Fusión®	1.43	-----	-----	-----	-----	-----
			2.86	-----	-----	-----	<0.01	-----
Argentina (f)	Montes de Oca	Fusion@	1.43	-----	<0.01	-----	-----	-----
			2.86	-----	<0.01	-----	-----	-----
South Africa	Benson Farms	Punch-Xtra®	1.07	<0.05(g)		-----	-----	-----
			2.14	<0.05(g)		-----	-----	-----
South Africa	Benson Farms	Capitan®	1.07	<0.05(g)	-----	-----	-----	-----
			2.14	<0.05(g)	-----	-----	-----	-----
South Africa	Denleigh Farm	Punch-Xtra®	1.07	-----	-----	<0.05(g)	-----	-----
South Africa	Denleigh Farm	Capitan®	2.14	-----	-----	<0.05(g)		-----

One application.
LOQ = 0.050 mg/kg

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates				PHI Days[a]	Residues (mg/kg)[b]
	Formulation - Test Material	No	g as/ha	oz ai/A		
France, Buzet, Tarn 1990, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	72	<0.01 grain
France, Buzet, Tarn 1990, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	72	<0.01 cake
France, Buzet, Tarn 1990, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	72	<0.01 oil
France, Fauverney, Côte d'Or 1990, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	48	0.01[c] grain
France, Fauverney, Côte d'Or 1990, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	48	0.01 cake
France. Fauverney, Côte d'Or 1990, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	2	200	2.86	48	0.03 oil
Number of tests						2
Average at Normal Harvest (48-72 days)						0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

[c] duplicate samples

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates: Formulation - Test Material	No	g as/ha	oz ai/A	PHI Days[a]	Residues (mg/kg)[b]
Brazil, Rondonopolis 2004, 1	Alert 125 g flusilazole + 250 g MBCIL	3	75	1.07	14	0.01
Brazil, Rondonopolis 2004, 1	Alert 125 g flusilazole + 250 g MBCIL	3	150	2.14	14	0.01
Brazil, Rondonopolis 2004, 1	Alert 125 g flusilazole + 250 g MBCIL	3	75	1.07	28	<0.01
Brazil, Rondonopolis 2004, 1	Alert 125 g flusilazole + 250 g MBCIL	3	150	2.14	28	<0.01
Brazil, Ponta Grossa 2004, 2	Alert 125 g flusilazole + 250 g MBC/L	3	75	1.07	14	0.01
Brazil, Ponta Grossa 2004, 2	Alert 125 g flusilazole + 250 g MBC/L	3	150	2.14	14	0.02
Brazil, Ponta Grossa 2004, 2	Alert 125 g flusilazole + 250 g MBC/L	3	75	1.07	28	<0.01
Brazil, Ponta Grossa 2004, 2	Alert 125 g flusilazole + 250 g MBC/L	3	150	2.14	28	<0.01
Brazil, Londrina 2004, 3	Alert 125 g flusilazole + 250 g MBC/L	3	75	1.07	0 7 14 21 28	0.06 0.01 <0.01 <0.01 <0.01
Brazil, Londrina 2004, 3	Alert 125 g flusilazole + 250 g MBC/L	3	150	2.14	14	0.01
Brazil, Londrina 2004.3	Alert 125 g flusilazole + 250 g MBCIL	3	150	2.14	28	<0.01
Number of tests						3
Average at Normal Harvest (14-28 days)						0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates				PHI Days[a]	Residues (mg/kg)[b]
	Formulation - Test Material	No	g as/ha	oz ai/A		
Brazil, Rondonopolis 2004, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	125	1.07	14	0.01
Brazil, Rondonopolis 2004, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	250	2.14	14	0.02
Brazil, Rondonopolis 2004, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	125	1.07	28	<0.01
Brazil, Rondonopolis 2004, 1	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	250	2.14	28	<0.01
Brazil, Ponta Grossa 2004, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	125	1.07	14	0.01
Brazil, Ponta Grossa 2004, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	250	2.14	14	0.02
Brazil, Ponta Grossa 2004, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	125	1.07	28	<0.01
Brazil, Ponta Grossa 2004, 2	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	250	2.14	28	<0.01
Brazil, Londrina 2004, 3	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	75	1.07	0 7 14 21 28	0.06 0.02 0.01 0.01 <0.01
Brazil, Londrina 2004, 3	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	150	2.14	14	0.02
Brazil, Londrina 2004.3	Punch™ CS 250 g flusilazole + 125 g MBC/L	3	150	2.14	28	<0.01
Number of tests						3
Average at Normal Harvest (14-28 days)						0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates				PHI Days[a]	Residues (mg/kg)[b]
	Formulation - Test Material	No	g as/ha	oz ai/A		
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	75	1.07	14	<0.01
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	14	<0.01
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	75	1.07	28	<0.01
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	28	<0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	75	1.07	14	0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	14	0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	75	1.07	28	<0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	28	<0.01
Brazil, Londrina 2004, 3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	75	1.07	0 7 14 21 28	0.05 0.01 0.01 <0.01 <0.01
Brazil, Londrina 2004, 3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	14	0.01
Brazil, Londrina 2004, 3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	150	2.14	28	<0.01
Number of tests						3
Average at Normal Harvest (14-28 days)						0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

SUMMARY OF MAGNITUDE OF **FAMOXADONE** RESIDUES I N SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates: Formulation - Test Material	No	g as/ha	oz ai/A	PHI Days[a]	Residues (mg/kg)
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	70	1.0	14	0.01
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	14	0.02
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	70	1.0	28	0.01
Brazil, Rondonopolis 2004, 1	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	28	0.01
Brazil, Ponta Grossa 2004,2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	70	1.0	14	0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	14	0.01
Brazil, Ponta Grossa 2004.2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	70	1.0	28	0.01
Brazil, Ponta Grossa 2004, 2	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	28	0.01
Brazil, Londrina 2004, 3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	70	1.0	0 7 14 21 28	0.05 0.03 0.02 0.01 0.01
Brazil, Londrina 2004.3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	14	0.02
Brazil, Londrina 2004.3	Charisma™ 107 g flusilazole + 100 g famoxadone/L	3	140	2.0	28	0.01
Number of tests						3
Average at **Normal Harvest** (14-28 days)						0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates				PHI Days[a]	Residues (mg/kg)[b]
	Formulation - Test Material	No	g as/ha	oz ai/A		
Argentina, Peyrano 2003, 1	Fusión 125 g flusilazole + 250 g MBC/L	1	100	1.43	60	<0.01
Argentina, Peyrano 2003, 1	Fusión 125 g flusilazole + 250 g MBC/L	1	200	2.86	60	<0.01
Argentina, Victoria 2003, 2	Fusión 125 g flusilazole + 250 g MBC/L	1	100	1.43	54	<0.01
Argentina, Victoria 2003, 2	Fusión 125 g flusilazole + 250 g MBC/L	1	200	2.86	54	<0.01
Argentina, Montes de Oca 2003.3	Fusión 125 g flusilazole + 250 g MBC/L	1	100	1.43	38	<0.01
Argentina, Montes de Oca 2003.3	Fusión 125 g flusilazole + 250 g MBC/L	1	200	2.86	38	<0.01
Number of tests						3
Average at Normal Harvest (38-60 days)						<0.01[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.010 mg/kg (ppm)

SUMMARY OF MAGNITUDE OF FLUSILAZOLE RESIDUES IN SOYBEAN SEED

Country, Location, Year, Test No	Actual Application Rates (assuming a density of 1)				PHI Days[a]	Residues (mg/kg)[b]
	Formulation - Test Material	No	g as/ha	oz ai/A		
South Africa Benson Farms 2002, 1	Punch-Xtra 125 g flusilazole + 250 g MBC/L	2	75	1.07	34	<0.05
South Africa Benson Farms 2002, 1	Punch-Xtra 125 g flusilazole + 250 g MBC/L	2	150	2.14	34	<0.05
South Africa Benson Farms 2002, 1	Capitan 250 g flusilazole/L	2	75	1.07	34	<0.05
South Africa Benson Farms 2002, 1	Capitan 250 g flusilazole/L	2	150	2.14	34	<0.05
South Africa Denleigh Farm 2002, 2	Punch-Xtra 125 g flusilazole + 250 g MBC/L	2	75	1.07	48	<0.05
South Africa Denleigh Farm 2002.2	Capitan 250 g flusilazole/L	2	150	2.14	48	<0.05
Number of tests						2
Average at Normal Harvest (34-48 days)						<0.05[b]

[a] Days after last application

[b] Limit of Quantitation (LOQ) = 0.050 mg/kg (ppm).

References for Residue Data

The following reports have not been submitted to US EPA, but are available for review upon request.

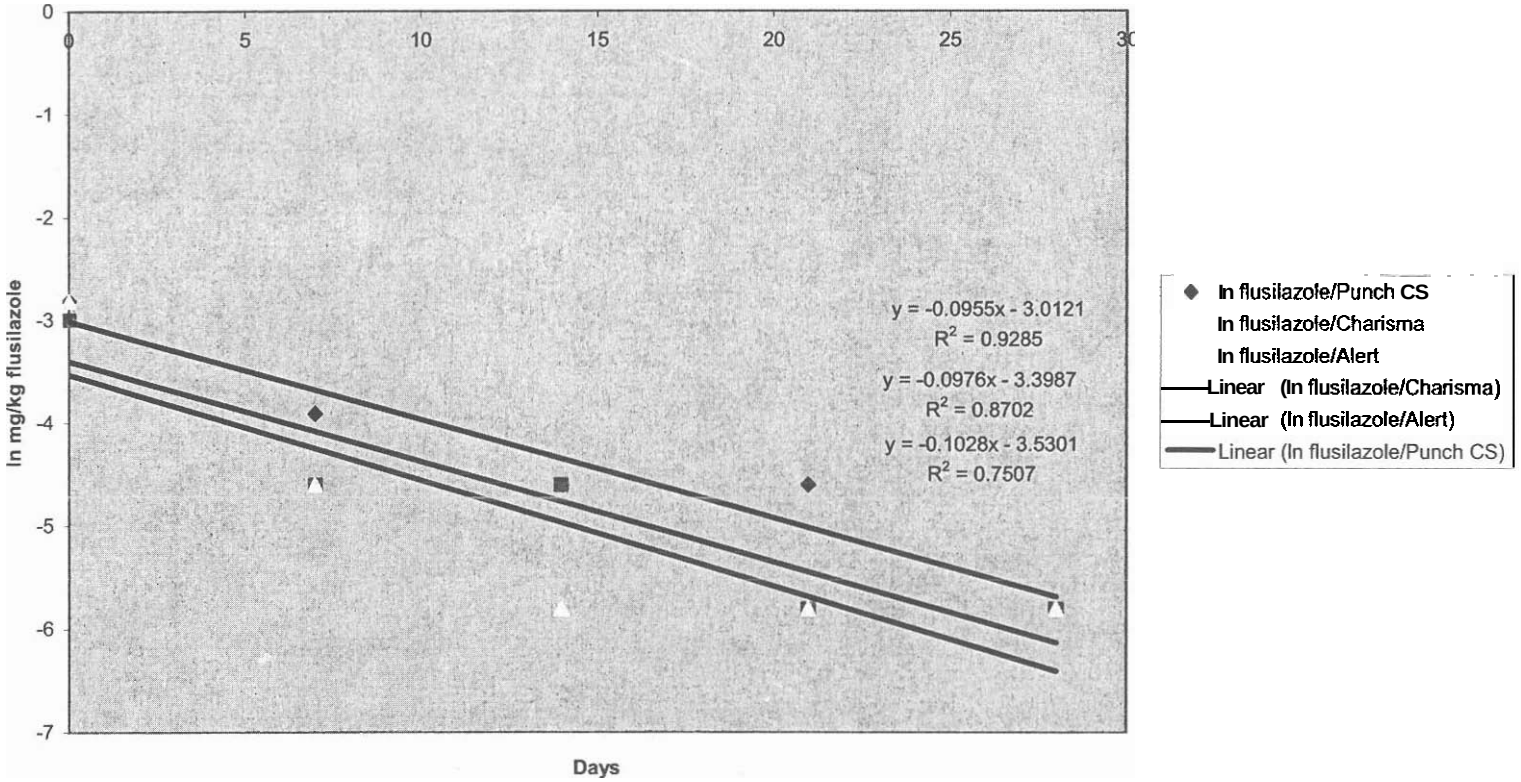
Brodsky, J. 1991. Determination of Residues of Flusilazole (DPX-H6573) in Soybeans by GC-MS following Treatment with "Punch CS" (Season 1990 – France). Battelle-Institut E.V. Frankfurt, Germany. BE-A-I I-91-01-BF. Unpublished.

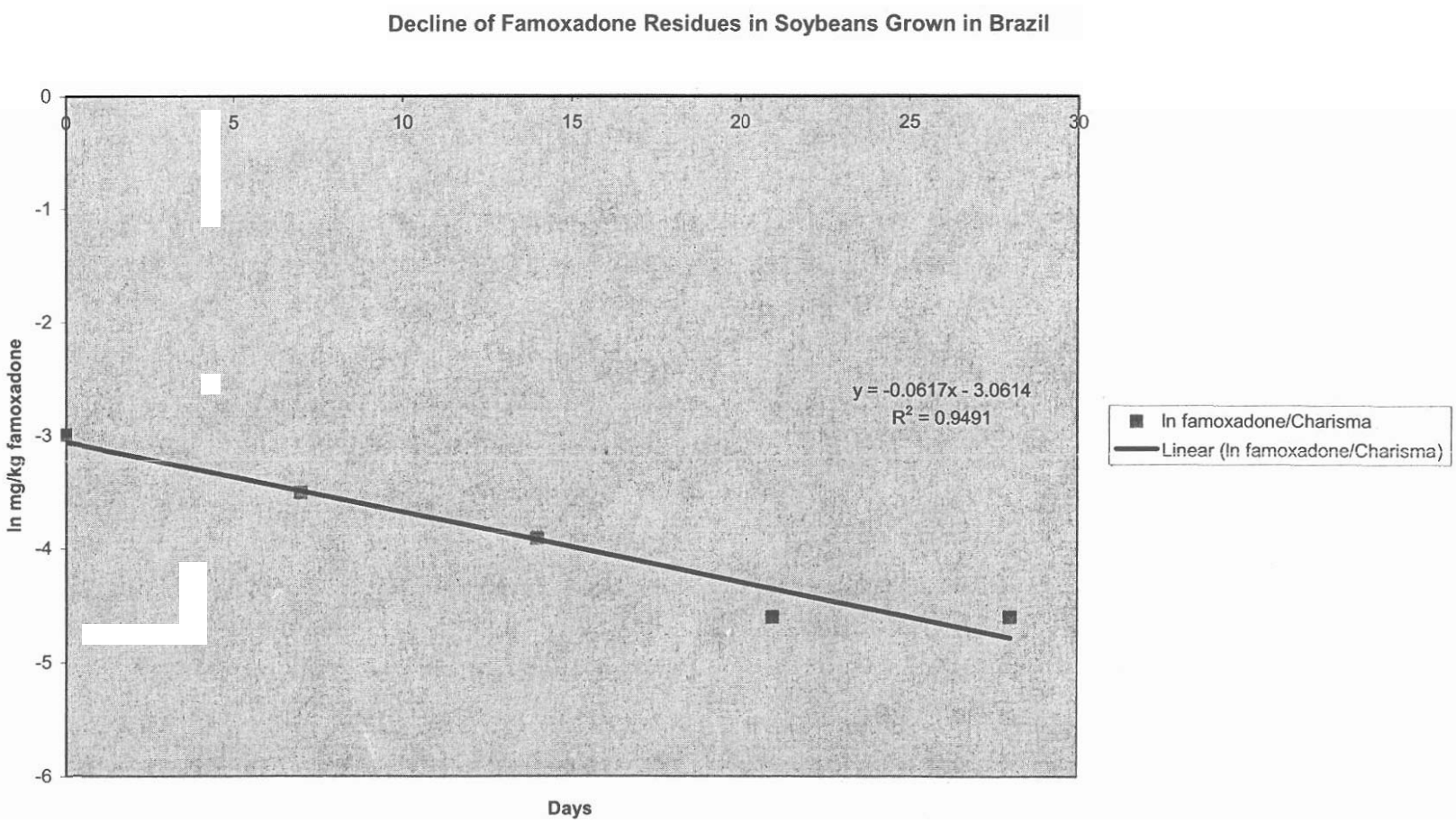
DuPont Brazil Study Numbers: RBR-04-276, RBR-04-277, RBR-04-278; Study Director: André Luis Moraes. 2004. Unpublished.

San Juan, M., Morre, J. 2004. Magnitude of Residues of DPX-H6573 (Flusilazole) in Cultivars of Soybean (*Glycine max* L. Merr.) for the Registration of the Product FUSIÓN® (Fungicide) (Flusilazole 12.5% + Carbendazim 25% SC) Trials canied out in the Argentine Republic Season 2003. DuPont Argentina Study Number: 005-2004. Unpublished.

Garbers, H.V. 2003. Determination of Flusilazole and Carbendazim Residues in Soya. SABS, Pretoria, South Africa. Report No. 7214/2126256/W393. . Unpublished.

Decline of Fluzilazole Residues in Soybeans Grown in Brazil




Decline of Famoxadone Residues in Soybeans Grown in Brazil
ln mg/kg famoxadone
Days
y = -0.0617x - 3.0614
R² = 0.9491
ln famoxadone/Charisma
Linear (ln famoxadone/Charisma)
0
-1
-2
-3
-4
-5
-6
0
5
10
15
20
25
30

D1.b. Metabolism

Metabolism of ^{14}C-Flusilazole in Plants, Livestock and Rotational Crops

Metabolism of ^{14}C-Flusilazole in Plants

General experimental conditions

The metabolism of [triazole-3-^{14}C]- and [phenyl (U)-^{14}C]flusilazole has been investigated in wheat, grapes, apples, bananas, sugar beets, and to a limited extent in peanuts (phenyl label only).

Plants were selected to represent four different crop groups; cereals (wheat), root vegetables (sugar beets), fruit (apples, grapes, and bananas) and oil seed legume. Plants were treated in a manner to simulate actual use conditions.

The foliage of greenhouse-grown Era spring wheat was treated with either phenyl- or triazole-labeled flusilazole at a rate of 200 g ai/ha. At treatment, the wheat plants were approximately 30-days old and 8-10 inches high. Plants were harvested 5, 10-12, 20, and approximately 70 (mature crop) days after treatment.

Separate branches of foliage and grapes of Catawba grape vines were treated with phenyl- or triazole-labeled flusilazole under field conditions at Newark, DE, USA. The branches were sprayed just to runoff to simulate actual use conditions. The berries were harvested 41 days after the application.

Separate isolated branches of Rome apple trees were treated with either phenyl- or triazole-labeled flusilazole under field conditions at Newark, DE, USA. Branches were treated four times at 14-day intervals at rates of approximately 8 mg/100 mL. Mature fruit were harvested 14 days after the final application (56 days after the initial application).

Banana plants are treated commercially by aerial overspraying while the fruit is bagged. Since banana fruit is generally not directly exposed during commercial application, special application techniques were used in the banana metabolism study to assess translocation to banana pulp. Phenyl- or triazole-labeled flusilazole was applied directly to unpeeled green bananas and to leaves of immature banana palm plants growing under greenhouse conditions. The bananas were analyzed at intervals of 0, 2, 4, 7, and 11 days and the leaves were analyzed at intervals of 0, 7, 14, and 18 days.

Sugar beets (variety Hilma) were planted in 10-gallon pots containing a loamy sand soil in a greenhouse at DuPont Experimental Station, Wilmington, DE, and treated post-emergence with either [triazole-3-^{14}C]flusilazole or [phenyl(U)-^{14}C]flusilazole (DPX-H6573). The test substance was applied as an over the top spray at an application rate of 124-131 g/ai/ha 63 or 46 days after planting, respectively. Applications were repeated 14

and 28 days after the initial application at the same rate. The total application was 372-393 g ai/ha.

A preliminary investigation was carried out in peanuts with [phenyl (U)-^{14}C]flusilazole, applied to the foliage at 140 g a.i./ha. (2 oz a.i /acre) 52 clays prior to harvest. Peanut foliage was sampled at 0, 3, 7, 14, 21 and 52 days. Peanuts (nut and shells) were harvested at 52 days (maturity).

Distribution of radiolabel in plant parts

Flusilazole is applied directly to the edible portion of crops such as apples and grapes. In the case of apples and grapes, the uptake and distribution of radiolabel are not relevant in terms of consumer risk.

Flusilazole can be applied to wheat at mid-tillering so the distribution of radiolabel between the forage, straw and grain was evaluated. In forage, total residue levels fell from 32.3 and 8.6 pprn for the phenyl and triazole label, respectively, to approximately 6 pprn by Days 10-12. In grain, there were negligible residues (0.01 ppm) from phenyl-label flusilazole. In the triazole-treated wheat, grain residues of 4.4-ppm flusilazole equivalents were comprised of triazolyl alanine and triazole acetic acid. This data indicate that although metabolites containing the triazole ring can be translocated, intact flusilazole is not translocated to grain.

In the case of bananas, flusilazole distribution from the peel to the pulp is negligible since even after 11 days, 98-99% of the radioactivity applied to the peel remained in the washings and peel. Autoradiographs showed that flusilazole applied to banana leaves did not translocate from the treated areas.

The concentrations of total radioactivity in sugar beets, harvested immediately after the spray solution had dried and 14, 28, and 59 or 77 days (maturity) after three applications of [triazole-3-^{14}C]flusilazole or [phenyl(U)-^{14}C]flusilazole were determined as ^{14}C flusilazole equivalents. Radioactive residues were consistently higher in the foliage than in the roots. Immediately after the third treatment, total radioactive residues expressed as parent equivalents ranged between 1.54 and 7.16 pprn in the foliage for triazole- and phenyl-labeled flusilazole, respectively. At each sampling interval, total radioactive residues in the roots were lower for the phenyl-treated plants (<0.01 pprn maximum) than for the triazole-treated plants (0.147 pprn maximum). With time, the total radioactive residues in both the foliage and roots decreased.

Total radioactive residues in the foliage of peanut plants declined from 3.41 ppm at Day 0 to 0.38 pprn at Day 52. There was no significant translocation of phenyl labeled metabolites to the peanut seed (total residue in the seed was 0.018 ppm) or peanut shell (0.03 pprn).

Identification of plant metabolites

Wheat

Extensive metabolism occurred in wheat plants. Unchanged flusilazole accounted for only 15% of the residue in mature straw. No flusilazole was found in triazole-labeled grain samples and negligible residues (0.01 ppm) were found in phenyl-labeled grain samples. Extraction was exhaustive, leaving only low levels of unextracted radioactivity (6% maximum).
The major triazole-labeled wheat metabolites were triazolyl alanine and triazole acetic acid. Other metabolites, arising from the triazole label and comprising less than 10% of the total radioactivity, included the phenol (IN-37722) and its glucose phosphate and glucose malonate conjugates. The major phenyl-labeled wheat residues were flusilazole and the glucose phosphate conjugate of the phenol (IN-37722). Other metabolites, arising from the phenyl label and comprising less than 10% of the total radioactivity, included the silanol (IN-F7321), disiloxane, the hydroxy phenol (IN-37722) and its conjugates, and IN-37738 and its conjugates. Unidentified minor metabolites were present in triazole and phenyl ^{14}C-flusilazole treated wheat straw, however, no unidentified metabolites exceeded 4% of the total radioactive residue.

