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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

**MEMORANDUM**

Date: 30-MAY-2006

Subject: Registration# 05MN12. **Revised Section 18 Quarantine Exemption for the Application of Flusilazole to Soybeans.** DP# 328024. Decision# 356743. PC Code 128835.

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To Dan Rosenblatt/Carmen Rodia; RM 05  
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**NOTE:** This document supercedes "Registration# 05MN12. Revised Section 18 Quarantine Exemption for the Application of Flusilazole to Soybeans," DP# 325945, dated 1/30/06.

The MN Department of Agriculture and Food proposed a Section 18 Quarantine Exemption for the application of flusilazole (1-[[bis(4-fluorophenyl)methylsilyl]methyl]-1H-1,2,4-triazole) to soybeans for control of the Australasian soybean rust. This is the first Section 18 request for this use. A summary of the estimated human-health risk resulting from the requested and registered uses of flusilazole is provided in this document.

**Conclusions/Recommendations:** Based on the proposed/registered uses and the toxicological database, the acute dietary risk estimates are <2% of the acute population-adjusted dose (aPAD), the aggregate chronic dietary exposures are <22% chronic population-adjusted dose (cPAD) and the aggregate cancer risk for the general U.S. population is  $4.5 \times 10^{-7}$ . HED notes that the dietary analysis incorporated drinking water estimates in the exposure assessments.

**Provided that the labels are amended as specified below, HED concludes that the toxicological, residue chemistry, dietary exposure, and occupational/residential exposure assessments are adequate to support time-limited tolerances for residues of flusilazole per**

**se of 0.04 ppm in/on soybean seed, 2.6 ppm in/on aspirated grain fractions, and 0.10 ppm in/on soybean oil.**

**Requested label amendments for Charisma™:**

- specify that use of soybean hay and forage for livestock feed is prohibited
- specify plantback intervals (PBIs) of 30 days for root and leafy vegetables and 40 days for small grains and all other crops
- specify the use of only closed-loading systems of liquids in support of aerial applications (1,200 acres or more per day)
- specify restricted entry interval (REI) of 3 days

**Requested label amendments for Punch™:**

- specify that use of soybean hay and forage for livestock feed is prohibited
- specify PBIs of 30 days for root and leafy vegetables and 40 days for small grains and all other crops
- specify the use of only closed-loading systems of liquids in support of aerial applications (1,200 acres or more per day)
- specify REI of 7 days

## **1.0 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. In particular, products containing flusilazole or flusilazole plus other fungicidal active ingredients, including famoxadone, have demonstrated efficacy against Australasian soybean rust (*Phakospora pachyrhizi*) in South Africa, Brazil, and Argentina. Flusilazole is registered for use on soybeans in South Africa and Argentina, and registration