Grapes

Flusilazole was the predominant residue extracted from both the phenyl-labeled and triazole-labeled grape berries, comprising between 57 and 31% of the recovered radioactivity, respectively. The principal degradation product from phenyl-labeled flusilazole was the silyl methanol metabolite (IN-H7169). Four identified minor metabolites containing the phenyl label (IN-F7321, IN-V5571, IN-A7634, and Metabolite IN-T7866) together accounted for <10% of the recovered radioactivity. In addition to flusilazole, triazolyl alanine was a major degradation product in triazole-labeled grape berries. Unextractable residues from fruit accounted for between 5 and 14% of the recovered radioactivity.

Apples

Flusilazole was the predominant residue extracted from both the phenyl-labeled and triazole-labeled apple fruit, comprising between 71 and 48% of the recovered radioactivity, respectively. Three identified minor metabolites containing the phenyl label (IN-F7321, IN-V5571, and IN-H7169) together accounted for approximately 11% of the recovered radioactivity. Triazolyl alanine was a significant triazole-containing metabolite. Unextractable residues from the apple fruit accounted for between 8 and 14% of the recovered radioactivity.

Bananas

Eleven days after application of phenyl- or triazole-labeled flusilazole to the peel of detached green banana fruit, intact flusilazole accounted for greater than 87% of the

radioactivity in the peel rinses, peels and flesh. Greater than 95% of the radioactivity in banana flesh and peel was extracted.

Sugar Beets

Flusilazole was the major residue in the foliage, accounting for a maximum of 89% of the total radioactivity present in the foliage. No flusilazole was detected in root extracts.. Minor metabolites found included IN-G7072 and IN-37722. Numerous minor metabolites were also seen. Residues in the roots consisted of polar materials that were not resolved by HPLC. These results are consistent with previous plant metabolism studies showing significant polar residues with the triazole label after cleavage of flusilazole between the triazole and phenyl rings. Therefore, at an application rate approximately equivalent to the maximum seasonal application in the EU, flusilazole is not present in washed sugar beet roots and is the major expected residue in mature sugar beet foliage.

Peanuts

Flusilazole (parent) was the major residue in the foliage at all sampling intervals, declining from 3.15 ppm at Day 0 to 0.19 ppm at Day 52. There was no significant translocation of phenyl labeled metabolites to the peanut seed (total residue in the seed was 0.018 ppm). Flusilazole (parent) at 0.006 ppm and "water soluble metabolites" also at 0.006 ppm, appeared to be present in the seed with the remaining residue unextractable.

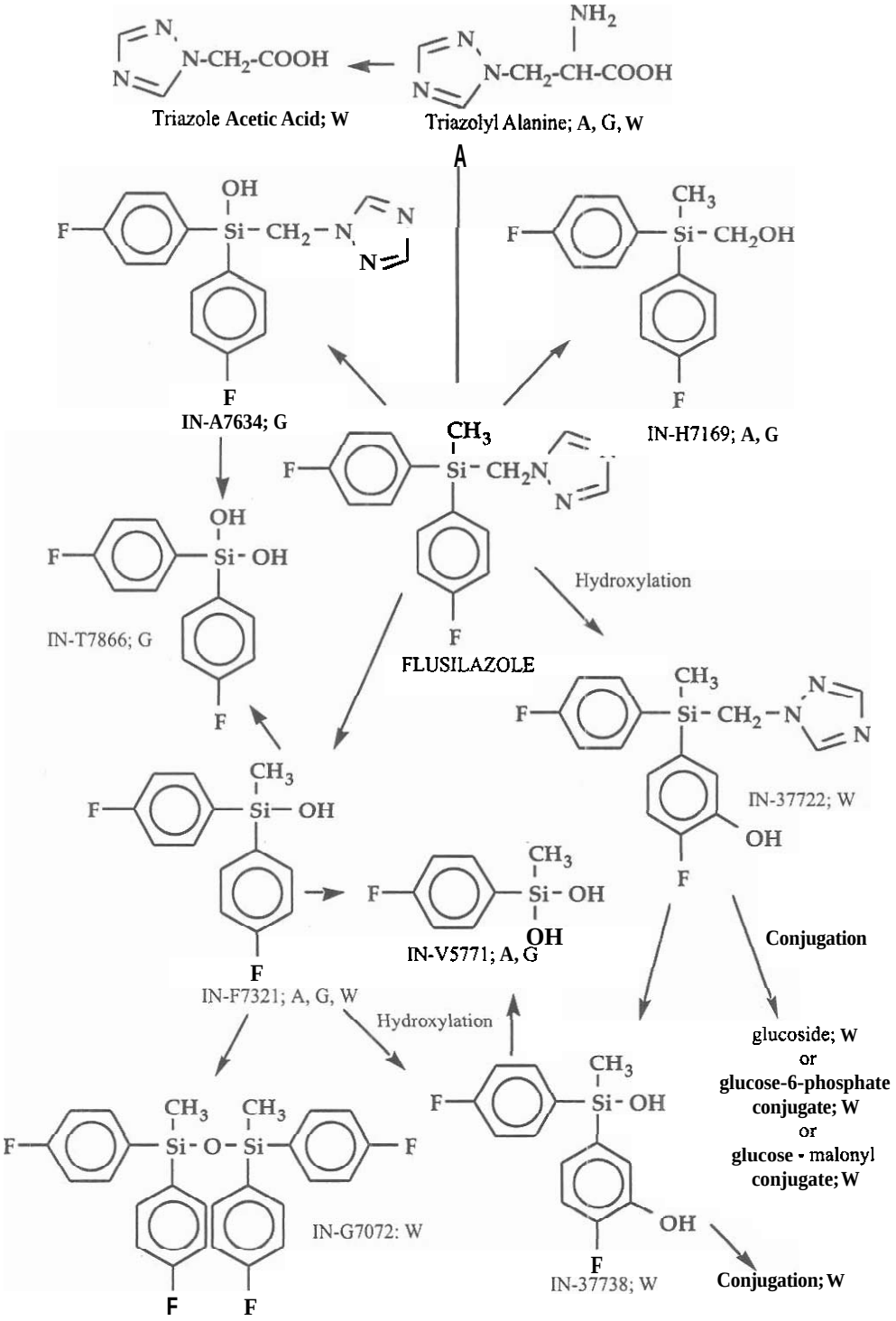
Metabolic pathway of ^{14}C-Flusilazole in plants

Plant metabolism studies conducted with apples, grapes, and wheat show qualitatively similar metabolism among the crops. The metabolic pathway in plants involves hydroxylations, conjugations, and cleavage between the silicon and the triazole ring. As the interval between treatment and sampling increases, there are decreasing residues of unchanged flusilazole and increased metabolism and conjugation. Only unchanged flusilazole was identified in bananas, possibly due to the short sampling intervals.

The metabolic pathway for flusilazole in plants is shown in the following figure (Figure 2). The letter following the metabolite identification indicates in which plants the metabolites were identified.

A major metabolic route in plants is cleavage of the Si-CH2 bond to form the silanol (IN-F7321) which may be further metabolized to the silane diols (IN-V5771 and IN-T7866) or to disiloxane (IN-G7072). Hydroxylation can occur on the phenyl ring of intact flusilazole or IN-F7321 resulting in phenolic metabolites IN-37722 and IN-37738, respectively. The phenolic groups become the sites for conjugation reactions. The major plant metabolite arising from triazole-labeled flusilazole is triazolyl alanine, which is subsequently metabolized to triazole acetic acid.

FIGURE 2 METABOLIC PATHWAYS FOR FLUSILAZOLE IN PLANTS



The letters following the code number denote crops in which the metabolites were identified; A, Apple; G, Grape; W, Wheat

Conclusions

The metabolic fate of flusilazole in plants is adequately understood. Exhaustive extraction techniques ensured that more than 86% of the radiolabeled plant residues were characterized. Due to the extensive degradation of flusilazole by multiple mechanisms to many minor metabolites, there are no major flusilazole metabolites in plants, other than triazolyl alanine. With the exception of triazolyl alanine and triazole acetic acid, individual metabolites generally account for less than 14% of the total radioactivity in the plants.

Metabolism of ^{14}C-Flusilazole in Goats

General experimental considerations

Two lactating goats were each dosed daily be gelatin capsule for 6 days (phenyl label) or 5 days (triazole label) with 50 mg (50 ppm dietary equivalent) of phenyl- or triazole-^{14}C-labelled flusilazole.

Distribution of radiolabel in tissues and milk

Urine, feces, milk, blood, and tissues were sampled for characterization and quantitation of residues. Residues recovered as a percentage of the administered dose from the phenyl and triazole labels, respectively, were urine (44.7 and 23.3), feces (8.1 and 12.8), milk (0.34 and 1.3) and tissues (8.2 and 2.5). The lack of material balance is attributed to unexcreted radioactivity associated with the GI tract and radioactivity associated with the carcass.

Bioaccumulation potential for flusilazole residues is low. Flusilazole was extensively metabolized to more polar compounds that were rapidly excreted.

As a percentage of the administered dose calculated as flusilazole, residues in edible tissue ranged from 0.06% in the muscle to 5.3% in the liver for the phenyl label and 0.01% in fat to 1.5% in the liver for the triazole label. Tissue residues, calculated as mg flusilazole/kg equivalents (ppm), for the phenyl label ranged from 13.5 ppm in the liver to 0.41ppm for leg muscle. Tissue residues, calculated as mg flusilazole/kg, for the triazole label ranged from 3.5 ppm in the liver to 0.15 ppm for peripheral fat.

Residues levels in milk reached a plateau 2-5 days after the initial dose, and did not continue to increase throughout the dosing period. Milk residues from the phenyl label

ranged from 0.09 to 0.74 pprn flusilazole equivalents. Milk residues from the triazole label ranged from 0.36 to 0.74 pprn flusilazole equivalents.

Identity of Goat Metabolites

Flusilazole was well absorbed and extensively metabolized. Except in the liver, unchanged flusilazole accounted for less than 10% of the tissue radioactivity. The metabolic pathway in the goat involves cleavage between the triazole and silicon. The metabolic products include bis (4-fluorophenyl)(methyl)silanol (IN-F7321), which can condense to form disiloxane (IN-G7072), 1,3,4-triazole, and [bis(4-fluorophenyl)(methyl)silyl]methanol (IN-H7169)and its glucuronopyranoside conjugate.

Metabolism of ^{14}C-Flusilazole in Poultry

General experimental considerations

Hens were dosed with phenyl- or triazole-^{14}C-labelled flusilazole at 0.36 or 18 mg/day, equivalent to 3 and 150 pprn in the diet. Hens from the exaggerated dose group were dosed for 5 days while the low dose group was dosed for 14 days. Excreta from the highest dose group was used for metabolite isolation and identification. Flusilazole had no effect on behavior, body weight, feed consumption, or egg production.

Distribution of radiolabel in tissues and eggs

Residues were quantitated in eggs, tissues, excreta, and blood in hens. Flusilazole was extensively metabolized and rapidly excreted in the feces. Approximately 80% of the radioactive dose was eliminated in the excreta. Elimination of radioactivity in the excreta became constant after 48 hours. Residues in edible tissues were low, less than 1% of the administered dose.

In hens receiving phenyl labelled flusilazole, highest residues were found in the liver (0.60-ppm flusilazole equivalents) and in the fat (0.52-ppm flusilazole equivalents). Residue levels in the muscle were the lowest. In hens receiving triazole labelled flusilazole, residues were comparable in liver and muscle (0-33-0.38 ppm) and lower in fat (0.07-ppm flusilazole equivalents).

Flusilazole was well absorbed and extensively metabolized. Bioaccumulation potential for flusilazole residues is low. In eggs from hens dosed at 3 pprn for 14 days, radioactivity reached a steady state after about 8 days at about 2% of the radiolabel administered with a plateau residue level of 0.21-0.26 pprn flusilazole equivalents (from phenyl and triazole treated hens).

Identity of Poultry metabolites

Flusilazole was well-absorbed and extensively metabolized. Phenyl silane diol (IN-V5771) was the main metabolite in liver, kidney, and muscle, and a major residue in 12-day eggs of hens dosed with 3-ppm phenyl label. The silanol (IN-F7321) was the main residue in the fat and eggs and a major one in the liver. Phosphate conjugates were found in liver, kidney, and eggs. The metabolic pathway showed phenyl ring hydroxylation and phosphorylation of both the phenyl and silyl methanol hydroxyl groups.

Residues identified in the low dose triazole group were triazole, thymine and flusilazole, with triazole the major metabolite in all tissues. Triazole residues ranged from 0.57 ppm in liver to nondetectable levels in fat. Flusilazole levels ranged from 0.018 ppm in liver to 0.044 ppm in fat. No flusilazole was detected in muscle. In eggs at 12 days, triazole and thymine were the major residues, 0.043 and 0.009 ppm respectively, with low levels of flusilazole, 0.006 ppm.

Metabolic pathway of flusilazole in livestock

The metabolism of flusilazole was investigated in both lactating goats and laying hens. Flusilazole was extensively metabolized in both goats and hens with the majority of the radioactivity eliminated in the excreta. Bioaccumulation potential is low since levels of radioactive residues in the milk and eggs plateaued within five and eight days, respectively. The extraction procedures were exhaustive with 89% or more of the total tissue radioactivity extracted and characterized from animal tissues, respectively. The proposed metabolic pathway for flusilazole in animals is shown in Figure 3.

Residues in goats and hens were similar. Generally unchanged flusilazole was present at levels lower than the metabolites. In goat liver and chicken fat of animals dosed with triazole-labeled flusilazole, flusilazole levels were higher than levels of the metabolite 1,2,4-triazole, perhaps due to the polar nature of triazole. Except in goat liver and chicken fat, 1,2,4-triazole was the major metabolite arising from triazole-labeled flusilazole. The silanol metabolite (IN-F7321) was also common to both. The main difference between the goat study and the hen studies was the occurrence of the silanediol (IN-V5771) as a major metabolite in hens. Other phenyl-labeled metabolites, resulting from hydroxylation and conjugation reactions, were present at relatively low levels in chicken tissues and eggs.

Conclusions

The metabolic fate of flusilazole in livestock is adequately understood. Exhaustive extraction techniques ensured that more than 89% of the radiolabeled livestock residues were characterized. Major flusilazole metabolites in livestock metabolism studies include 1,2,4-triazole, IN-F7321, and silanediol (IN-V5771). Other individual metabolites generally accounted for a minor portion of the total radioactivity in livestock.

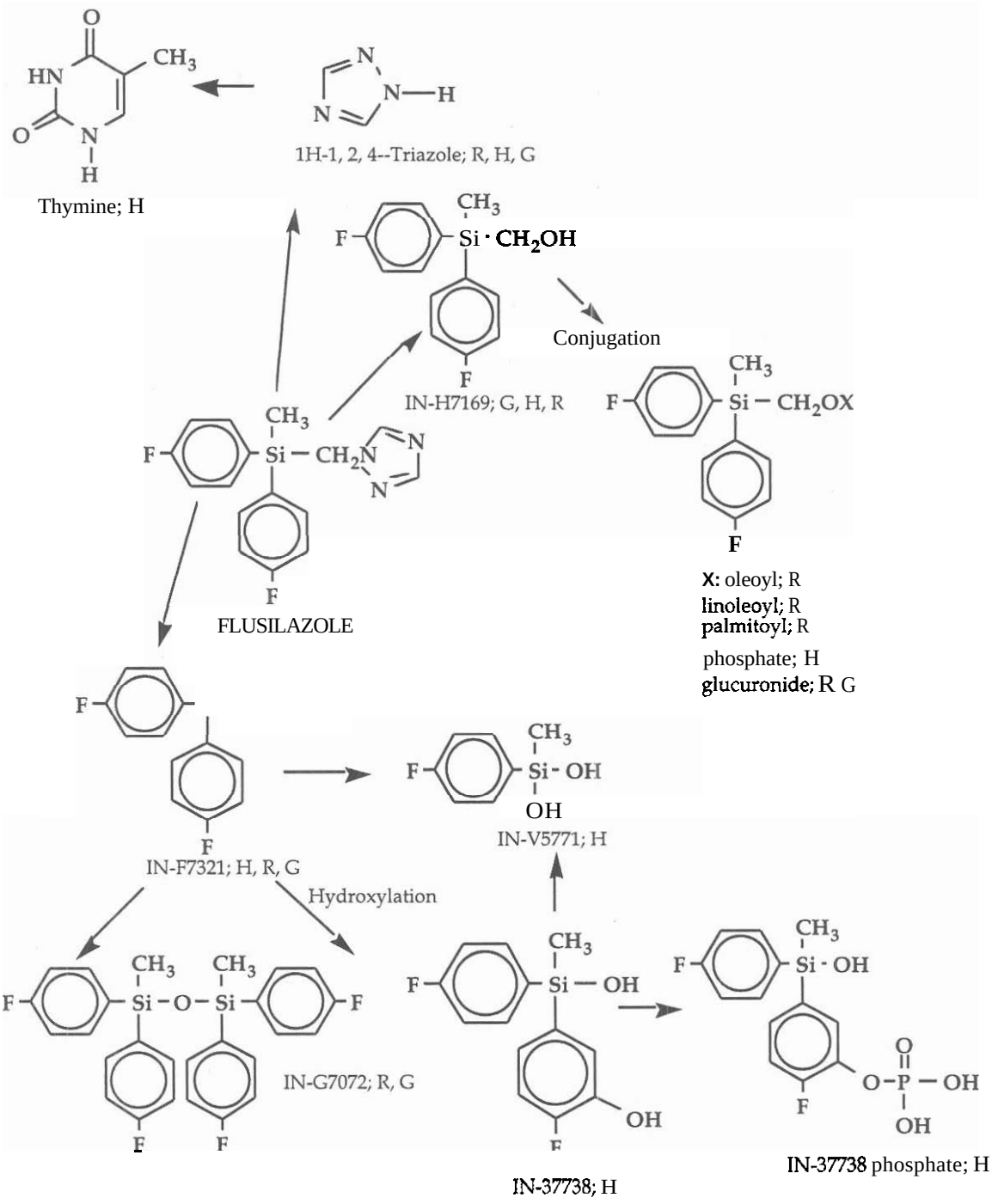
Metabolism of Flusilazole in Rats

A metabolism study was conducted in rats with radiolabeled flusilazole. The tissue residues and excretion of [phenyl(U)-^{14}C]- and [triazole-3-^{14}C]-labeled flusilazole were studied in groups of male and female CD rats after single oral doses of the labeled compound at low levels (8 ppm), with or without preconditioning, and at the exaggerated levels of 200 or 224 ppm (single dose only).

The compound was rapidly excreted, such that after 48 hours, 50-65% (phenyl) and more than 90% (triazole) of the administered compound was excreted. By 168 hours, 78-96% of the dose was excreted by the rats dosed with phenyl-labeled flusilazole. The fecal route accounted for the bulk of phenyl label eliminated, and the urinary route that of the triazole label. Excreta were used as the source for the purification and identification of several of the metabolites using TLC, HPLC and MS. Preconditioning did not affect the rate of excretion.

The major metabolites identified in urine and fecal samples were IN F7321; IN-H7169 (and its glucuronide (in male rats, there were also conjugates with fatty acids), 1,2,4-triazole; and IN-G7072; in addition to unchanged flusilazole. A metabolic pathway was proposed that involved initial cleavage of the Si-C-N linkages, releasing the triazole moiety, followed by formation of IN F7321, IN-H7169 and their conjugation products. The major metabolic pathways for flusilazole in rats are consistent with livestock (see Figure **3).**

FIGURE 3 METABOLIC PATHSWAYS FOR FLUSIWOLE IN ANIMALS



Confined Accumulation in Rotational **Crops**

Two confined ^{14}C-flusilazole rotational crop studies were conducted. The initial study examined the potential for uptake of phenyl-containing residues into four crops (barley, beets, cabbage, and soybeans) from soil aged for 30 or 120 days under greenhouse conditions. The subsequent study examined the potential for uptake of phenyl- or triazole-containing residues into three crops (cabbage, wheat, and beets) from soils aged for 120 or 360 days under field conditions.

General experimental considerations

In the initial study, sandy loam soil was treated with phenyl-labeled flusilazole at rates of 289 or 543 g ai/ha. After aging for 30 days or 120 days in the greenhouse, the soil was planted with a small grain crop (barley), a root crop (beets), a leafy vegetable (cabbage), and soybeans. Crops were sampled at intervals beginning 30 days after planting until maturity. These short aging intervals would represent the worst case situation.

In the second study two radiolabeled forms of the test substance were used. Silt loam soil was treated at 1129 g aiiha, more than 4.5 times the proposed recommended seasonal application rate for soybeans. After aging for 120 or 360 days under field conditions, soil was transferred to pots in the greenhouse and planted with a leafy vegetable (cabbage), root crop (red beets), and a small grain crop (wheat). Crops samples were taken at intervals beginning 30 days after planting until maturity.

Distribution of radiolabel in soil and plant parts and identification of the residue

During both confined rotational crop studies, radioactive residue levels in the soil remained relatively constant during the aging and plant growth periods. Soil residues ranged from 0.04 to 0.12 pprn (289 g aiiha application rate), 0.12 to 0.20 pprn (543 g ai/ha application rate) and 0.21 to 0.44 pprn (1129 g ai/ha) flusilazole levels and the percentage of extractable radioactivity decreased with time. Major soil residues included flusilazole, the silanol (IN-F7321), and triazole (IN H9933).

Residue levels in mature crops from the initial study with phenyl-labeled flusilazole ranged from 0.02 pprn (soybean seeds and barley grain) to 2.16 pprn flusilazole equivalents (barley straw). The high radioactive levels in the straw can be partially attributed to the loss of water during maturation. The residues were comprised of flusilazole, IN-F7321, and unidentified polar (water-soluble) metabolites.

In the second study, residue levels in mature crops from the phenyl label ranged from 0.03 (beet tubers) to 3.32 pprn flusilazole equivalents (wheat straw). The high levels of residues in the straw can be partially attributed to the decreased fresh weight (decreased water content) of the tissue. Residue levels in plants grown in soil treated with the phenyl label were about a tenth of those treated with the triazole label.

The crop residues arising from the phenyl label were comprised of flusilazole, the silanol (IN F7321), the silanediol (IN-V5571), and high levels of bound residues. The subsequent wheat metabolism study identified major metabolites of phenyl-labeled flusilazole in wheat as IN F7321 and IN-V5571 (both identified in the crop rotation study) and other hydroxylated metabolites and their conjugates. Thus the unidentified metabolites in the wheat samples of the crop rotation study were likely to be similar to those in the wheat metabolism study.

Residue levels in mature crops grown in soil treated with the triazole label ranged from 0.28 (beet foliage) to 17.5 ppm flusilazole equivalents (wheat straw). Triazolyl alanine and an unidentified polar metabolite were the major plant metabolites from the triazole label in addition to high levels of bound residues. In a subsequent wheat metabolism study (AMR 445-85), residues in wheat grain were identified as primarily triazolyl alanine (69%) and triazolyl acetic acid (24%). Since triazolyl alanine was identified in wheat grain in the crop rotation study, it is likely that the unidentified polar residues consist primarily of triazolyl acetic acid.

Conclusions

There was no significant accumulation of residues from either label in cabbage, soybeans, or beets in the confined rotation studies. Accumulation did occur in mature small grain fractions of wheat grown in soil treated with [triazole-3-^{14}C]flusilazole. The extent of accumulation was similar in comparable samples from all aging periods. A major wheat metabolite was triazolyl alanine with flusilazole comprising <20% of the radioactivity in the wheat grain or straw. This suggests that a triazole-containing fragment, rather than intact flusilazole, translocates from soil into wheat.

Several studies conducted in Europe are also available for submission to EPA that support the above conclusions. Field rotation studies (single or sequential year applications) conducted in France and Denmark, and a field soil uptake study conducted at 3 locations in the United Kingdom, confirmed the low potential for flusilazole uptake by rotational crops. Data from these field rotation studies show that there will be minimal flusilazole residues (generally less than or equal to the limit of quantitation 0.01 ppm), taken up by spring rape (canola) and spring wheat or barley grown in fields the year following single or multi year applications with flusilazole (160-500 g a.i./ha/year). In the field plant uptake study, barley, rape, and sugar beets were planted in soil shortly after flusilazole application to soil at several treatment rates (100, 500, 1000 and 2500 g a.i./ha). The short interval between treatment and planting (12 days) and the exaggerated treatment rates (up to 2500g a.i./ha) would simulate a worst-case soil uptake situation. Results of the field plant uptake study demonstrated little or no uptake (<0.03 ppm) of flusilazole or its phenyl metabolites (IN F7321 and IN-H7169) in barley grain, rape seed, or sugar beet roots at usage rates up to 500g/ha (greater than 2X the maximum proposed seasonal soybean application rate).

References for Metabolism Section

D. Chan Leach, L. G. Carter, and J. Harvey, Jr., (1988). Metabolism of [Phenyl(U)-^{14}C]DPX-H6573 and [Triazole-3-^{14}C]DPX-H6573 in Greenhouse Wheat. Revision 1, DuPont Report No. AMR 445 85. USEPA MRID # 41567607

L. G. Carter and K. D. Monson. (1986). Metabolism of [Phenyl(U)-^{14}C]DPX-H6573 and [Triazole-3-^{14}C]DPX-H6573 in Grapes. DuPont Report No. AMR 446-85. USEPA MRID # 40042133

L. G. Carter and K. D. Monson. (1986). Supplement to Metabolism of [Phenyl(U)-^{14}C]DPX-H6573 and [Triazole-3-^{14}C]DPX-H6573 in Grapes. DuPont Report No. AMR 446-85. USEPA MRID #40804702

J. Harvey, D. Chan Leach, M. A. Stadalius, and P. K. Tseng. (1986). Metabolism of [Phenyl(U)-^{14}C] DPX-H6573 and [Triazole-3-^{14}C] DPX-H6573 in Apples. DuPont Report No. AMR 409-85. USEPA MRID # 40042134

Smyser, B.P. and Moghaddam, M. F. (1997) Metabolism of [Phenyl(U)^{14}C] and [Triazole-3-^{14}C] DPX-H6573 in Sugar Beets. DuPont Report No. AMR 2994-94 (EU submission only; not submitted to USEPA).

Harvey, John, Jr. (1984). Metabolism of DPX-H6573 in Peanuts. DuPont Study AMR 161-83. (Interim report) USEPA MRID # NA

McFetridge, R. D., Rhodes, B. C. (1987). "Experiments in the Translocation and Metabolism of ^{14}C-DPX-H6573 in Bananas and Banana Palm Leaves." Du Pont Report AMR 636-86. USEPA MRID # 40114301

Lin, P. T. (1986). Metabolism Study of [Phenyl(U)^{14}C]DPX-H6573 in Laying Hens. Du Pont Report No. AMR 638-86-1. USEPA MRID # 40804707

Lin, P. T. (1988) Metabolism Study of Triazole-3- Carbon 14 DPX-H6573 in Laying Hens: Project IDs. AMR 638-86-2. USEPA MRID # 40804708.

Lin, P. (1988) Metabolism Study of Phenyl(U)- Carbon 14 DPX-H6573 in Laying Hens: Supplement: Du Pont Report: AMR 638-86-1 USEPA MRID # 40953605

Lin, P. T. (1988) Supplement to Metabolism Study of Triazole-3- Carbon 14 DPX-H6573 in Laying Hens: Du Pont Report. AMR 638-86-2. USEPA MRID # 40953606

Anderson, Jeffrey J. (1984). Metabolism of [^{14}C]DPX-H6573 in the Goat. Du Pont Report AMR 162-83 USEPA MRID # 40042135

Anderson, Jeffrey J. (1986). Supplement to Metabolism of [^{14}C]DPX-H6573 in the Goat. USEPA MRID # 40042135

Harvey, John, Jr. (1983). Crop Rotation Study with ^{14}C-DPX-H6573 in the Greenhouse. Du Pont Report AMR 165-83. USEPA MRID # 163918

Priester, Thomas M. (1986). ^{14}C-DPX-H6573 Confined Accumulation Studies on Rotational Crops. Du Pont Report. AMR 585-86 USEPA MRID # 41567609

Priester, Thomas M. (1992). ^{14}C-DPX-H6573 Confined Accumulation Studies on Rotational Crops. Supplement No. 1 Du Pont Report AMR 585-86 USEPA MRID # NA

Anderson, J. J.; Leach, D. C.; Slates, S. S.; Stadalius, M. A., (1986). Metabolism of ^{14}C DPX H6573 in Rats. DuPont Report No. AMR 196-84. USEPA MRID # 40042115

Metabolism of ^{14}C-Famoxadone in Plants, Livestock and Rotational Crops

Metabolism of ^{14}C-Famoxadone in Plants

The metabolism of famoxadone has been investigated in potatoes, grapes, and tomatoes. The residue of concern was determined to be famoxadone during assessment of the Section 3 registration application for famoxadone. (DuPont Report Nos. AMR 2904-94 (MRID No. 44302448), AMR 2481-92 + Suppl. 1 (MRID No. 44302447) + Rev. 1 (MRID No. 44302446), AMR 4792-97 (MRID No. 44946415)). Plants were treated in a manner to simulate actual use conditions – multiple foliar applications.

Metabolism of ^{14}C-Famoxadone in Goats

Residue chemistry data have been determined to be adequate to set tolerances for ruminants during assessment of the Section 3 package for famoxadone. Famoxadone is the residue of concern in ruminants. (DuPont Report Nos. AMR 2832-93 (MRID No. 44967205), AMR 2832-93 SU1 (MRID No. 44946416), DuPont-4613 (MRID No. 45840601))

Metabolism of ^{14}C-Famoxadone in Poultry

Residue chemistry data was not adequate to set poultry tolerances. The nature of the residue in poultry tissues was not adequately understood in the poultry metabolism study (10-ppm feeding level) submitted with respect to unextracted residues in liver. A new poultry metabolism study was required for uses on significant poultry feed items during the Section 3 package evaluation. (DuPont Report No. AMR 2833-93 (MRID No. 44946417))

Confined Accumulation in Rotational Crops

Additional data was submitted subsequent the the Section 3 package review to support a 30-day plantback. The data was accepted. [DuPont Report Nos. AMR 3181-94 (MRID No. 44946411) + Suppl. 1 (MRID No. 44946412), DuPont-3436 (field, MRID No. 45845601), DuPont-13204 (paper to obtain plantback, MRID No. not available, submitted 6/6/2003)]

Conclusions

For the uses on soybeans – foliar applications of soybeans with 1 oz famoxadone/A applied twice with a 14-day interval and a 30-day PHI – the plant and ruminant livestock residue profile is adequately addressed since the use rate, number of applications and PHI are substantially lower than those for famoxadone on the current label for Tanos® 50WG. Considering the available residue data for famoxadone on soybeans, the levels of residues in poultry feed items would be low (0.010 mg/kg following 3 applications of Charisma® EC at 1-2 oz famoxadone/A).

D2. Environmental Fate

An extensive data package exists for environmental fate studies on flusilazole, many of which have been submitted to US EPA in support of previous registration applications. Additional studies have been conducted more recently which will be submitted in the registration application for flusilazole on soybeans. These studies will fulfill the Subdivision N requirements for laboratory and field studies with flusilazole.

The results of the studies have shown a consistent picture between lab and field, with generally biphasic degradation and limited mobility in soil. A range of DT_{50} values are seen due to microbial degradation. Triazole and silanol metabolites are not found in high concentration in soil.

Flusilazole rapidly partitions into sediment from the water column

Several supplemental studies are also available for submission to EPA which support the above conclusions, including 10 field dissipation sites in Germany, a field dissipation study in Canada (1 site with turf cover), field soil accumulation trials from Europe in cereals, orchards and vineyards, run-off study in orchards, and soil cylinder field dissipation studies with multiple applications over 4 years

No accumulation of flusilazole in soil is expected when applied to crops according to the proposed use pattern.

A sample drinking water assessment has been conducted for the ground application of flusilazole on soybeans and is included herein. Aerial application of flusilazole is also proposed. Summary tables of flusilazole's environmental fate endpoints are provided at the end of this section.

Information on the environmental fate and behavior of famoxadone can be found in the US EPA Fact Sheet for famoxadone in Attachment 1. A separate drinking water assessment was not conducted for famoxadone since the proposed use rate of famoxadone in Charisma™ on soybeans is much lower than the approved label rate for famoxadone in Tanos™ on any crop registered in the US, with fewer applications and a longer PHI.

Drinking Water Exposure Assessment for Use of Flusilazole on Soybeans

1.0 Summary

The objective of this exposure assessment is to determine the potential concentrations of flusilazole (DPX-H6573) in drinking water as a result of application to soybeans. Estimated environmental concentrations (EEC) for flusilazole were calculated for groundwater using the SCIGROW screening model

while EECs for surface water were determined using the screening model FIRST. The maximum proposed use pattern of flusilazole on soybeans is two applications of 125 g ai/ha, applied with a minimum interval of 14 days. Appropriate values of the physical and chemical properties of flusilazole were calculated and used in each model.

The EEC of flusilazole in groundwater was 0.010 µg/L using SCIGROW. This result represents a potential concentration of flusilazole in a highly vulnerable environmental setting (e.g. a sandy, low organic carbon soil profile; shallow groundwater; high annual precipitation). The low concentration in groundwater is due to the relatively low use rate combined with a relatively high sorption coefficient.

FIRST provides an EEC for a small watershed (–173 ha) that drains into a small drinking water reservoir (5.26 ha x 2.74m deep). For flusilazole, the highest daily drinking water concentration from a surface water source was simulated to be 2.057 µg/L, representing a potential acute concentration. The annual average concentration of flusilazole in drinking water from a surface water source was 0.445 µg/L. These relatively low concentrations are primarily the result of the high sorption coefficient of flusilazole which results in minimal losses from treated areas via runoff.

In summary, it is reasonable to conclude that flusilazole has the potential to be detected at low levels in surface water and it is unlikely that this chemical would be found in groundwater at significant concentrations.

2.0 Introduction and Objectives

Flusilazole (DPX-H6573) is a triazole fungicide effective against Asian soybean rust (ASR) which is caused by ***Phakopsorapachyrhizi.***

This study had two major objectives:

(1) Determine estimated environmental concentrations (EEC) of flusilazole in drinking water abstracted from groundwater using the SCIGROW model

(2) Determine EEC of flusilazole in drinking water abstracted from surface water sources using the FIRST model

All calculations were performed following the guidance provided by the USEPA for use of the SCIGROW and FIRST models for initial screening assessments of potential concentrations of agricultural chemicals in drinking water [1, 2].

SCIGROW: [1] "SCIGROW Description", from website http://www.epa.gov/oppefed1/models/water/index.htm

FIRST: [2] "FIRST Description", from website http://www.epa.gov/oppefed1/models/water/index.htm

3.0 Model Inputs and Simulation Methods

3.1 Agronomics

A summary of the proposed use pattern for flusilazole on soybeans is provided in Table 14. The maximum proposed use rate is two applications of 125 g DPX-H6573/ha which is applied to the developing soybean crop with a minimal application interval of 14 days to provide fungicidal protection against ASR.

3.2 Chemical Properties

A summary of the soil adsorption data for flusilazole is provided in Table 15 [3]. The median Koc value which is required for use in SCIGROW is 2754 ml/g. The lowest Kd value for a non-sand soil (e.g. not sand, loamy sand or sandy loam) is 79.0 mllg and this sorption value was used in FIRST, as specified in the guidance document. These sorption values indicate that flusilazole is expected to have a slight mobility in soil under normal agronomic conditions. In addition, runoff from treated fields is expected to have relatively low concentrations of flusilazole since this compound is primarily associated with soil. Potential concentrations reaching water will decline relatively quickly due to rapid sorption to sediment.

Aerobic soil degradation studies on two soils have been performed for flusilazole and the results are summarized in Table 16 [4]. The mean aerobic soil degradation half-life, for use in SCIGROW, is 445 days while the 90^{th} percentile soil half-life, for use in FIRST, is 865 days. The 90^{th} percentile value is calculated using a Student-t distribution which results in a relatively long half-life value since there are only two studies and the standard deviation of the DT_{50} values is relatively large. Flusilazole degrades relatively slowly in soil, due in part to its high sorption to soil. Since the primary transformation mechanism for flusilazole is microbial degradation, extensive sorption to soil removes this chemical from the solution phase and slows the observed rate of degradation. This behavior is commonly observed in highly sorptive chemicals which degrade solely by microbial degradation.

The degradation products of flusilazole include IN-F7321 (silanol) and IN-H9933 (1,2,4-triazole). The degradation pathway in aerobic soils is shown in Figure 4. Unextractable residues ranged from 24-34% of applied radioactivity and were characterized by alkaline fractionation. The unextractable residue did not contain intact flusilazole, but was shown to contain degradation products [4-8]. Since the rate of degradation of these metabolites is typically much faster than the rate of formation, neither metabolite exceeds 10% of parent in laboratory [4] or field degradation studies [5, 6]. Therefore, all subsequent evaluations of drinking water focus only on the parent chemical.

Degradation in anaerobic systems was studied in two soils [7, 8]. The rate of degradation in anaerobic systems ranged from 224 to 364 days. The route of degradation of flusilazole in anaerobic systems was the same as seen in the aerobic soil metabolism studies (Figure 4).

Flusilazole is stable to hydrolysis in aqueous buffer [9] and stable to photolysis in both water [10, 11] and on soil [12, 13]. The degradation of flusilazole has been studied in two water/sediment systems [14]. Flusilazole dissipates rapidly from the water column, but degrades slowly in sediment.

Numerous field soil dissipation trials have been conducted using flusilazole, with both single and multiple applications for up to 3 years [15, 16]. The range of half-lives measured in these trials (237 - 475 d) are similar to those measured in laboratory studies.

A summary of the chemical and physical properties of flusilazole is provided in Table 17, together with the specialized values of sorption and rate of degradation that are needed in the SCIGROW and FIRST models.

3.3 SCIGROW (Screening Concentration in Groundwater)

SCIGROW is a screening model using inputs of total seasonal application rate, median Koc and mean aerobic soil half-life to estimate the potential concentration of a crop protection chemical in groundwater. The model is a regression equation based on groundwater monitoring results from a series of prospective groundwater (PGW) studies conducted primarily in highly vulnerable hydrogeologic locations. In most of these studies, the soil profiles were sandy and had low organic carbon content. In addition, PGW studies are normally conducted at sites with relatively shallow water tables (e.g., typical depths of 5 to 30 feet below land surface) and high annual precipitation. As a result, it is appropriate to view the resulting groundwater EEC values from SCIGROW as an upper bound of the range of concentrations expected in actual agronomic settings.

A complete list of the SCIGROW input parameters and the resulting EEC value is provided in Table 18.

3.4 FIRST (FQPA Index Reservoir Screening Tool)

FIRST is a meta-model designed to provide simulation results that mimic those obtained from the more complex linked PRZM3 and EXAMS 2.97.7 models. This simulation tool uses a conceptual watershed of 172.9 ha (427 ac) that drains into a 5.26 ha (13 ac) drinking water reservoir. The fraction of the watershed that is cropped varies as a function of the crop and ranges from a low of 0.20 for wheat and cotton to a high of 0.87 for minor crops. For soybeans, the fraction of crop treated is assumed to be 0.41.

The EEC concentrations generated by FIRST are expected to represent upper bounds on actual concentrations in drinking water reservoirs due to the high "drainage area to normal capacity" or DANC ratio of the watershed and receiving

water body. The simulation scenario used in the FIRST model has a ratio of 172.9 x 10^4 m^2/ 144,000 m^3 or 12 m^2/m^3. With a DANC value of 12 m^2/m^3 and an annual runoff depth of 0.1-0.2 m, the annual turnover in the FIRST drinking water reservoir is 1.2 to 2.4, meaning that the volume of the reservoir is potentially exchanged once or twice a year. Less vulnerable watersheds in other geographic regions of the USA typically have smaller DANC ratios. As a result, these watersheds have lower peak concentrations but concentrations of aquatically persistent chemicals could potentially persist longer due to the slower rate of turnover in the less vulnerable watersheds.

A complete list of the FIRST input parameters and the resulting EEC values is provided in Table 19.

4.0 Results and Conclusions

4.1 Groundwater results from SCIGROW

The EEC for flusilazole in groundwater was calculated to be 0.010 µg/L using SCIGROW. This low concentration in potential drinking water abstracted from groundwater resources is due to a combination of a relatively low seasonal use rate combined with extensive sorption to soil.

4.2 Surface water results from FIRST

The highest daily (i.e. acute) concentration of flusilazole simulated in a small drinking water reservoir was 2.057 µg/L. The annual average (i.e. chronic) concentration was calculated to be 0.445 µg/L. In an actual reservoir in which flusilazole enters via a combination of spray drift, runoff and erosion, the primary routes of entry are expected to be spray drift and erosion. The resulting aquatic concentration is expected to decline rapidly due to the high sorption coefficient of flusilazole.

4.3 Estimated environmental concentrations of flusilazole in drinking water

It should be noted that neither of these screening models considers the potential impact of water treatment processes on removal of pesticide from the water that eventually reaches consumers.

The highest EEC values of flusilazole in drinking water are in surface water with peak (acute) concentrations of 2.057 µg/L and longer-term, chronic concentrations of 0.445 µg/L. The EEC in groundwater 0.010 µg/L which is two orders of magnitude less than the acute surface water value and one order of magnitude less than the chronic value.

In summary, it is reasonable to conclude that flusilazole has the potential to be detected at low levels in surface water and it is unlikely that this chemical would be found in groundwater at significant concentrations.

5.0 References

[1] SCIGROW 2.2, executable model and description", from USEPA website http://www.epa.gov/oppefed1/models/water/index.htm

[2] FIRST 1.0, executable model and description", from USEPA website http://www.epa.gov/oppefed1/models/water/index.htm

[3] Priester, T. (1985) Batch Equilibrium (Adsorption/Desorption) and Soil Thin-layer Chromatography Studies with [Phenyl-carbon-14- (U)] DPX-H6573. DuPont Report No. AMR 323-85. US EPA MRID # 155615.

[4] Chrzanowski, R. (1984) Aerobic Soil Metabolism of ^{14}C-DPX-H6573. DuPont Report No. AMR 140-83 Revision No.1. US EPA MRID# 144214.

[5] Chrzanowski, R. (1986) Field Soil Dissipation of [^{14}C]-DPX-H6573 in Delaware, North Carolina, Florida, Mississippi and Idaho. DuPont Report No. AMR 441-85 Revision No. 1. US EPA MRID# 40042148.

[6] Chrzanowski, R. (1986) Field Soil Dissipation of [^{14}C]-DPX-H6573 in Delaware, North Carolina, Florida, Mississippi and Idaho. DuPont Report No. AMR 441-85 Supplement No. 1. US EPA MRID# 41088302.

[7] Chrzanowski, R. (1986) Anaerobic Aquatic Metabolism of ^{14}C-DPX-H6573. DuPont Report No. AMR 447-85 Revision No. 1. US EPA MRID# 40042146.

[8] Chrzanowski, R. (1989) Anaerobic Aquatic Metabolism of ^{14}C-DPX-H6573. DuPont Report No. AMR 447-85 Supplement No. 1. US EPA MRID# 41088301.

[9] Cadwgan, G. E. (1983) Hydrolysis of ^{14}C-phenyl-labeled and ^{14}C-triazole-labeled DPX-H6573. DuPont Report No. AMR 159-83. US EPA MRID# 252481

[10] Carter, L. (1984) Photodegradation of [Phenyl(U)-^{14}C] DPX-H6573 and [Triazole-3-^{14}C] DPX-H6573 in Water. DuPont Report No. AMR 393-85 Revision No. 1. US EPA MRID# 40042143.

[11] Leach, D. (1988) Photodegradation of [Phenyl(U)-^{14}C] DPX-H6573 and [Triazole-3-^{14}C] DPX-H6573 in Water Under Sunlight. DuPont Report No. AMR 255-84 Revision No. 1. US EPA MRID# 41088304.

[12] Carter, L. (1984) Photodegradation [Phenyl(U)-^{14}C] DPX-H6573 and [Triazole-3-^{14}C] DPX-H6573 on Soil. DuPont Report No. AMR 255-84 Revision No. 1. US EPA MRID# 40042144.

[13] Carter, L. (1986) Photodegradation of [Phenyl(U)-^{14}C] DPX-H6573 and [Triazole-3-^{14}C] DPX-H6573 on Soil under Natural Sunlight. DuPont Report No. 506-86. US EPA MRID# 40042145.

[14] Knoch, E. (1992) Degradation and metabolism of flusilazole (DPX-H6573) in water/sediment systems. DuPont Report No. AMR 2385-92.

[15] Smyser, B.P. (1993) Field soil Dissipation of Nustar® fungicide. DuPont Report No. 791-87 Revision No.1.

[16] Smyser, B.P. (1993) Long-term field soil dissipation of (Phenyl (U)-^{14}C) DPX-H6573 at Stine Farm, Delaware. DuPont Report No. AMR 556-86 Revision No. 1.

TABLE 14 PROPOSED USE PATTERN FOR FLUSILAZOLE ON SOYBEANS IN THE USA

CROP	APPLICATION METHOD	MAXIMUM APPLN RATE PER TREATMENT	MAXIMUM NUMBER OF APPLICATIONS	MINIMUM APPLICATION INTERVAL (DAYS)	POST-HARVEST INTERVAL (DAYS)
Soybeans	ground application	125 g ai/ha (= 0.111 lb ai/ac)	2	14	30

TABLE 15 SUMMARY OF SOIL ADSORPTION DATA FOR FLUSILAZOLE

Soil	Texture	%OM	%OC	Kd (mL/g)	Koc (mL/g)
Woodstown	sandy loam	1.1	0.6	19.3	3025
Cecil	sandy loam	2.1	1.2	20.1	1650
Flanagan	silt loam	4.3	2.5	79.0	3168
Keyport	silt loam	7.5	4.4	108.0	2483

Lowest non-sand Kd:

Mean Koc:

Median Koc: 2754

Data source: Reference [3]

TABLE 16 SUMMARY OF SOIL DEGRADATION DATA FOR FLUSILVOLE

Soil	Texture	%OM	Temperature (°C)	DT_{50} (d)
Flanagan	Silt loam	4.02	25	308
Woodstown	Sandy loam	1.4	25	581

Mean DT_{50}:	444.5
N:	2
Standard deviation:	193.0
Student t_{90}:	3.078
Upper 90th percentile DT50:	864.6

Upper 90th percentile DT50 = t_{90} * (std dev)/sqrt(N) + mean

Data source: Reference [4]

TABLE 17 SUMMARY OF PHYSICAL AND CHEMICAL PROPERTIES OF FLUSILAZOLE (DPX-H6573)

PARAMETER	FLUSILAZOLE (DPX-H6573)	VALUE USED IN SCIGROW	VALUE USED IN FIRST
Physical properties			
Molecular weight	315.1	NA	NA
Water solubility at 20°C (mg/L)	50	NA	50
Chemical properties ***Sorption***			
Kd (mL/g)	19.3, 20.1, 79.0, 108.0	79.0 (lowest non-sand)	NA
Koc (mL/g)	1650, 2483, 3025, 3168	NA	2754 (median)
Degradation studies			
aerobic soil half-life (d)	308, 581	445 (mean)	865 (90th percentile)
hydrolysis half-life (d)	stable	stable	NA
aerobic aquatic half-life (d)	stable	stable	NA
aqueous photolysis half-life (d)	stable	stable	NA

NA: not applicable

TABLE 18 INPUT DATA AND RESULTS FOR SCIGROW MODEL

PARAMETER	VALUE	UNITS
Chemical	flusilazole	--
Application rate	0.1 **11**	lb ai/ac
Number of applications	**2**	--
Koc (median)	**2754**	ml/g
Aerobic soil half-life mean)	**445**	d

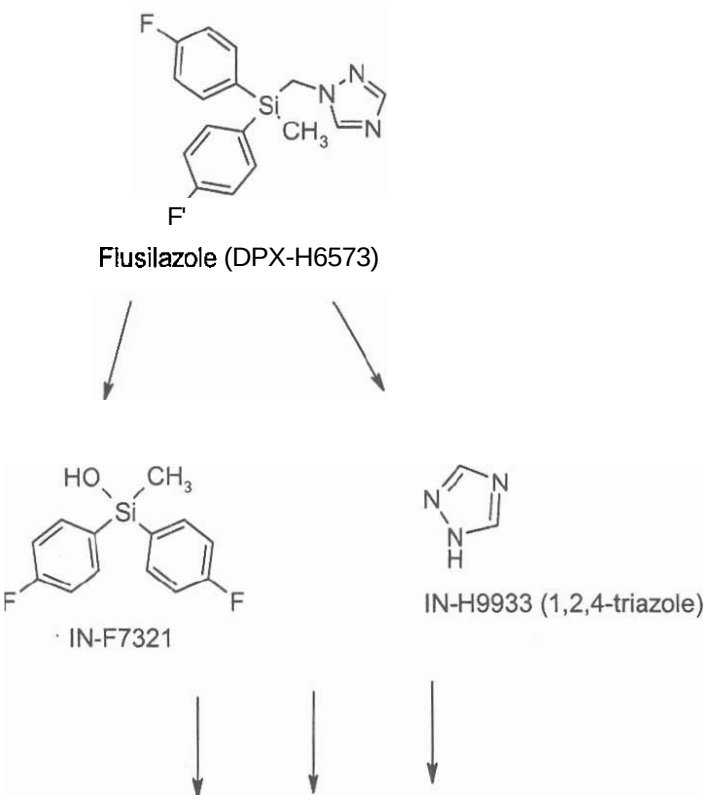
Screening concentration in groundwater:	0.010	µg/L

TABLE 19 INPUT DATA AND RESULTS FOR FIRST MODEL

PARAMETER	VALUE	UNITS
Chemical	flusilazole	--
Crop	soybeans	--
Application rate	0.111	lb ai/ac
Number of applications	2	--
Days between applications	14	d
Percent cropped area	41	% (soybean)
Application method	ground (incorporation = 0 in, drift = 6.4%, appln efficiency = 99%)	--
Wetted in (yes/no)	no	--
Solubility	50	ppm
Kd (lowest non-sand value)	79.0	ml/g
Aerobic soil half-life (90^{th} percentile)	865	d
Hydrolysis half-life	stable	d
Aerobic aquatic half-life	stable	d
Aqueous photolysis half-life	stable	d

Peak day concentration	2.057	µg/L
Annual ave concentration	**0.445**	µg/L

FIGURE 4 PROPOSED DEGRADATION PATHWAY OF FLUSILAZOLE IN AEROBIC AND ANAEROBIC SOILS AND SEDIMENTS



APPENDIX 1 OUTPUT FROM SCIGROW MODEL

SCIGROW

VERSION 2.2: **NOVEMBER 1,** 2003

RUN No. 1 FOR flusilazole ** INPUT **VALUES** **

APP **RATE** (LBS/AC)	APPS/ **YEAR**	**TOTAL/ SEASON**	**SOIL KOC**	**AEROBIC SOIL** METAB HALFLIFE **(DAYS)**
.111	2	.222	2754.0	445.00

GROUND-WATER SCREENING CONCENTRATION (IN UG/L - PPB)

,010155

APPENDIX 2 OUTPUT FROM FIRST MODEL

RUN No. 1 FOR flusilazole ON soybean * INPUT VALUES *

RATE (#/AC) ONE(MULT)	No.APPS & INTERVAL	SOIL Kd	SOLUBIL (PPM)	APPL TYPE (%DRIFT)	%CROPPED AREA	INCORP (IN)
.Ill(.221)	2 14	79.0	50.0	GROUND(6.4)	41.0	.0

FIELD AND RESERVOIR HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (RESERVOIR)	PHOTOLYSIS (RES.-EFF)	METABOLIC (RESER.)	COMBINED (RESER.)
865.00	2	N/A	.00- .00	******	1730.00

UNTREATED WATER CONC (MICROGRAMS/LITER (PPB)) Ver 1.0 AUG 1, 2001

PEAK DAY (ACUTE) CONCENTRATION	ANNUAL AVERAGE (CHRONIC) CONCENTRATION
2.057	.445

E. EFFICACY

1.0 Summary

Twenty field trials in 3 countries demonstrate the efficacy of products containing flusilazole in controlling Asian soybean rust when applied at 75-125 g ai/ha as flusilazole (Punch™ 250, Punch™ 400), 53-75 g ai/ha in combination with famoxadone (Charisma™), and 100-125 g ai/ha in combination with carbendazim (Punch™ CS). Efficacy is equivalent or superior to other triazole fungicides as well as fungicides with other modes of actions currently sold or being developed for this use.

2.0 Introduction and Purpose

The purpose of these trials was to verify the efficacy of fungicides containing the active ingredient flusilazole and mixtures for control of Asian soybean rust.

Flusilazole, a silicotriazole fungicide from DuPont, has several useful attributes that contribute to its excellent activity against this disease. It provides extended protectant activity as well as curative control of newly established infections. Its rapid uptake and local systemic movement ensure good redistribution of fungicide for thorough protection and resistance to wash-off. Flusilazole has demonstrated activity in the vapor phase against some fungal diseases on wheat (Smith, *et al.*, 1992), an attribute that improves disease control throughout the crop canopy and may compensate for non-optimum spray coverage. Additional studies demonstrating the technical benefits of flusilazole, like vapor effects, rainfastness and systemicity, on Asian soybean rust are in progress. In addition to its high fungitoxicity against Asian soybean rust, flusilazole also controls other important fungal diseases of soybeans, such as powdery mildew, frogeye leaf spot, Altemaria leaf spot, and Cercospora leaf spot and blight, and brown spot.

Flusilazole and its mixtures provide excellent tools for soybean production, protecting yield and quality if threatened by fungal diseases such as Asian soybean rust. In the Republic of South Africa, Argentina, and Brazil, several products containing flusilazole alone or in mixtures with either famoxadone or carbendazim have been selected for commercialization based on customer needs and soybean diseases in each region.

Charisma, the mixture of flusilazole and famoxadone, combines fungicides with two different modes of action for soybean disease control. Famoxadone is an oxazolidinedione QoI fungicide that is different from the strobilurin chemistry but with similar activity against Asian soybean rust. Famoxadone offers a broad spectrum of plant disease control, controlling fungal diseases

caused by Oomycete, Ascomycete as well as Basidiomycete fungi. Famoxadone also increases the suppression of bacterial diseases from standard copper / mancozeb treatment shategies. Control of barley leaf rust (*Puccinia* ***hordei)*** and rust diseases on other crops by famoxadone has been confirmed and field results demonshate that famoxadone contributes to the performance against Asian soybean rust in the mixture with flusilazole. The mixture of famoxadone plus flusilazole, combining fungicides with 2 different modes of action and complementary attributes against Asian soybean rust, also is an excellent tool for management of resistance to both QoI and ergosterol biosynthesis inhibiting fungicides like flusilazole and other triazoles.

Although mixtures of flusilazole with carbendazim have been evaluated extensively for Asian soybean rust control, carbendazim does not significantly contribute to the Asian soybean rust control provided by flusilazole (Appendix 4) but is included primarily for its activity on other soybean diseases in the countries in which these mixtures are being sold.

The excellent control of Asian soybean rust provided by products containing flusilazole has been acknowledged in several recent publications (2, 3).

3.0 Methods

Consultants from universities, research stations, and private investigators in Brazil, Paraguay, and the Republic of South Africa conducted a total of 20 trials. Punch™ and Charisma™ were applied at rates ranging from 300-700 mL/ha (75-125g aiiha). These field trials were conducted under varying environmental conditions over a four-year period.

4.0 Results

The results are shown in Tables 1-20 with supplemental information about the field trials in Appendices 3, 4, and 5.

See Appendix 3 for use rates of mixture components for each test. See Appendix 4 for number and timing of fungicide applications. See Appendix 5 for authors and institutions conducting field trials with flusilazole and mixtures for the control of Asian soybean rust.

5.0 Conclusious

The products proposed for use in the US for control of Asian soybean rust are Punch™, a 40% EC formulation of flusilazole, and Charisma™, an EC formulation that contains 9.7% flusilazole and 9.1% famoxadone. The data presented in this report support the use of Punch™ at 4 oz prod/A (1.75 oz flusilazole ai/A) and Charisma™ at 9 oz prod/A (1.0 oz famoxadone + 1.07 oz

flusilazole ai/A). For all soybeans varieties tested at a range of temperatures and climatic conditions, flusilazole and its mixtures showed no phytotoxicity to soybeans.

Punch™ and Charisma™ will provide:

A. effective preventive control of Asian soybean rust as well as control of other common soybean diseases such as powdery mildew, frogeye leaf spot, Alternaria leaf spot, Cercospora leaf spot and blight, and brown spot

B. curative activity: Research conducted by private and public organizations showed a significant difference within the triazoles and mixtures to control Asian soybean rust when the pathogen was already present (showing symptoms or not). This attribute allows farmers flexibility in scheduling their spray programs for Asian soybean rust and makes flusilazole a preferred choice.

C. residual activity (i.e. the active ingredient remains stable and effective over a long period of time) is important to avoid extra sprays by farmers. Flusilazole provides better residual activity than many other triazoles and mixtures.

D. effective resistance management: Charisma™ provides two fungicides with different modes of action and targets an even broader spectrum of diseases in addition to Asian soybean rust. The preventive use of fungicide mixtures minimizes the risk of build-up of resistant strains. This is very important for an aggressive pathogen like that causing Asian soybean rust.

6.0 References

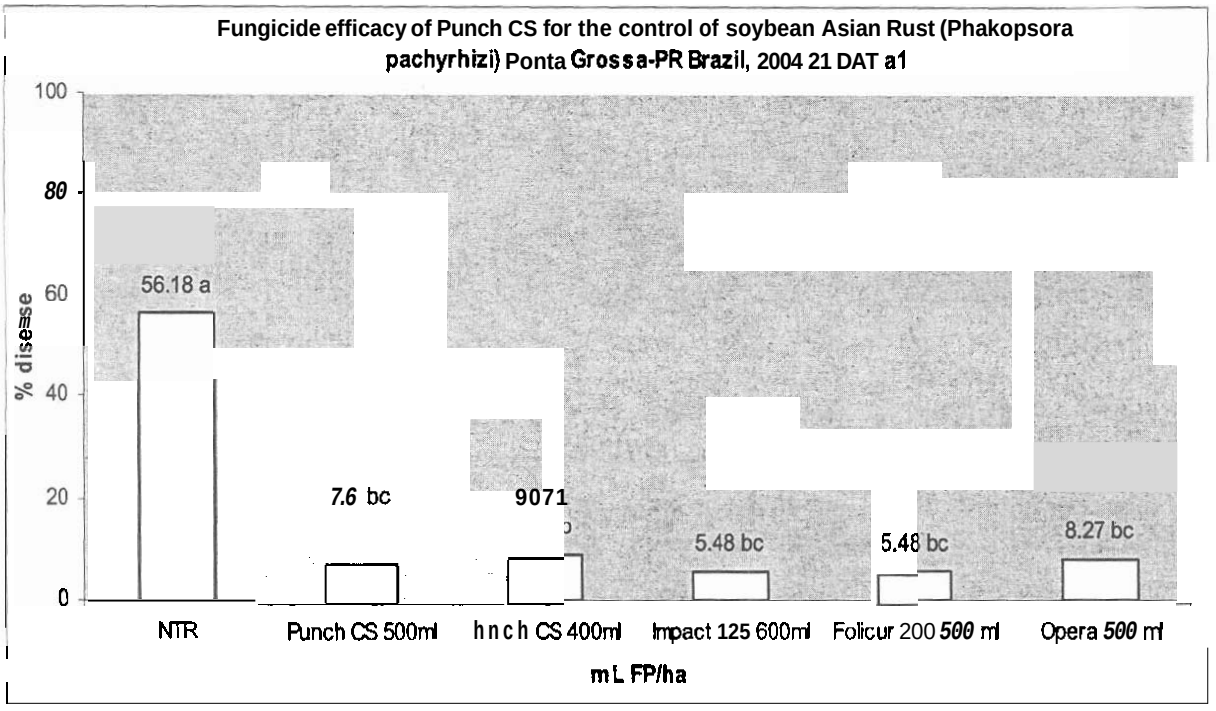
1. Smith, C.M.; Klapproth, M.C.; Saunders, D.W.; Johnson, L.E.B.; and Trivellas, A.E. (1992). Biological properties of flusilazole contributing to its field performance. British Crop Protection Conference, Pests and Diseases. Pp. 639-644.

2. Miles, M. R.; Frederick, R. D.; Hartman, G. L. (2003) Soybean rust: Is the U. S. soybean crop at risk? APSnet (American Phytopathological Society) Feature Article, http://www.apsnet.org/online/feature/rust

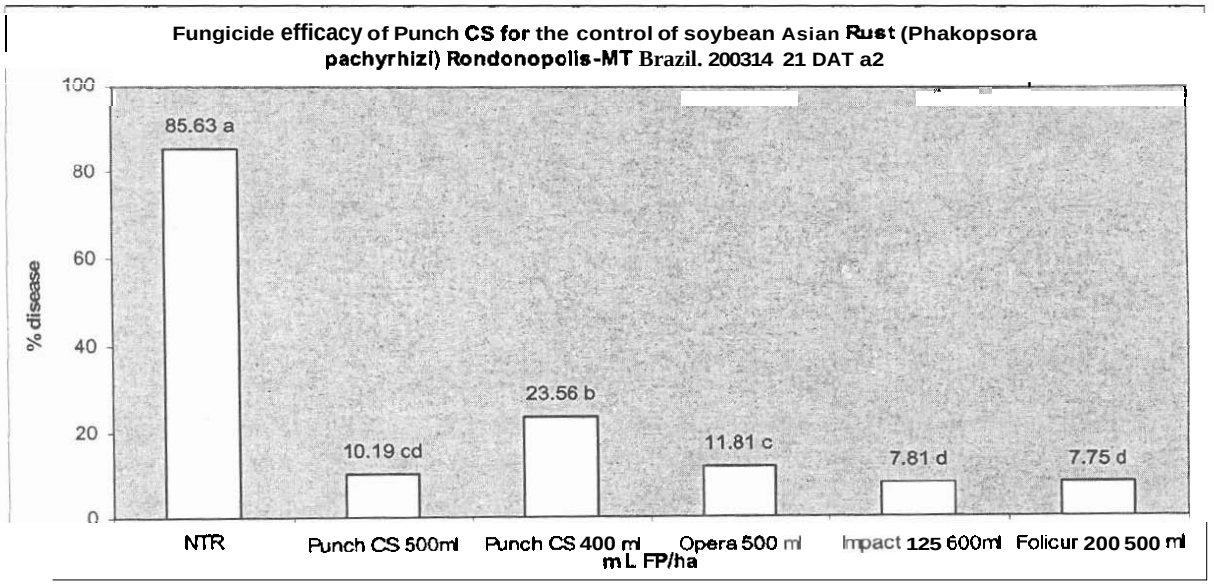
3. Miles, M.R., Hartman, G.L., Levy, C., Morel, W., (2003) Current Status Of Soybean Rust Control By Fungicides, Pesticide Outlook, October 2003. Pp. 197-200.

4. Relatorio tecnico dos ensaios conduzidos para registro de Punch, Alert, e Charisma. (2004). Summary of efficacy data by consultants in Brazil. (DuPont confidential).

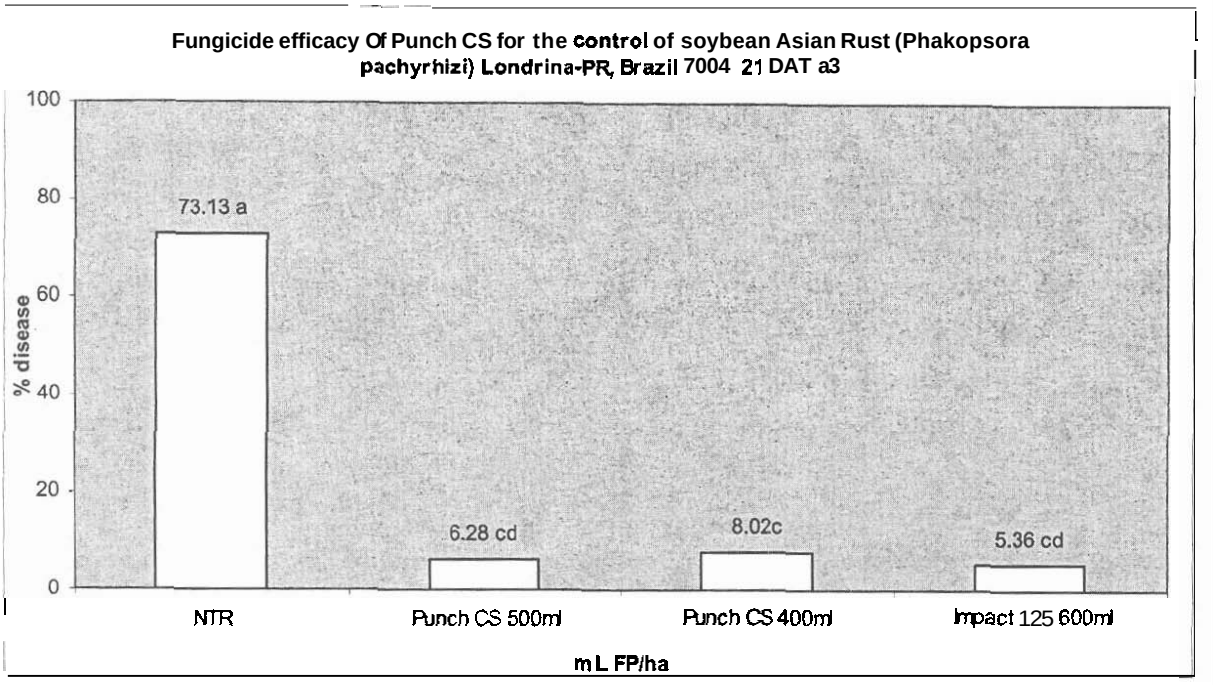
Graph 1. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust *(Phakopsorapachyrhizi)*. Ponta Grossa-PR, Brazil, 2004 Evaluated 21 days after treatment (DAT). ML FP/ha = milliliters of formulated product per hectare.



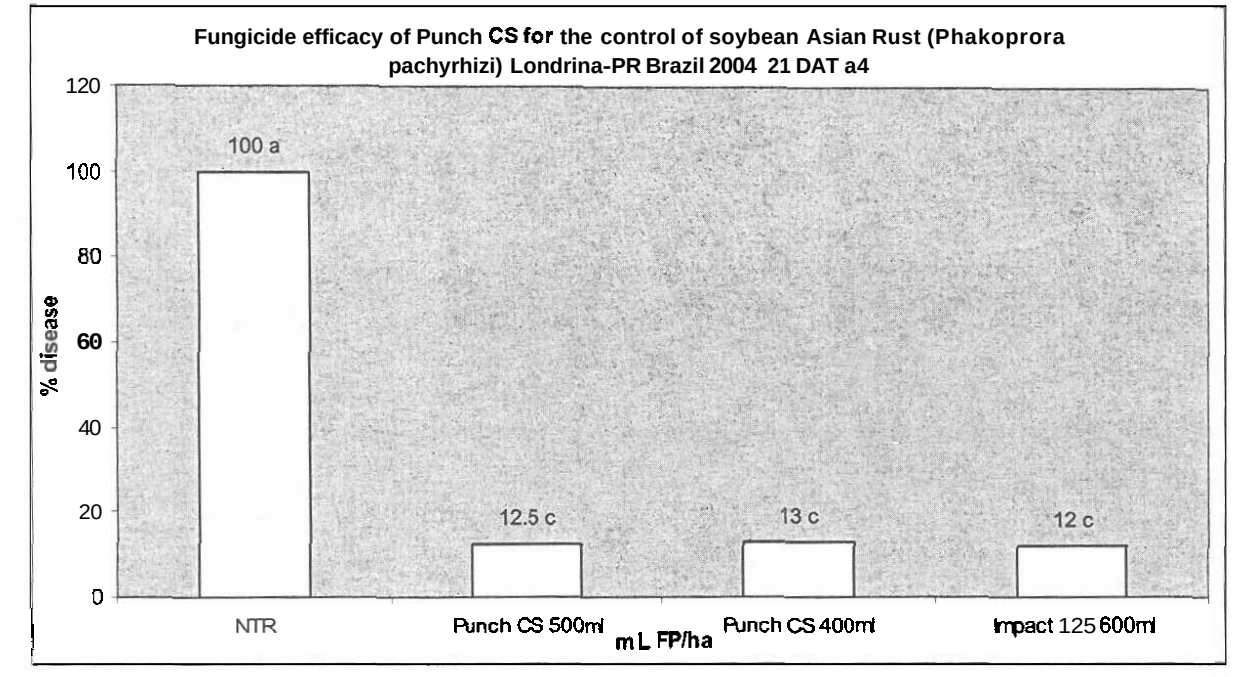
Graph 2. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust *(Phakopsorapachyrhizi)*. Rondonopolis-MT, 2003 21D



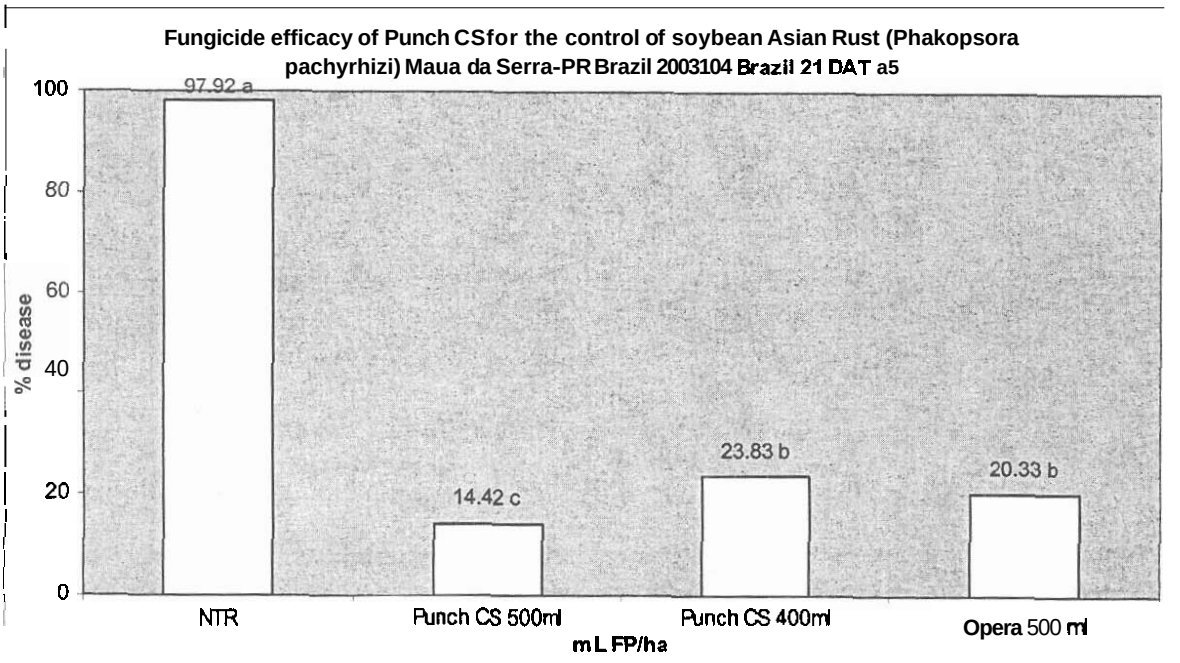
Graph 3. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust *(Phakopsorapachyrhizi)*. Londrina-PR, 2004 21DAT



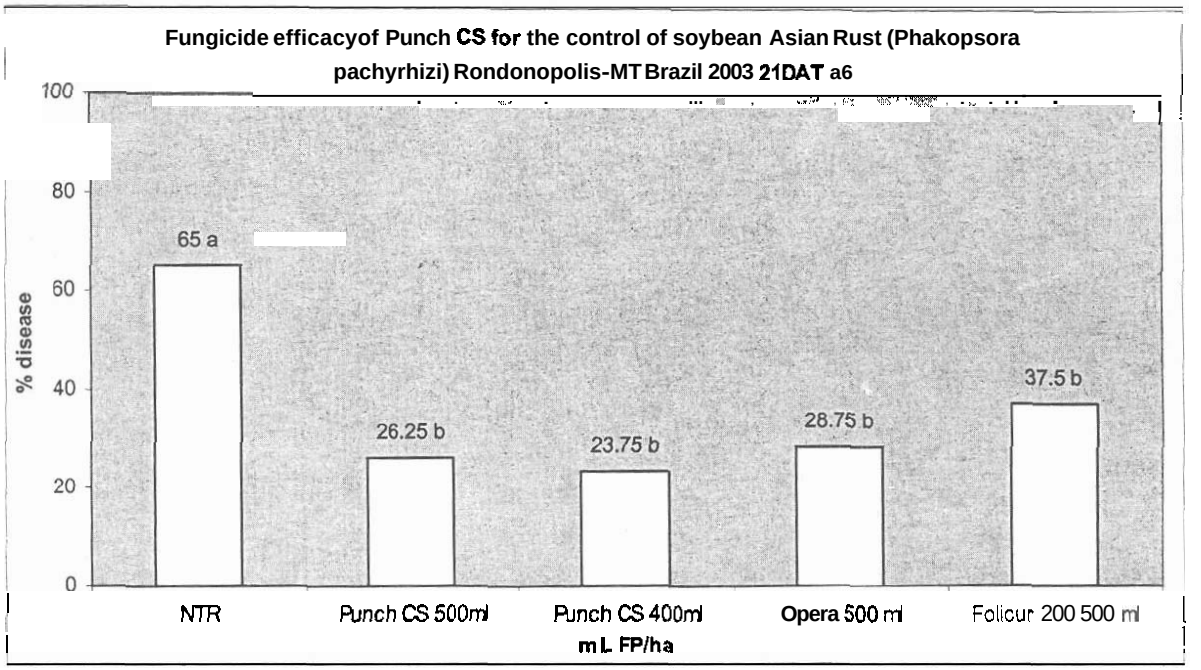
Graph 4. Fungicide efficacy of Punch™ CS for the control of Asian soybean mst *(Phakopsorapachyrhizi)*. Londrina-PR, 2004 21DAT



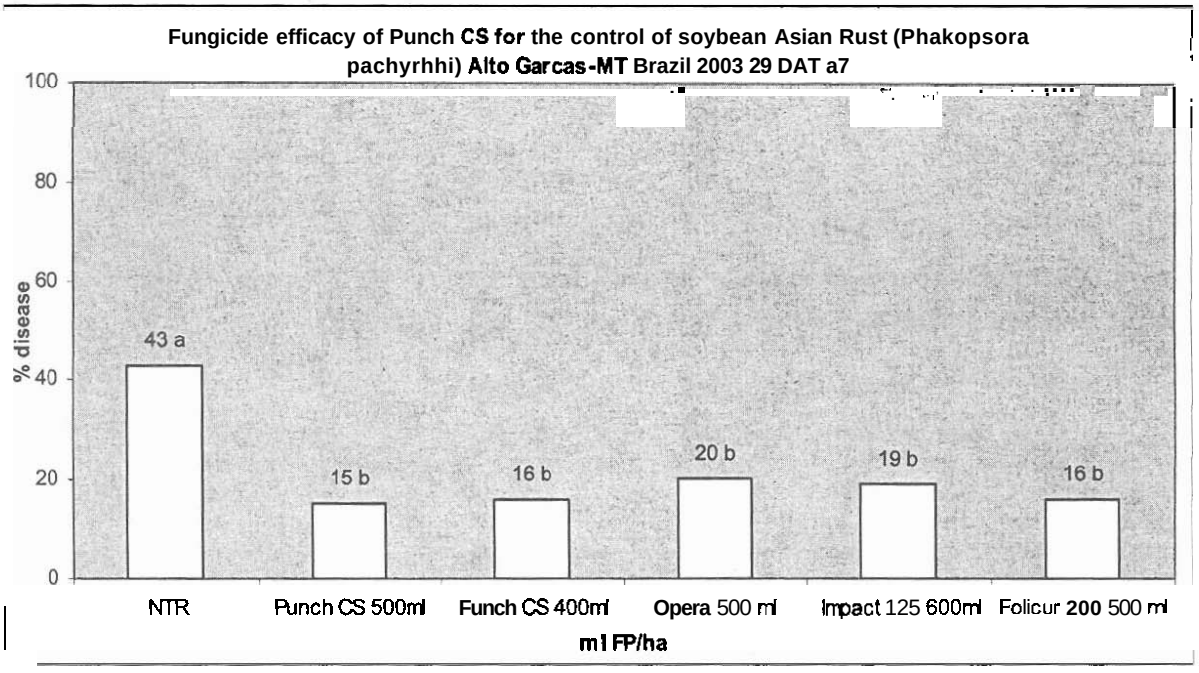
Graph 5. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust (Phakopsorapachyrhizi). Maua da Serra-MT, 2003 21DAT



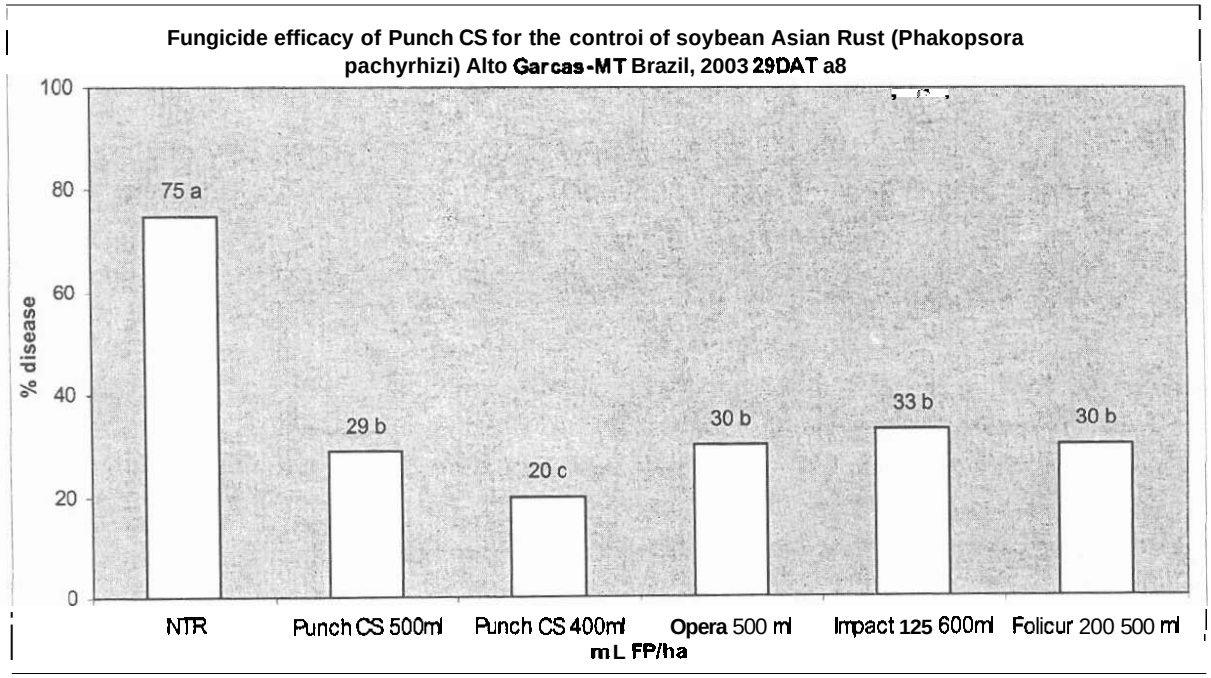
Graph 6. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust (Phakopsorapachyrhizi). Rondonopolis-MT, 2003 21DAT



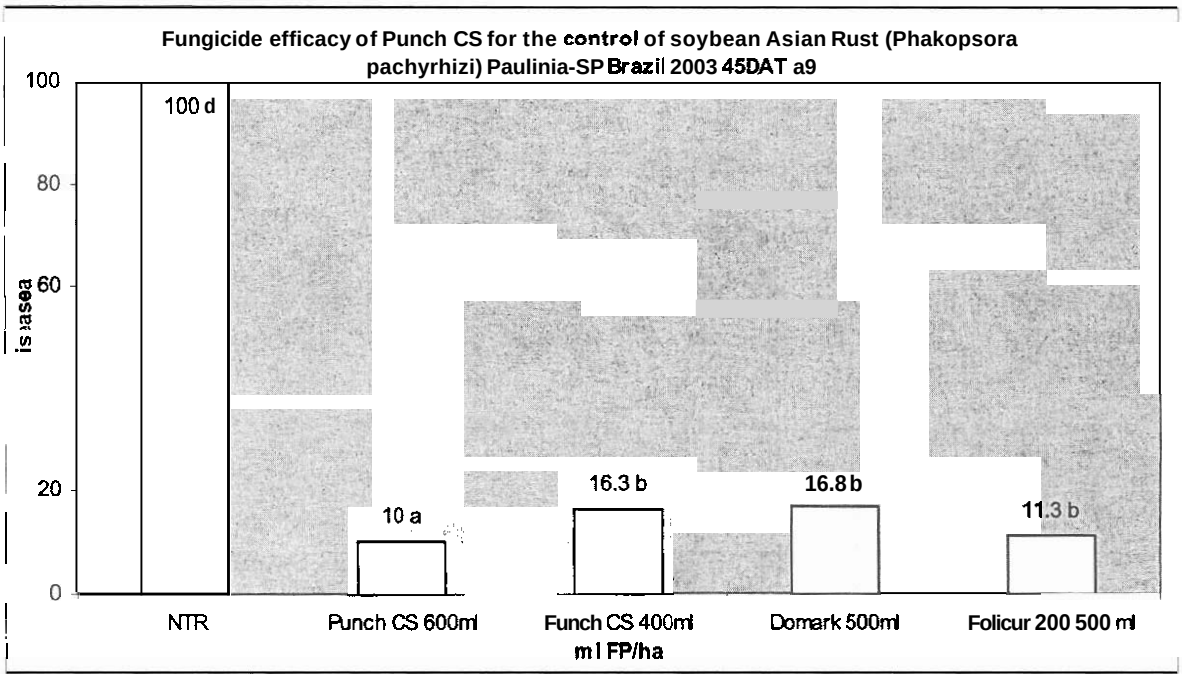
Graph 7. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust ***(Phakopsorapachyrhizi).***Alto Garcas-PR, 2003 29DAT



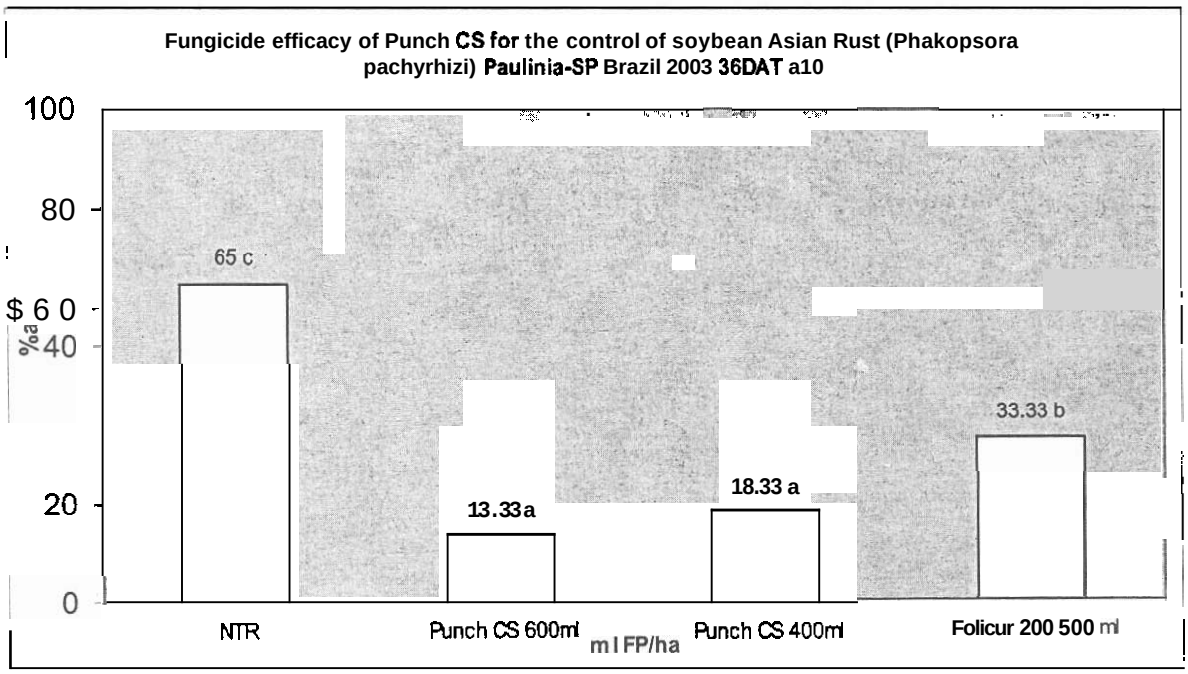
Graph 8. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Alto Garcas-MT, 2003 29DAT



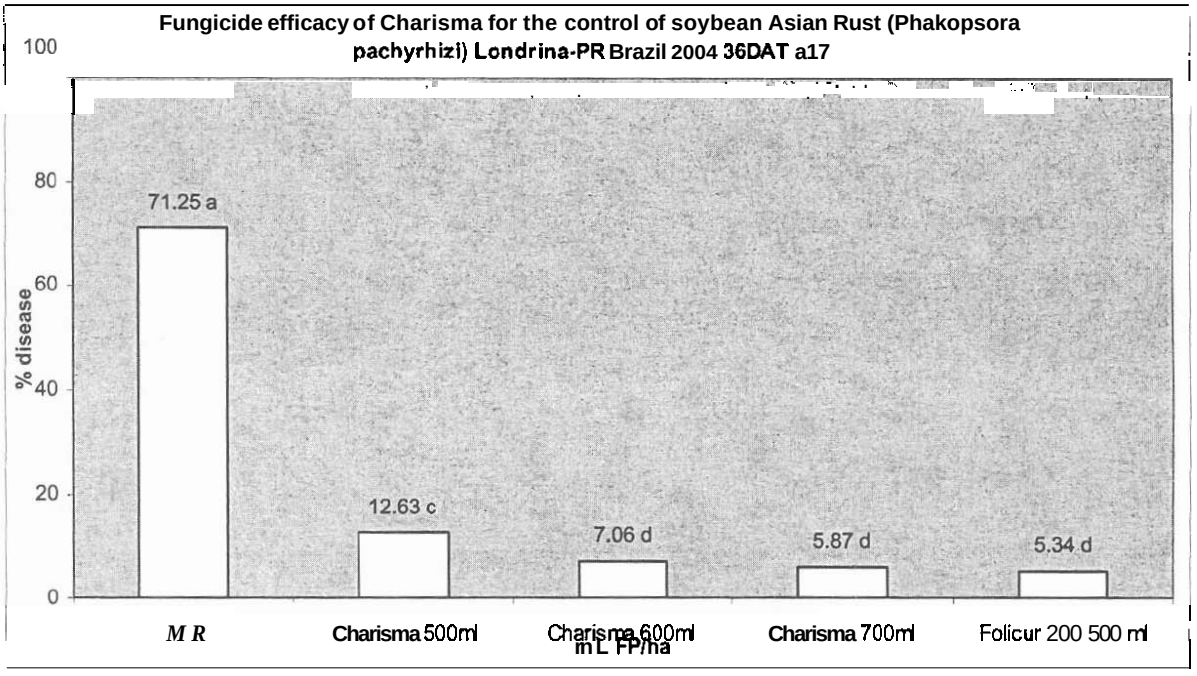
Graph 9. Fungicide efficacy of Punch™ CS for the control of Asian soybean rust *(Phakopsorapachyrhizi).* Paulinia-SP, 2003 *45* DAT



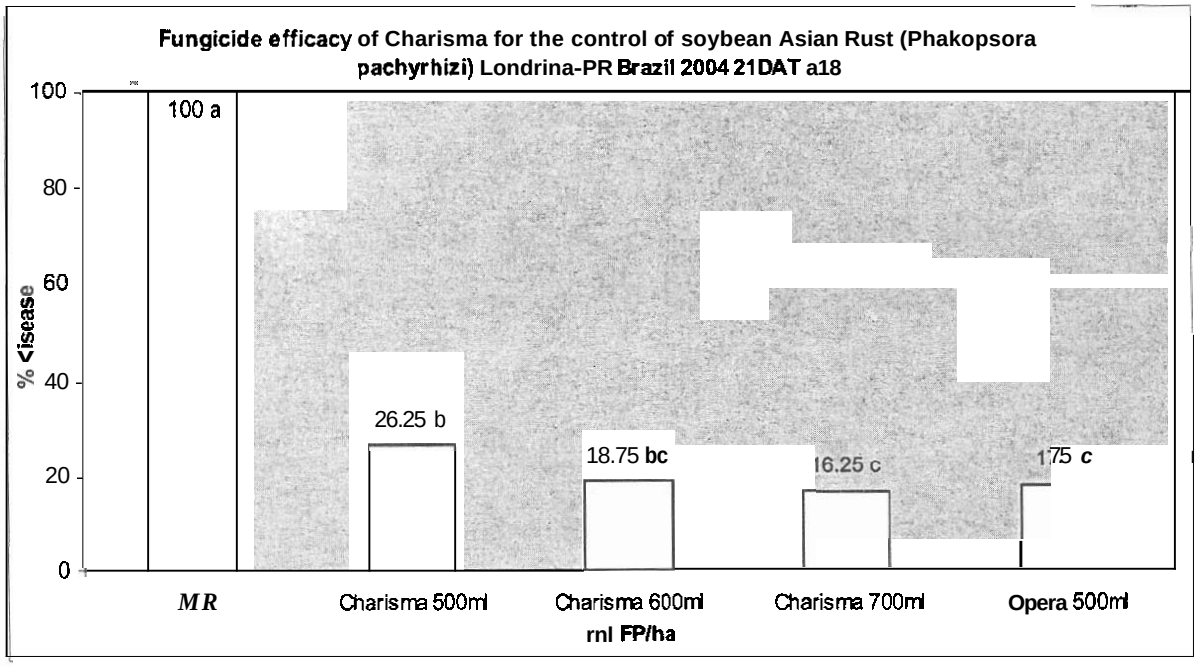
Graph 10. Fungicide efficacy of Punch™ CS for the control of **Asian** soybean rust *(Phakopsorapachyrhizi).* Paulinia-SP, 2003 36 DAT



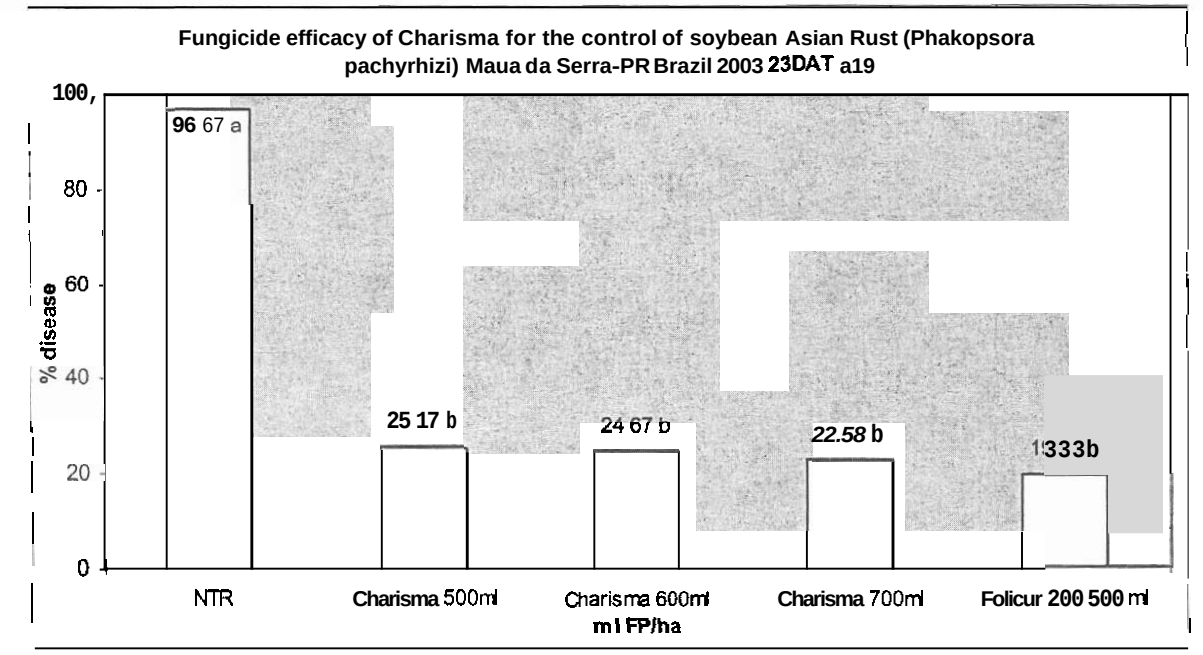
Graph 11. Fungicide efficacy of Charisma™ for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Londrina-PR, 2004 36DAT



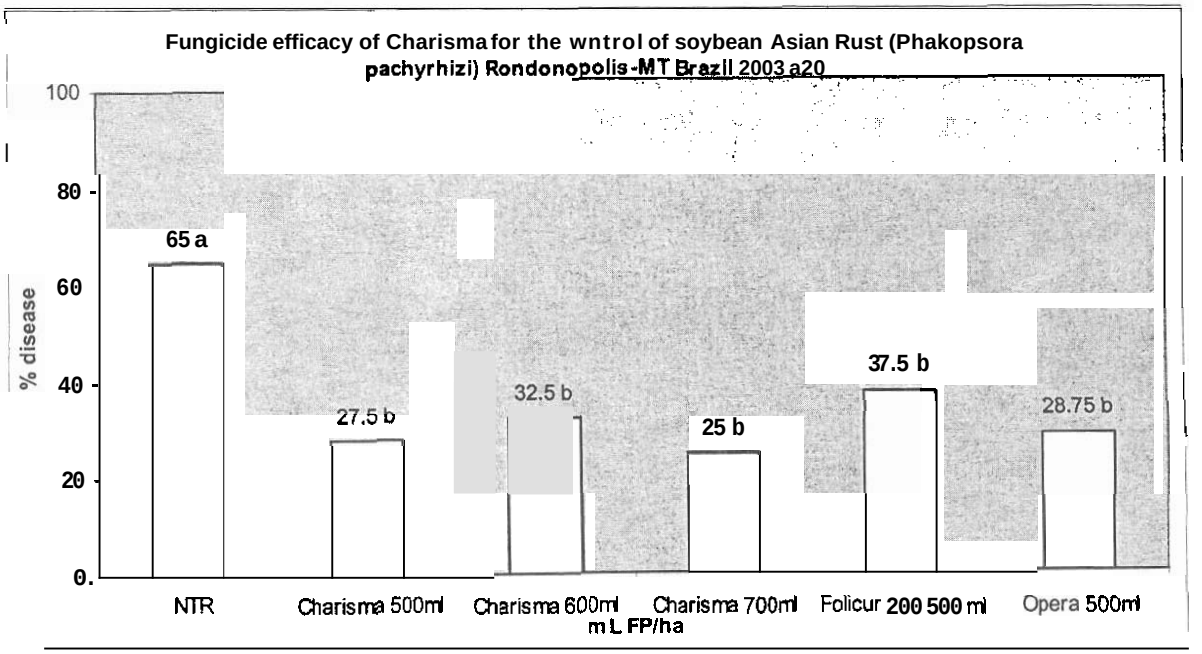
Graph 12. Fungicide efficacy of Charisma™ for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Londrina-PR, 2004 21DAT



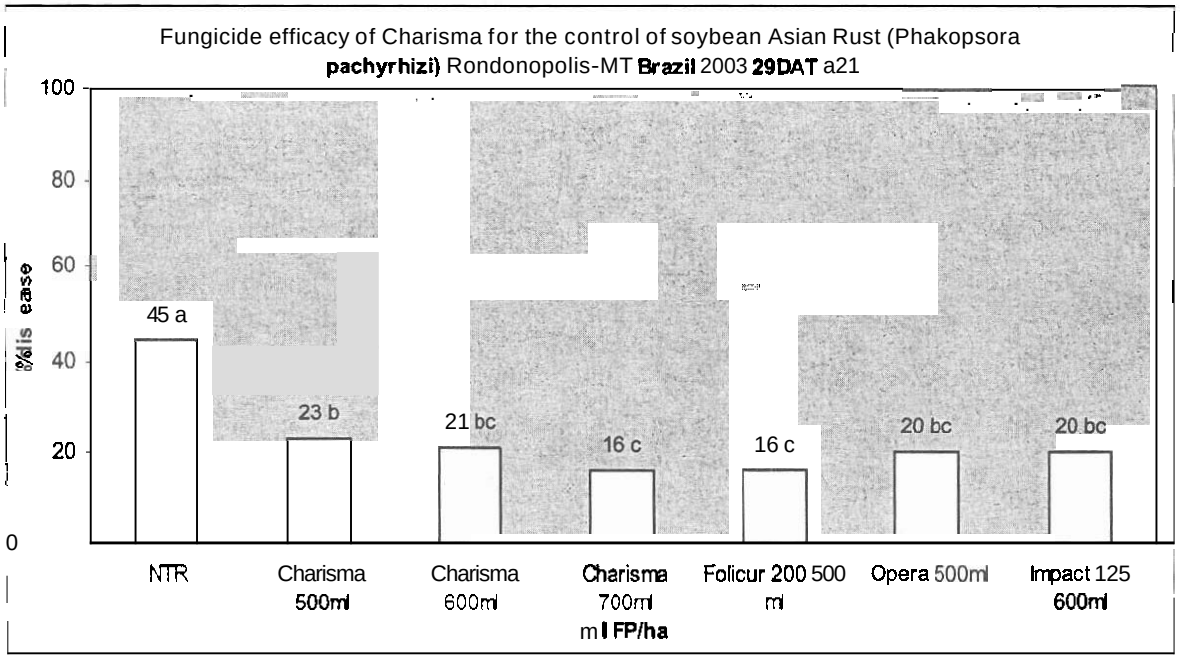
Graph 13. Fungicide efficacy of Charisma™ for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Maua da Serra-PR, 2003 23DAT



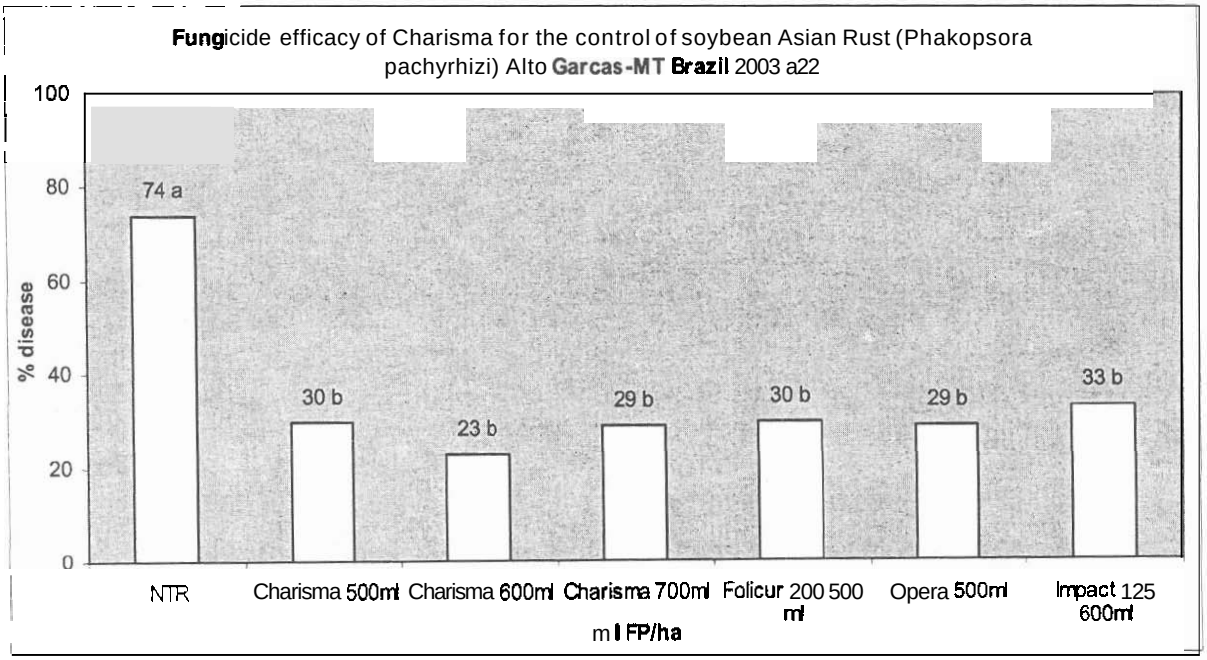
Graph 14. Fungicide efficacy of Charisma™ for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Rondonopolis-MT, 2003 21DAT



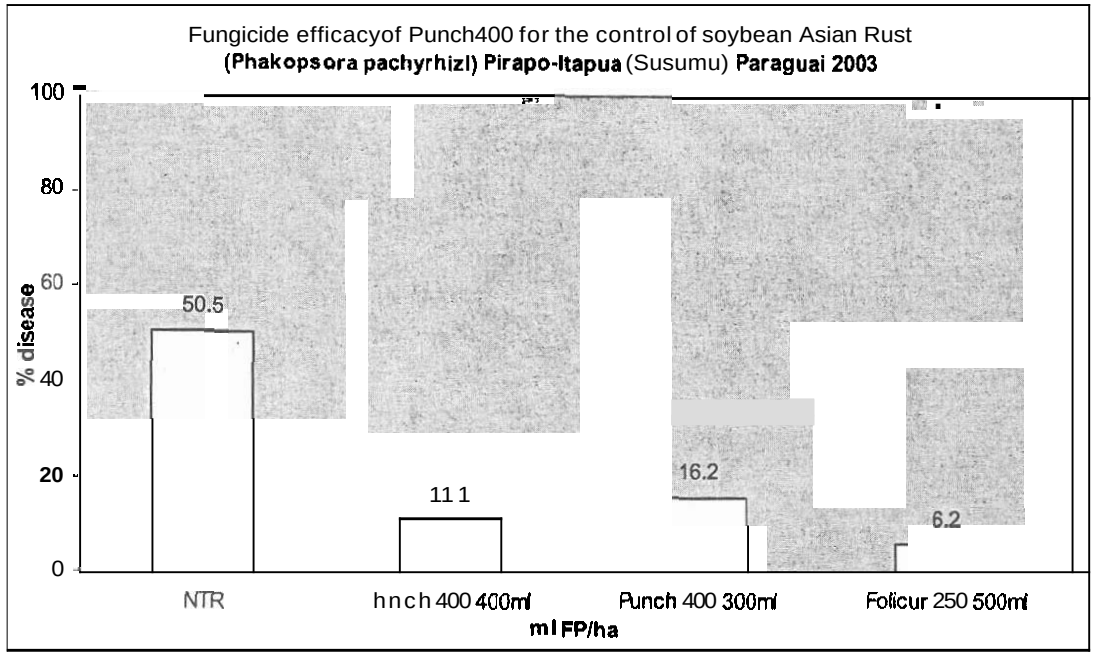
Graph 15. Fungicide efficacy of Charisma™ for the control of Asian soybean rust *(Phakopsora pachyrhizi)*. Rondonopolis-MT, 2003 29DAT



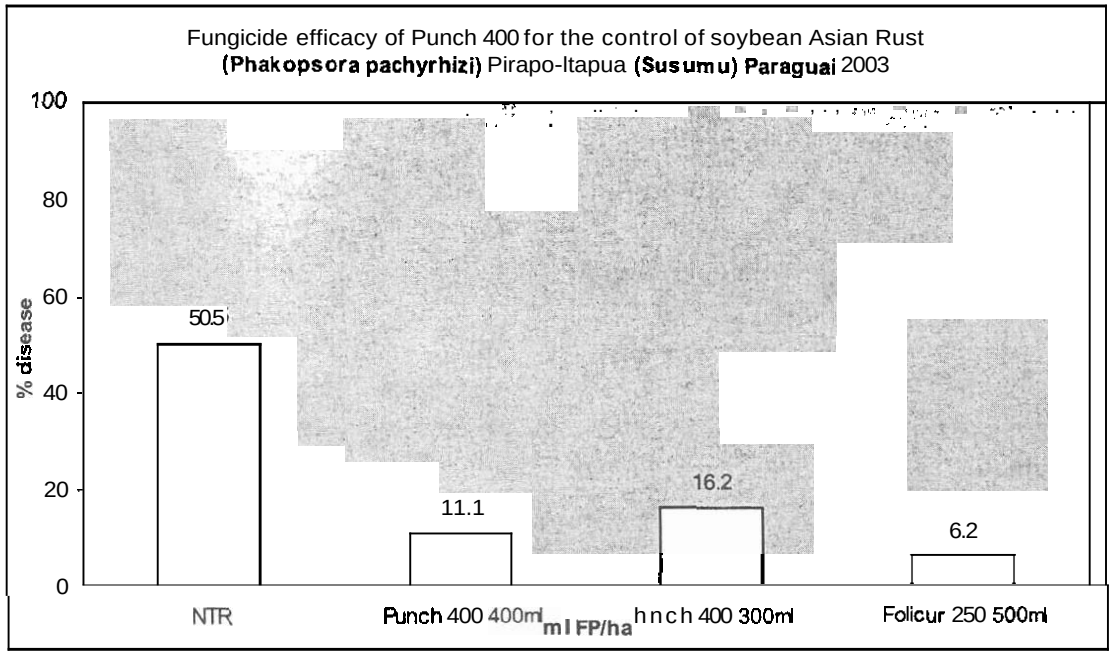
Graph 16. Fungicide efficacy of Charisma™ for the control of Asian soybean rust (*Phakopsora pachyrhizi*). Alto Garcas-MT, 2003 29DAT



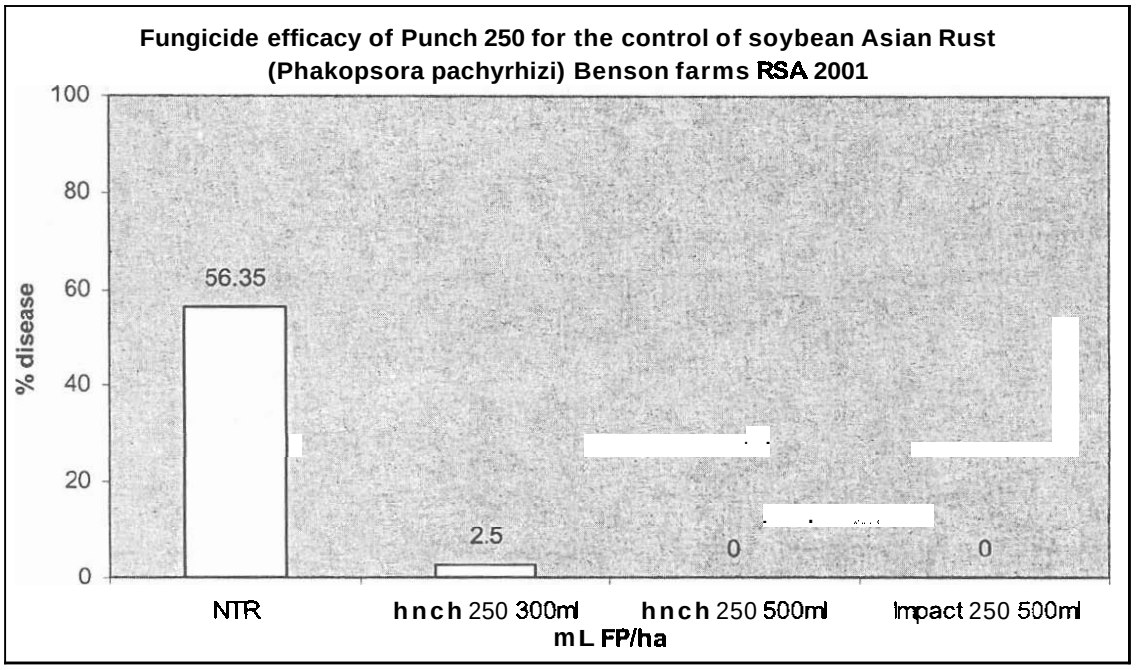
Graph 17. Fungicide efficacy of Punch™ 400 for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Pirapo-Itapua, Paraguay, 2003



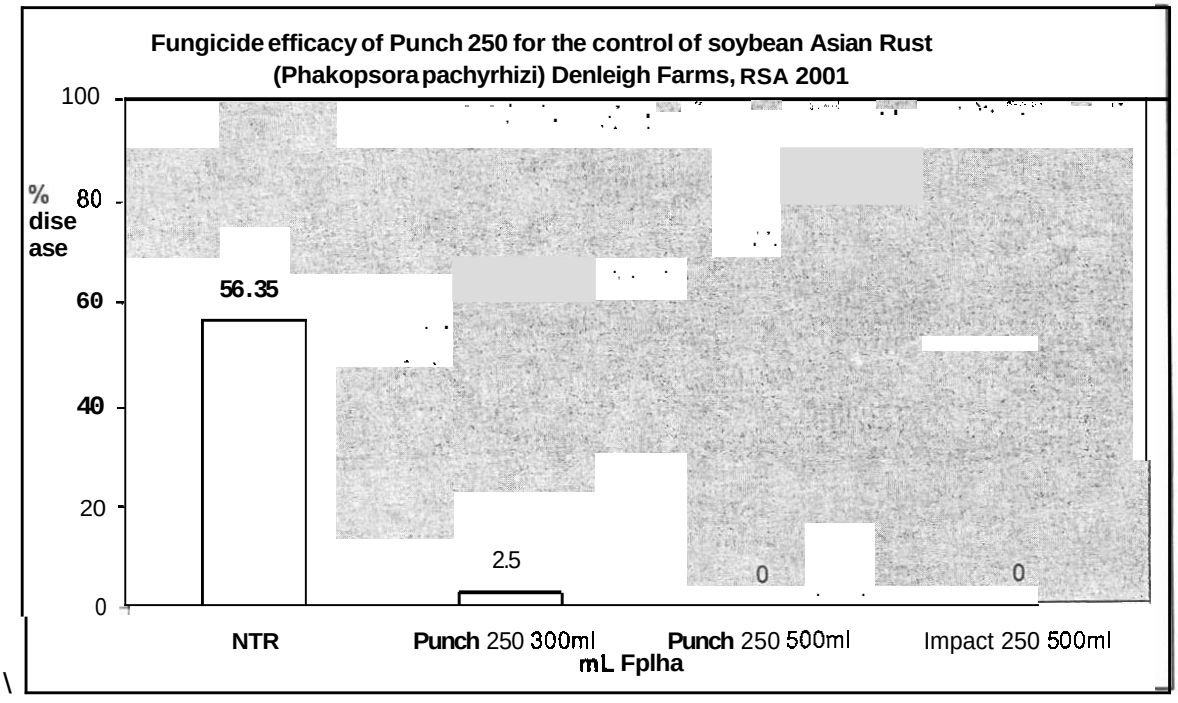
Graph 18. Fungicide efficacy of Punch™ 400 for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Pirapo-Itapua, Paraguay, 2003



Graph 19. Fungicide efficacy of Punch™ 250 for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Benson Farms, RSA 2001



Graph 20. Fungicide efficacy of Punch™ 250 for the control of Asian soybean rust ***(Phakopsorapachyrhizi).*** Denleigh Farms, RSA 2001



APPENDIX 3 SUMMARY OF FLUSILAZOLE MIXTURES AND PRODUCTS USED AS STANDARDS TO CONTROL ASIAN SOYBEAN RUST

Name	Country	Formulation	ai / L	dose gai / ha	dose ml FP / ha
Punch CS	Brazil	SE	250 gai flusilazole + 125 gai carbendazim	100 gai flusilazole + 50 gai carbendazim	400 ml
Punch CS	Brazil	SE	250 gai flusilazole + 125 gai carbendazim	125 gai flusilazole + 62,5 gai carbendazim	500 ml
Punch 250	RSA	EW	250 gai flusilazole	75 gai flusilazole	300 ml
Punch 250	RSA	EW	250 gai flusilazole	125 gai flusilazole	500 ml
Punch 400	Paraguai	EC	400 gai flusilazole	120 gai flusilazole	300 ml
Punch 400	Paraguai	EC	400 gai flusilazole	160 gai flusilazole	400ml
Charisma CE	Brazil	EC	106,7 gai flusilazole + 100 gai famoxadone	53,35 gai flusilazole + 50 gai famoxadone	500 ml
Charisma CE	Brazil	EC	106,7 gai flusilazole + 100 gai famoxadone	64,02 gai flusilazole + 60 gai famoxadone	600 ml
Charisma CE	Brazil	EC	106,7 gai flusilazole + 100 gai famoxadone	74,69 gai flusilazole + 70 gai famoxadone	700 ml
Opera	Brazil		133 gai pyraclostrobin + 50 gai epoxiconazole	66,5 gai pyraclostrobin + 25 gai epoxiconazole	500 ml
Impact 125	Brazil		125 gai flutriafol	75 gai flutriafol	600 ml
Impact 250	RSA		250 gai flutriafol	125 gai flutriafol	500 ml
Folicur 200	Brazil	EC	200 gai tebuconazole	100 gai tebuconazole	500 ml
Domark	Brazil	EC	100 gai tetraconazole	50 gai tetraconazole	500 ml

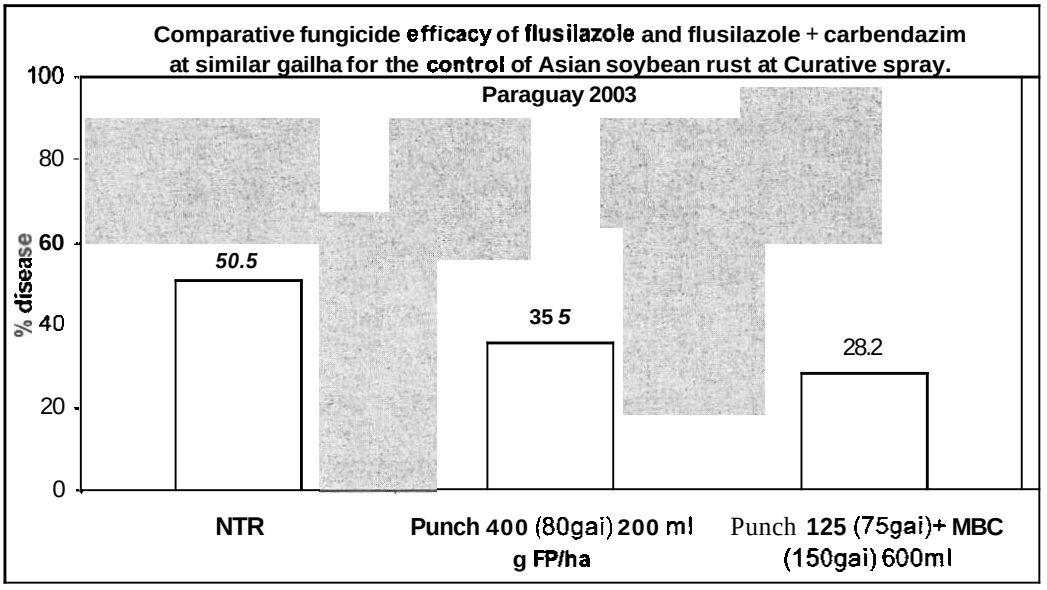
APPENDIX 4 SUMMARY OF TRIAL LOCATIONS WITH FLUSILAZOLE MIXTURES FOR ASIAN SOYBEAN RUST CONTROL

Location	Country	Location	Year	Product	Timing of application
1	Brazil	Ponta Grossa-PR	2004	Punch CS	R 5.1 and R 5.3
2	Brazil	Rondonopolis-MT	2003	Punch CS	R 5.3 and R 6
3	Brazil	Londrina-PR	2004	Punch CS	R 3 and R 5.2
4	Brazil	Londrina-PR	2004	Punch CS	R 5.1 and R 5.3
5	Brazil	Maua da Serra-PR	2003	Punch CS	R 3 and R 5.3
6	Brazil	Rondonopolis-MT	2003	Punch CS	R 5.1 and R 6
7	Brazil	Alto Garcas-MT	2003	Punch CS	R 3 and R 5.2
8	Brazil	Alto Garcas-MT	2003	Punch CS	R 4 and R 5.3
9	Brazil	Paulinia-SP	2003	Punch CS	R 1, R 2, and R 4
10	Brazil	Paulinia-SP	2003	Punch CS	R land R 2
11	Brazil	Londrina-PR	2004	Charisma	R 3 and R 5.2
12	Brazil	Londrina-PR	2004	Charisma	R 5.1 and R 5.3
13	Brazil	Maua da Serra-PR	2003	Charisma	R 3 and R 5.3
14	Brazil	Rondonopolis-MT	2003	Charisma	R 5.1 and R 6
15	Brazil	Rondonopolis-MT	2003	Charisma	R 5.1 and R 6
16	Brazil	Alto Garcas-MT	2003	Charisma	R 4 and R5.3
17	Paraguai	Pirapo	2003	Punch400	R 3
18	Paraguai	Pirapo	2003	Punch 400	R 3
19	RSA	Benson F	2001	Punch250	R 1
20	RSA	Denleigh F	2001	Punch 250	R 1

APPENDIX 5 COOPERATORS AND INSTITUTIONS CONDUCTING FIELD TRIALS ON EFFICACY OF FLUSILAZOLE AND MIXTURES FOR THE CONTROL OF ASIAN SOYBEAN RUST.

Graph	Location	Country	Year	Author	Institution
1	Ponta Grossa-PR	Brazil	2004	David J. Filho	Universidade Estadual de Ponta Grossa
2	Rondonopolis-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
3	Londrina-PR	Brazil	2004	Seiji Igarashi	Universidade Estadual de Londrina
4	Londrina-PR	Brazil	2004	Seiji Igarashi	Universidade Estadual de Londrina
5	Maua da Serra-PR	Brazil	2004	Carlos Utiamada	TAGRO
6	Rondonopolis-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
7	Alto Garcas-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
8	Alto Garcas-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
9	Paulinia-SP	Brazil	2003	Silvania Furlan	Instituto Biologico
10	Paulinia-SP	Brazil	2003	Silvania Furlan	Instituto Biologico
11	Londrina-PR	Brazil	2004	Seiji Igarashi	Universidade Estadual de Londrina
12	Londrina-PR	Brazil	2004	Seiji Igarashi	Universidade Estadual de Londrina
13	Maua da Serra-PR	Brazil	2004	Carlos Utiamada	TAGRO
14	Rondonopolis-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
15	Alto Garcas-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
16	Alto Garcas-MT	Brazil	2003	Erlei M. Reis	Universidade de Passo Fundo
17	Pirapo-Itapua	Paraguai	2003	Wilfrido Moreira	University of Paraguai
18	Pirapo-Itapua	Paraguai	2003	Wilfrido Moreira	University of Paraguai
19	Benson Farm	RSA	2001	Piet de Beer	DuPont
20	Denleigh Farm	RSA	2001	Piet de Beer	DuPont

APPENDIX 6 COMPARATIVE EFFICACY OF FLUSILAZOLE AND FLUSILAZOLE + CARBENDAZIM AT SIMILAR USE RATES FOR CONTROL OF ASIAN SOYBEAN RUST



F. PROPOSED TOLERANCE

Temporary tolerances can be proposed for flusilazole and famoxadone based on the preliminary residue data provided herein. Acute and chronic dietary risk assessments were conducted for flusilazole, as it is not yet registered in the US. **A** summary of the assessment results is presented in the Toxicology section, page 31. The most highly exposed population group was infants with only 1.4% of the acute RfD used. The results tables and the residue input file are provided following this section. These results indicate a very small percentage of the reference dose was used and that there would be a reasonable certainty of no harm from use of flusilazole on soybeans.

Famoxadone tolerances have been established on crops other than soybeans, as listed on page 9. **A** separate dietary risk assessment was not conducted for famoxadone on soybeans but is not expected to be of concern.

Proposed Time-Limited Tolerances

Based upon the residue results from Brazil, Argentina, South Africa, and France, and the proposed use directions for Punch and Charisma under the section 18 emergency exemption, tolerances can be proposed for the active ingredients flusilazole and famoxadone on soybeans.

Active Ingredient	Proposed time-limited tolerance on soybeans
Flusilazole	0.02 ppm
Famoxadone	0.05 ppm

ACUTE RESULTS

DuPont Agricultural Products Ver. 7.87
DEEM ACUTE Analysis for FLUSILAZOLE (1994-98 data)
Residue file: flusilazole.RS7 Adjustment factor P2 NOT used.
Analysis Date: 11-30-2004/12:42:46 Residue file dared: 11-30-2004/12:41:03/2
NOEL (Acute) = 0.500000 mg/kg body-wt/day
Daily totals far food and foodform consumption used.
Run Comment: ""

Summary calculations (per capita):

	5th Percentile			1st Percentile			0.1st Percentile	
	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. Population:	0.000012	0.24	41116	0.000024	0.48	20787	0.000068	1.36	7349
All infants:	0.000068	1.35	7388	0.000099	1.98	5039	0.000141	2.82	3541
Females 13-19 (not preg or lactating):	0.000009	0.18	54610	0.000013	0.26	38987	0.000020	0.40	25279
Females 20+ (not preg or lactating):	0.000007	0.15	66816	0.000011	0.22	45897	0.000018	0.35	28419
Females 13-50 yrs:	0.000008	0.16	61332	0.000012	0.24	41259	0.000018	0.35	28178
Males 13-19 yrs:	0.000012	0.24	41685	0.000017	0.34	29450	0.000024	0.48	20905
Males 20+ yrs:	0.000009	0.17	58529	0.000014	0.27	36534	0.000026	0.53	18998
Seniors 55+:	0.000007	0.13	74271	0.000010	0.21	47975	0.000022	0.45	22320
Children 1-2 yrs:	0.000022	0.45	22438	0.000035	0.70	14298	0.000064	1.29	7756
Children 3-5 yrs:	0.000020	0.4	24425	0.000033	0.66	15134	0.000052	1.03	9666
Children 6-12 yrs:	0.000015	0.30	33670	0.000023	0.45	22148	0.000036	0.72	13925
Youth 13-19 yrs:	0.000011	0.21	46748	0.000015	0.31	32648	0.000024	0.48	20858
Adults 20-49 yrs:	0.000009	0.17	58323	0.000013	0.27	37200	0.000022	0.44	22938
Adults 50+ yrs:	0.000007	0.14	73102	0.000010	0.21	47941	0.000018	0.36	27787
Females 13-49 yrs:	0.000008	0.16	61234	0.000012	0.24	41027	0.000018	0.36	28076

CHRONIC RESULTS

DuPont Agricultural Products Ver. 7.87
DEEM Chronic analysis for FLUSILAZOLE (1994-98 data)
Residue file name: C:\Documents and Settings\KLEMENAS\Desktop\flusilazole.RS7
Adjustment factor 1\2 NOT used.
Analysis Date 11-30-2004/12:44:25 Residue file dated: 11-30-2004/12:41:03/2
Reference dose (RfD, Chronic1 = .007 mg/kg bw/day

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000004	0.1%
U.S. Population (spring season)	0.000005	0.1%
U.S. Population (summer season)	0.000004	0.1%
U.S. Population (autumn season)	0.000004	0.1%
U.S. Population (winter season)	0.000004	0.1%
Northeast region	0.000004	0.1%
Midwest region	0.000005	0.1%
Southern region	0.000004	0.1%
Western region	0.000004	0.1%
Hispanics	0.000004	0.1%
Non-Hispanic whites	0.000004	0.1%
Non-Hispanic blacks	0.000005	0.1%
Non-Hisp/non-white/non-black	0.000005	0.1%
All infants (< 1 year)	0.000024	0.3%
Nursing infants	0.000008	0.1%
Non-nursing infants	0.000031	0.4%
Children 1-6 yrs	0.000009	0.1%
Children 7-12 yrs	0.000006	0.1%
Females 13-19 (not preg or nursing)	0.000004	0.1%
Females 20+ (not preg or nursing)	0.000003	0.0%
Females 13-50 yrs	0.000003	0.0%
Females 13+ (preg/not nursing1	0.000004	0.1%
Females 13+ (nursing)	0.000004	0.1%
Males 13-19 yrs	0.000005	0.1%
Males 20+ yrs	0.000004	0.1%
Seniors 55+	0.000003	0.0%
Children 1-2 yrs	0.000009	0.1%
Children 3-5 yrs	0.000009	0.1%
Children 6-12 yrs	0.000006	0.1%
Youth 13-19 yrs	0.000004	0.1%
Adults 20-49 yrs	0.000004	0.1%
Adults 50+ yrs	0.000003	0.0%
Females 13-49 yrs	0.000003	0.0%

RESIDUE INPUT FILE

DuPont Agricultural Products Ver. 7.87
DEEM Chronic analysis far FLUSILAZOLE 1994-98 data
Residue file: C:\Documents and Settings\KLEMENAS\Desktop\flusilazole.RS7
Adjust. #2 NOT used
Analysis Date 11-30-2004 Residue file dated: 11-30-2004/12:41:03/2
Reference dose (RfD) = 0.007 mg/kg bw/day

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors #1	#2	Comment
255	6A	Soybeans-sprouted seeds	0.010000	0.330	1.000	
297	6A	Soybeans-ail	0.010000	1.000	1.000	
303	6A	Soybean-other	0.010000	1.030	1.000	
304	6A	Soybeans-mature seeds dry	0.010000	1.000	1.000	
305	6A	Soybeans-flour (full fat)	0.010000	1.000	1.000	
306	6A	Soybeans-flour (low fat)	0.010000	1.000	1.000	
307	6A	Soybeans-flour (defatted)	0.010000	1.000	1.000	
482	O	Soybeans-protein isolate	0.010000	1.000	1.000	

,–

ATTACHMENT 1 EPA PESTICIDE FACT SHEET FOR FAMOXADONE

United States Environmental Protection Agency

Office of Prevention, Pesticides and Toxic Substances (7501C)

EPA

Pesticide Fact Sheet

Name of Chemical: **Famoxadone**
Reason for Issuance: **New Chemical**
Date Issued: **July, 2003**

Description of Chemical

Chemical Name:	3-anilino-5-methyl-5-(4-phenoxyphenyl)-1,3-oxazolidine-2,4-dione (IUPAC)
Common Name:	Famoxadone
Trade Name:	Famoxate™ Technical
Chemical Class:	Oxazolidinedione
EPA Chemical Code:	113202
Chemical Abstracts Service (CAS) Number:	131807-57-3
Year of Initial Registration:	2003
Pesticide Type:	Fungicide
U.S. Producer:	E.I. DuPont Nemours and Company DuPont Agricultural Products P.O. Box 30 Newark, DE 19711-3507

Use Pattern and Formulations

Famoxadone is used in the U.S. in combination with cymoxanil in the formulated product Tanos DF (water dispersible granules with 25% Famoxadone/25% cymoxanil) for the control of

various fungal diseases on fruiting vegetables, tomatoes, potatoes, curcurbits, head lettuce and imported grapes, including raisins. For example, the uses of Tanos 50DF include treating downy mildew on curcurbits and head lettuce and early and late blight on potatoes and fruiting vegetables.

Famoxadonc belongs to the oxazolidinedione class of chemicals and is highly active against spore germination and mycelial growth of sensitive fungi. The biochemical mechanism of action of famoxadone is inhibition of the fungal mitochondrial respiratory chain at Complex III, resulting in a decreased production of ATP by the fungal cell.

SUMMARY OF SCIENCE FINDINGS

Acute Toxicity: Technical grade famoxadone has minimal to moderate acute toxicity in acute oral, dermal and inhalation tests, it is moderately irritating to the eyes and skin, and is not a dermal sensitizer.

Subchronic Toxicity: In subchronic feeding studies in rats, mice, and dogs, famoxadone generally caused decreased body weights and body weight gains that were often accompanied by decreased food consumption and food efficiency. A mild regenerative hemolytic anemia was regularly observed. Secondary effects of the anemia were frequently observed in the spleen, bone marrow and liver. Famoxadone frequently induced a mild hepatotoxicity in treated animals characterized by elevated levels of clinical chemistry enzymes indicative of liver damage and/or by histopathological lesions in the liver. Adaptive hepatocellular responses indicating stimulation of the liver microsomal/peroxisomal enzyme system were also regularly observed, but were not considered to be adverse effects. Both the anemia and the hepatotoxicity wen mild and did not significantly compromise the overall health status of the treated animals. In a subchronic dermal study in rats, the systemic effects were similar to those observed in oral studies in rats. No dermal irritation was observed. Additional treatment-related effects were observed in dogs, but were not observed in other species. In a subchronic feeding study, myotonic twitches were noted in male and female dogs at the highest dose tested starting on day 21 and continuing throughout the remainder of the study. Lens lesions (cataracts) were observed in dogs at the end of the 90-day study.

Chronic Toxicity: In chronic fading studies in rats, dogs, Cynomolgus monkeys (gavage study) and mice, famoxadone generally caused decreased body weights and body weight gains that were often accompanied by decreased food consumption and food efficiency. A mild regenerative hemolytic anemia was regularly observed. Secondary effects of the anemia were frequently observed. in the spleen, bone marrow and liver. Famoxadone frequently induced a mild hepatotoxicity in treated animals characterized by elevated Levels of clinical chemistry enzymes indicative of liver damage and/or by histopathological lesions in the liver. Adaptive hepatocellular responses indicating stimulation of the liver microsomal/peroxisomal enzyme system were also regularly observed, but were not considered to be adverse effects. In a I-year chronic feeding study in dogs, famoxadone induced treatment-related cataracts in the lens in male and female dogs. Treatment-related cataracts in the lens of the eye were not observed in

the chronic feeding study in rats or in the I-year gavage study in Cynomolgus monkeys or in the carcinogenicity study in mice. Both the anemia and the hepatotoxicity were mild and did not significantly compromise the overall health status of the treated animals.

Carcinogenicity: In carcinogenicity studies in rats and mice, famoxadone did not demonstrate evidence of carcinogenic potential. Famoxadone is classified as 'not likely to be carcinogenic to humans."

Developmental Toxicity: In a developmental toxicity study in rats, no developmental toxicity was observed. In a developmental toxicity study in rabbits, an increased incidence of abortions was observed. The does which aborted also had markedly decreased body weight, body weight gain and food consumption. Since it could not be determined whether the abortions were due to maternal toxicity or due to an effect on reproductive/developmental mechanisms, the docs and fetuses were considered to be equally sensitive to the test material. There was also an equivocal increase in % postimplantation loss and mean number of resorptions per doe in this study. The results in the two developmental toxicity studies demonstrated no quantitative or qualitative evidence of increased susceptibility of fetuses or pups as compand to adults.

Reproductive **Toxicity:** In a 2-generation reproduction *study* in rats, decreased body weights for F_1 and F_2 pups were observed throughout lactation, but no reproductive toxicity was observed. The LOAEL for offspring toxicity was determined to be 800 ppm (44.7 mg/kg/day for males and 53.3 mg/kg/day for females), while a LOAEL for reproductive performance was not observed. The NOAEL for repmductive performance is 800 ppm. The results in the reproduction study demonstrated no quantitative or qualitative evidence of increased susceptibility of fetuses or pups as compared to adults.

Neurotoxicity: In an acute neurotoxicity study in rats, equivocal evidence of a possible slight neurotoxic effect at the limit dose of 2000 mg/kg was observed. In this study, an increased incidence of palpebral (eyelid) closure in the 13-week feeding study in dogs of myotonic twitching in the high dose level male and female animals In none of the other toxicity studies with famoxadone, including a subchronic neurotoxicity study in rats, were there any toxicologically significant evidence of treatment-related neurotoxicity.

Mutagenicity: Famoxadone may have a weak mutagenic potential, but this is not considered to be toxicologically significant. In three gene mutation studies, results were negative. In three chromosome aberration studies a weak clastogenic effect was observed in two *in vitro* chromosome aberration studies in human lymphocytes, but in an *in vivo* micronucleus study in mice using bone marrow cells. the results were negative. In four unscheduled DNA synthesis (UDS) studies, although a positive response was observed m an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocyte cultures, results in two repeat studies were negative. Also, results in an *in vivo/in vitro* UDS assay in primary rat hepatocyte cultures derived from male rats given oral doses of famoxadone were negative.

Chronic Reference Dose (cRfD) In a 13-week subchronic oral study famoxadone was administered by diet to 4 beagle dogs/sex/group at doses of 0, 40, 300, or 1000 ppm (equal to 0,

1.3/1.4, 10.0110.1, or 23.8/23.3 mg/kg/day in males/females). The dope and endpoint for establishing the cRfD is based on a LOAEL of 1.4 mg/kg/day, based on treatment-related microscopic lens lesions (cataracts) in eyes of female dogs. A NOAEL could not be determined.

Uncertainty Factor(s): 1000 (10X for inter-species extrapolation, 10X for intra-species variation; and an additional IOX for the use of a LOAEL and the use of a subchronic study. This endpoint is baaed on an oral study, which is the route of interest for a dietary risk estimate. This study and endpoint were selected because they would address the concerns for toxic effects observed in all the other available studies for this chronic risk assessment.

$$\text{Chronic RfD} = \frac{\text{1.4 mg/kg/day (LOAEL)}}{\text{1000 (UF)}} = \text{0.0014 mg/kg/day}$$

Physical/Chemical Properties

TABLE 1. Physicochemical Properties of Famoxadone

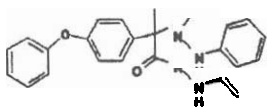
Parameter	Value
Color/Physical state	Pale cream powder
Molecular Structure	
Melting point/range	140.3- 141.8°C
pH of 1% aqueous suspension	6.56 at 20°C
Density or specific gravity	D^{20}_4 = 1.310 g/mL
Water solubility (20°C)	unbuffered 52 µg/L 2 143

TABLE 1. Physicochemical Properties of Famoxadone	
Parameter	Value
	3 191 5 243 7 111 9 38
Solvent solubility (20°C)	Solvent g/L acetone 274 acetonitrile 125 dichloromethane 219 ethyl acetate 125 hexane 0.0476 methanol 10.0 1-octanol 1.87 toluene 13.3
Octanol/water partition coefficient (K_{ow})	pH Log K_{ow} ± SD 3.0 4.59 ± 0.06 5.0 4.80 ± 0.13 7.0 4.65 ± 0.40 9.0 5.55 ± 0.26
Vapor pressure at 20°C	6.4×10^{-4} mPa (4.8×10^{-9} mm Hg)
Henry's Law Constant	4.6×10^{-3} Pa m^3 mol^{-1}, pH 7
Dissociation constant (pK_a)	Expected to be weakly basic. The dissociation constant could not be measured or inferred from solubility in octanol water partition coefficient.

Toxicological Characteristics:

Table 2. Acute Toxicity of Famoxadone Technical (Selected Studies)			
Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral, rats	44302407	M: LD_{50} = >5000 mg/kg F: LD_{50} = >5000 mg/kg	IV
870.1200 Acute dermal, rabbits	44302409	M: LD_{50} = >2000 mg/kg F: LD_{50} = >2000 mg/kg	III
870.1300 Acute inhalation, tats	44302410	M: LC_{50} = >5.3 mg/L F: LC_{50} = >5.3 mg/L	IV
870.2400 Primary eye irritation, rabbits	44302411	Moderately irritating	III

5

F70.2500 **Primary** skin **irritation,** rabbits	44946205	Moderately irritating	III
870.2600 Dermal sensitization, guinea pig	44302413	**Non-sensitizer**	NA

Table 3 **Toxicity Profile of Famoxadone** Technical (Selected **Studies)**

Guideline No./Study Type	Results
870.3100 90-Day oral toxicity. **rats**	NOAEL = M: 3.3 **mg/kg/day.** F: 4.2 **mg/kg/day.** LOAEL = M: 13.0 **mg/kg/day** based on mild **hemolytic anemia and** decreased glucose. F: 16.6 **mg/kg/day based** on decreased body weight gain, food consumption, and food efficiency; mild hemolytic anemia and **decreased globulin.**
870.3100 90-Dav oral **toxicity,** mice	NOAEL = **M:** 62.4 **mg/kg/day.** F: 79.7 **mg/kg/day.** LOAEL = M: 534 **mg/kg/day based** on mild **hemolytic** anemia **with** secondary **responses** in **spleen** and mild **hepatotoxicity** in the liver. F: 757 mg/kg/day based on mild **hemolytic** anemia with secondary **responses** in spleen and mild **hepatotoxicity** in the liver.
870.3 **150** 90-Day oral **toxicity,** dogs	**NOAEL =** M: 1.3 **mg/kg/day.** F: **<1.4 mg/kg/day.** LOAEL = M: 10.0 mg/kg/day based on lens **cataracts** in eyes. At **23.8/21.2** mg/kg/day, **also myotonic twitches (starting** on **day** 21); **decreased** body weight, body weight **gain, food** consumption, and food **efficiency; slight** anemia **and hyperkalemia.** F. 1.4 mg/kg/day **based** on lens cataracts in **eyes.** At **10.1** mg/kg/day, no additional effects. At **23.3/20.1** mg/kg/day, same effects as for males at 23.8R1.2 **mg/kg/day.**
870.3200 28-Day **dermal** toxicity, rats	NOAEL = M: 250 **mg/kg/day.** F **1000 mg/kg/day.** LOAEL = **M:** 500 **mg/kg/day based** on **increased** alkaline **phosphatase, alanine aminotransferase and sorbitol dehydrogenase;** and mild hepatotoxicity in the liver. F: none (>1000 mg/kg/day). No dermal irritation in M or F.
870.3700a **Prenatal** developmental toxicity, rats	Maternal NOAEL = 250 **mg/kg/day.** LOAEL = 500 mg/kg/day based on **transient** decreased body **weight** gain and food consumption. Developmental NOAEL = **1000 mg/kg/day.** LOAEL =none **(>1000 mg/kg/day).**
870.3700b	Maternal NOAEL = 350 **mg/kg/day.**

Prenatal developmental toxicity, rabbits	LOAEL = 1000 mg/kg/day based on abortions; decreased body weight, body weight gain, and food consumption; and abnormal stools. Developmental NOAEL = 350 mg/kg/day. LOAEL = 1000 mg/kg/day based on abortions and equivocal increases in postimplantationloss and mean resorptions per doe.
870.3800 Reproduction and fertility effects, rats	Parental/Systemic NOAEL = M/F: 11.3114.2 mg/kg/day. LOAEL = M/F: 44.7/53.3 mg/kg/day based on decreased body weight, body weight gain, and food consumption; and hepatotoxicity in the liver. Reproductive NOAEL = M/F: 44.7/53.3 mg/kg/day. LOAEL = M/F: none (>44.7/53.3 mg/kg/day). Offspring NOAEL = M/F: 11.3114.2 mg/kg/day. LOAEL = M/F: 44.7153.3 mg/kg/day based on decreased body weights for F_1 and F_2 pups throughout lactation.
870.4100b Chronic toxicity, dogs	NOAEL = M: 1.2 mg/kg/day. F: 1.2 mg/kg/day. LOAEL = M: 8.8 mg/kg/day based on lens cataracts in eyes. F: 9.3 mg/kg/day based on lens cataracts in eyes. No other adverse effects were observed in M or F.
870.4100 Chmnic toxicity, Cynomolgus monkeys (I-year gavagc study)	NOAEL = M: 100 mg/kg/day. F: 100 mg/kg/day. LOAEL = M: 1000 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen, liver and kidney; and sinus dilatation in spleen. F: 1000 mg/kg/day based on mild hemolytic anemia with secondary responses in spleen. liver and kidney; and sinus dilatation in spleen. No evidence of lens cataracts in eyes of M or F.
870.4200b Carcinogenicity, mice	NOAEL = M: 96 mg/kg/day. F: 130 mg/kg/day. LOAEL = M: 274 mg/kg/day based on alight hepatotoxicity in the liver; no anemia. F: 392 mg/kg/day based on amyloidosis and slight hepatotoxicity in the liver; no anemia. No evidence of carcinogenicity in M or F.
870.4300 Combined chronic toxicity/carcinogenicity, rats	NOAEL = M: 8.4 mg/kg/day. F: 2.2 mg/kg/day. LOAEL = M: 16.8 mg/kg/day based on slight hemolytic anemia with compensatory erythropoiesis and secondary responses in spleen and bone marrow; and mild hepatotoxicity in the liver. F: 10.7 mg/kg/day based on decreased body weight gain and slight hemolytic anemia. At 23.0 mgkglday, also secondary responses to anemia in spleen, bone marrow and/or liver, and mild hepatotoxicity in the liver. No evidence of carcinogenicity in M or F.
870.5100	Negative without and with S-9 activation up to limit dose of 5000

Reverse gene mutation (*S. typhi./E. coli)*	µg/plate.
870.5300 Forward gene mutation (CHO/HGPRT locus)	Negative without and with S-9 activation up to the limit of solubility (in DMSO) of 30 µg/mL.
870.5300 Forward gene mutation (CHO/HGPRT locus)	Negative without and with S-9 activation up to cytotoxic concentrations (≥200 µg/mL without S-9 and ≥150 µg/mL with S-9).
870.5375 Chromosome aberration (human lymphocytes)	Positive (weak clastogenic effect) without S-9 activation. Statistically significant increases in percentage of aberrant cells at several dose levels ranging from 5-15 µg/mL. Cytotoxicity was observed at 10-18 µg/mL. Negative with S-9 activation.
870.5375 Chromosome aberration (human lymphocytes)	Positive (weak clastogenic effect) without S-9 activation. Statistically significant increases in percentage of aberrant cells at several dose levels ranging from 15-30 µg/mL. Cytotoxicity was observed at 20-30 µg/mL. Negative with S-9 activation.
870.5395 Micronucleus assay (mouse bone marrow)	Negative at single oral doses of up to limit dose of 5000 mg/kg.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Positive response (increased net nuclear grain counts) observed at several treatment levels ranging from 0.05-10 µg/mL. Cytotoxicity was observed at 10 µg/mL.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Negative at treatment levels up to 10 µg/mL. Cytotoxicity was observed at 10 µg/mL.
870.5550 Unsched. DNA synthesis (prim. rat hepatocytes)	Negative at treatment levels up to 5.0 µg/mL. Cytotoxicity was observed at 2.5 and 5.0 µg/mL.
870.5550 Unsched. DNA synthesis (hepatocytes derived from male rats given Famoxadone)	Negative at single oral doses of up to 2000 mg/kg. No marked increases in net nuclear grain counts or percentage of cells in repair in hepatocyte cultures.
870.6200a Acute neurotoxicity screening battery,	NOAEL = M: 1000 mg/kg. F: 2000 mg/kg. LOAEL = M: 2000 mg/kg based on decreased body weight gain and food consumption (on days 1-2); and palpebral (eyelid) closure (on

rats	day 1 only). F: none (>2000 mg/kg).
870.6200b Subchronic neurotoxicity screening battery, rats	NOAEL = M: 11.7 mg/kg/day. F: 14.4 mg/kg/day. LOAEL = M: 47 mg/kg/day based on decreased body weight, body weight gain, food wnsumption and food efficiency. F: 59 mg/kg/day based on decreased body weight. body weight gain, food consumption and food efficiency. No evidence of neurotoxicity in M or F.

Occupational and Residential Exposure and Risk Characterization.

Chemical-specificdata for assessing human exposures during pesticide handling activities were not submitted for famoxadone. Therefore, the Agency used Pesticide Handlers Exposure Database (PHED V 1.1) to assess handler exposure. Based on the application rates and uses. exposures are expected to be short- and intermediate-term in duration. Since both dermal and inhalation endpoints were based on the same toxicological effects for short- and intermediate-term exposures, the route-specific MOEs were combined into a total MOE. All MOEs for handlers were greater then the target MOEs of 100 (short term) and 300 (intermediate-term) and therefore do not exceed the Agency's level of concern. The Agency is imposing a re-entry interval of 12 hours for the Tanos 50DF product The Agency will also be requiring on product labels personal protective equipment (PPE) required by the Worker Protection Standard (WPS).

For short-term (1-30 days) occupational dermal and inhalation exposures, the toxicology endpoint was selected from the subchronic feeding study in dogs in which myotonic twitches were observed in male and female does at the highest dose tested (23 mg/kg/day) starting on day 21. The next lower dose in this study–(10 mg/kg/day) was the dose selected for the short-term risk assessments. The cataracts observed in the eyes of dogs in this study and in the chronic feeding study in dogs did not occur until after 8 weeks (56 days) of exposure and therefore were not an appropriate endpoint on which to base a short-term (1-30 days) risk assessment. For short-term exposures, the target Margin of Exposure (MOE) is 100. For intermediate-term (1-6 months) and long-term (>6 months) occupational dermal and inhalation exposures, the toxicology endpoint was selected from the same subchronic feeding study in dogs, but was based on microscopic lens lesions (cataracts) observed in the eyes of female dogs at the LOAEL of 1.4 mg/kg/day. This dose/endpoint/study was also selected for long-termdietary risk ——sment. For intermediate-term exposures, the target MOE is 300. This MOE includes the conventional factor of 100 and an additional factor of 3 since a LOAEL. rather than a NOAEL. was selected for risk assessments. For long-term exposures, the target MOE is 1000. This MOE includes the conventional factor of 100 and an additional factor of 10 for the use of the LOAEL and dose from a subchronic study for long-term risk assessment For dermal exposures, a 5% dermal absorption factor was used. For inhalation exposures, a 100% inhalation absorption factor (default value) was used.

At this time, only agricultural uses have been proposed for famoxadone. There are no uses that would result in residential or recreational exposures. Assessments addressing residential

and recreational risks are not warranted at this time.

Aggregate Exposure and Risk Characterization.

The currently proposed uses for famoxadone encompass only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of fwd and drinking water were considered. No appropriate endpoint attributable to a single oral dose was identified in the available toxicology studies on famoxndone. Therefore. an acute aggregate risk assessment for famoxadone is not warranted.

Dietary exposure and risk estimates were evaluated using Dietary Evaluation Model, Version 1.3 (DEEM-FCID) These exposure estimates are based on average field trial residues but retain the conservative assumption of 100% crop treated and should be considered moderately refined.

For considering exposure to residues of famoxadone in drinking water, the Agency has calculated Drinking Water Levels of Comparison (DWLOCs). These values are the maximum concentration of a chemical that occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled estimated environmental concentrations (EECs) DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed the Agency s level of concern

As shown in Table 4, the DWLOCs for the general U.S. population and all of the representative population subgroups modeled by DEEM-FCID are greater than both the surface water and ground water EECs.

Famoxadone has b a n classified as not likely to be carcinogenic to humans. As such, a cancer aggregate risk assessment is not warranted.

Table 4. Chronic DWLOC Calculations.

Population Subgroup	mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day[a]	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (µg/L)[b]
General U.S. Population	0.0014	0.000505	0.000895	0.23	0.47	31
All Infants, (< 1 year old)	0.0014	0.000175	0.001225	0.23	0.47	12

Table 4. Chronic DWLOC Calculations.

Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day[a]	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (µg/L)[b]
Children, 1-2 years old	0.0014	0.001057	0.000343	0.23	0.47	3.4

[a] Maximum water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - food exposure (mg/kg/day)]

[b] DWLOC(µg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)] • [water consumption (L) x 10^{-3} mg/µg]. Consumption = 1 Uday for populations<13 years old and 2 L/day for populations ≥ 13 years old. Default body weights= 70 kg for males ≥ 13 years old and general U.S. population, 60 kg for females ≥ 13 y e . old, and 10 kg for all others. Values are rounded to 2 significant figures.

Human health aggregate risk assessments have been conducted for acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short-, intermediate-, and long-term aggregate assessments were not performed, since there are no registered or proposed residential uses. A cancer risk assessment was not performed, because the Agency classified famoxadone as 'not likely to be carcinogenic to humans.' All aggregate exposure and risk estimates are below the Agency's level of concern for the scenarios listed above.

Ecological Effects/Environmental Fate Characteristics:

Hydrolysis

The half-life for famoxadone is 31 - 41 days in pH 5 solution, 2 - 2.7 days in pH 7 solution, and 1.55 - 1.8 hours in pH 9 solution (in the dark at 25°C. sterile aqueous buffered solutions). Hydrolysis of the parent compound is pH dependent and the rate of degradation increases with increasing pH. Under neutral to basic conditions hydrolysis would likely be a significant mute of degradation.

Aqueous Photolysis

The half-life for famoxadone in irradiated solution (pH 5) is 1.1 - 1.9 days (equivalent to 2.6 - 4.6 days of natural sunlight) and in the dark control is 41 days.

Soil Photolysis

The half-life for famoxadone in irradiated soil is 3.3 - 4.9 days (after correction for dark

controls, equivalent to 9.5 - 16.2 days of natural sunlight)

Mobility

Famoxadone is of slight mobility using the general classification scheme of McCall. The mobility of famoxadone, at nominal concentrations of 5.0, 10.0, and 25.0 ng/mL, was investigated in three soils (sand. sandy loam, and sandy clay loam). K_d values ranged from 71.3 - 109.8 for the sand soil (2.29% o.c.); 33.9 - 51.9 for the sandy loam soil (1.34% o.c.), and 16.5 - 29.4 for the sandy clay loam soil (0.58% o.c.); 1/n values ranged from 0.737 to 0.831. Following adsorption, K_{oc} values were 3890 for the sand soil, 3300 for the sandy loam soil, and 4030 for the sandy clay loam soil.

Field Dissipation

In four different Terrestrial Field Dissipation Studies (three U.S. studies, one Canadian study), famoxadone had dissipation half-lives ranging from 6.5 - 32.9 days. Famoxadone was not detected (detection limit - 0.007 ppm) below the 15-cm soil depth at any of the sites.

Bioaccumulation

The accumulation of famoxadone in two different (^{14}C labeled in different ring positions) juvenile bluegill sunfish indicated bioconcentration factors of 971X - 1286X for the edible tissue, 3327X - 3608X for the noncdible tissue, and 2434X - 3425X for the whole fish tissues Depuration was rapid with 50% of the total residues accumulated by exposure day 28 eliminated by day 2 of the depuration period. Because of the rapid depuration of famoxadone, bioaccumulation is not expected to be a significant concern.

Spray Drift

No famoxadone-specific studies were reviewed. Droplet size spectrum (201-1) and drift field evaluation (201-2) studies are required since famoxadone may be applied aerially. The registrant. E.I. DuPont de Nemours is a member of the Spray Drift Task Force (SDTF), a membership of U.S. pesticide registrants. The Agency ha. been working with the SDTF, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency has completed its evaluation of the data base submitted by the SDTF and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessment for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in the spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate. Due to risks associated with exposures via spray drift. product labels should include a strong enforceable statement to avoid off-target spray drift.

ECOLOGICAL CHARACTERISTICS

Acute Freshwater Fish
Bluegill 96-hr LC_{50} = 13 (9.3, 21) µg/L NOAEC–9.3 µg/L
Rainbow trout 96-hr LC_{50} = 12 (5.2, 72) µg/L NOAEC = 5.2 µg/L

Acute Estuarine/Marine Fish
Sheepshead minnow 96-hr LC_{50} = 49.4 (44.1, 56.1) µg/L NOAEC = 27.7 µg/L

Chronic (Early-Life) Freshwater Fish
Rainbow trout NOAEC 1.4 µg/L LOAEC = 4.1 µg/L

Chronic (Early-Life) Estuarine/Marine Fish
Sheepshead minnow NOAEC 5.6 µg/L LOAEC = 11.2 µg/L

Acute Freshwater Invertebrates
Daphnia magna 48-hr EC_{50} = 11.8 (10.1, 14.5) µg/L NOAEC = 3.5 µg/L
Chironomus riparius Pore water concentrations:
28-day EC_{50} = 15 (12.7, 18.2) mg/L NOAEC < 0.55 mg/L
Sediment concentrations.
28-day EC_{50} = 2.4 (2.0, 2.8) mg/kg NOAEC <0.07 mg/kg

Acute Estuarine/Marine Invertebrates
Eastern oyster (Shell deposition) 96-hr EC_{50} = 1.6 (1.0.2.7) µg/L NOAEC < 1.10 µg/L
Mysid shrimp 96-hr EC_{50} = 3.8 (2.2.4.9) µg/L NOAEC = 22 µg/L

Chronic (Life-Cycle) Freshwater Invertebrate
Daphnia magna NOAEC = 0.085 µg/L LOAEC = 0.29 µg/L

Chronic (Life-Cycle) Estuarine/Marine Invertebrate
Mysid shrimp NOAEC = 0.83 µg/L LOAEC = 1.72 µg/L

Aquatic Plants

Lemna gibba	14-day EC_{50} >81 µg/L	NOAEC = 81µg/L
Skeletonema costatum	120-hr EC_{50} >75 µg/L	NOAEC = 75 µg/L
Selenastrum capricornutum	120-hr EC_{50} = 23 (12.29) µg/L	NOAEC = 3.9µg/L
Navicula pelliculosa	120-hr EC_{50} =13 (9.6, 19.0) µg/L	NOAEC <9.87µg/L
Anabaena flos-aquae	120-hr EC_{50} >84.3 µg/L	NOAEC =42.6 µg/L

Avian Acute Single Oral Dose
Bobwhite quail LD_{50} > 2250 mg/kg-bw NOAEC = 2250 mg/kg-bw
Bobwhite quail LD_{50} > 511 mgkg-bw NOAEC = 66 mg/kg-bw
Avian Acute Dietary

Bobwhite quail	LC_{50} > 5620 mg/kg-diet	NOAEC = 5620 mg/kg-diet
Mallard duck	LC_{50} > 5620 mg/kg-diet	NOAEC = 5620 mg/kg-diet

Avian Chronic

Bobwhite quail	NOAEC = 46 mg /kg-diet	LOAEC = 252 mg/kg-diet
Mallard duck	NOAEC = 46 mg/kg-diet	LOAEC = 252 mg/kg-diet

Earthworm

Eisenia fetida andrei 14-day LC_{50} = 470 mg/kg-soil NOAEC < 62.5 mg/kg-soil

Terrestrial Plants

Species studied were: common onion, wm, winter wheat, sorghum. sugar beat, soybean, pea, tomato, rape, cucumber. For all endpoints in the emergence study and the vegetative vigor study, the EC_{25} > 0.187 lb/acre and the NOAEC = 0.187 lb/acre.

Environmental Risk Summary:

Agency analysis indicates that famoxadone presents the greatest risks m fish and aquatic invertebrates through spray drift and runoff in the dissolved phase as compared to the other taxonomic groups evaluated in this assessment.

For aquatic and terrestrial plants, LOCs are not exceeded for the proposed uses of famoxadone In this risk assessment, modeling results did not indicate potential concerns for aquatic or terrestrial plants.

ENVIRONMENTAL RISK MITIGATION

The Agency bas conducted a screening level analysis to assess potential ecological risks posed by famoxadone. The exceedance of a RQ does not necessarily indicate 'high risk" to a species as the RO is not an absolute estimate of the likelihood, magnitude, or severity of risk. Inputs into this screening level assessment were designated m overestimate likely exposures and effects of famoxadone Given the slight exceedences of the RQs and the risk mitigation that will be imposed for famoxadone, the Agency, believes that potential ecological risks are low.

FRESHWATER FISH/INVERTEBRATES: Based on a screening level analysis, the Endangered Species LOC and Acute Restricted Use LOC for freshwater fish and invertebrates are slightly exceeded Acute Fish RQs and Acute Invertebrate RQs ranged from 0 04 - 0 24 Chronic Fish RQs ranged from 0 08 - U 24. while Chronic Invertebrates RQs ranged from 2 47 - 8 35

ESTUARINE/MARINE FISH/INVERTEBRATES Based on a screening level analysis, the Endangered Species LOC for estuarine/marine fish was exceeded for Florida tomatoes, Ronda peppers, and Maine potatoes. The Endangered species LOC and Acute Restricted Use LOC for estuarine/marine invertebrates was exceeded in all scenarios; however, there are currently no

federally listed endangered estuarine invertebrates. RQs ranged from 0.01 - 1.81. Chronic RQs ranged from 0.02 - 0.86.

AVIAN: Based on a screening level analysis, Chronic RQs for herbivorous birds, insectivorous birds and herbivorous mammals exceeded the LOCs from exposure to famoxadone residues in wildlife food items indicating potential for chronic risks. Chronic RQs ranged from 0.3 - 4.7 at the estimated maximum residue levels, and ranged from 0.1 to 1.70 at the predicted mum residue levels. Shon grass eating birds had the highest RQs of 1.7 at the estimated mean residues level and 4.7 at the estimated maximum residue level, these are the only exceedances of the Avian Chronic LOC. For chronic exposure the predicted mean residue is the appropriate level for risk assessment The only Endangered species that feeds exclusively on shon grasses is native to Hawaii and the commodities that famoxadone is registered for use on are generally not grown in that area.

MAMMALS: RQs were not calculated to evaluate potential acute risks to mammals because of the low toxicity to mammals (LD_{50} >5000 mg/kg). Acute risk is low at the proposed application rates. Chronic effects are not expected for mammals using anticipated mean residue levels, which is the appropriate level for use in a chronic analysis.

BENEFICIAL INSECTS: Famoxadone may have negative effects on beneficial insects (e.g., hoverfly and green lacewing). The Agency has concerns with the potential for negative impacts on endangered insects.

ENVIRONMENTAL RISK MITIGATION: The Agency believes that famoxadone presents the greatest risk to fish and aquatic invertebrates through spray drift and runoff in the dissolved phase. In order to mitigate this risk the Agency will be requiring use limitations. label warning statements and/or restrictions on the end-use product label:

** Maximum number of use per season - The Agency is restricting the maximum number of applications per season to six and limiting the maximum seasonal use rate.

** The Agency will quire spray drift language on all end use products.

** The Agency will also require a beneficial insect warning statement on all end use products.

In addition, the Agency will he requiring a 25-foot vegetative buffer ship around treated fields. While the Agency cannot quantify the reduction in risk to non-target/endangered species resulting from this restriction on the use, it should significantly reduce the potential for spray drift and/or runoff. which are the maior concerns. The Agency also notes that this product has a relatively low seasonal maximum use rate compared to current alternatives.

Famoxadone is an alternative to other fungicides some of which mav have higher seasonal use rates, a different maximum number of applications, or shorter re-treatment intervals. Thus while the Agency cannot strictly compare the RQs from those various fungicides the Agency does

note that the issues with this fungicide are similar and that the RQ for the same use site are comparable. The Agency believes that by restricting the maximum seasonal use rate and by employing the use of vegetative buffer strips, actual ecological risks are significantly lower than model estimates.

The Agency notes that W o n t is a member in the FIFRA Endangered Species Task Force.

SUMMARY OF DATA GAPS

Environmental Fate and Effects Data Requirements:

835.1220	163-1 Leaching/Adsorption/Desorption (one additional soil type which should be finer-grained than those previously tested • which were sand, sandy/loam, and sandy/clay/loam)
850.1075	72-1 Acute freshwater fish (Rainbow trout) guideline study using the end-use product
850.1735	Whole sediment acute toxicity invertebrates, freshwater (chironomids, the 28-day test
850.3020	Honey-bee acute contact with the end-use product
850.3030	Honey Bee Toxicity of residues on foliage with the end-use product

Contact person at USEPA

Mailing address:

Cynthia Giles-Parker
Product Manager (22)
Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7505C)
Fungicide Branch
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Office location and telephone number:

Room 249. Crystal Mall #2
1921 Jefferson Davis Highway
Arlington, VA 22202
703-308-7740

DISCLAIMER: The information in this Pesticide Fact Sheet is for information only and is not to be used to satisfy data requirements for pesticide registration. The information is believed to be accurate as of the date on the document.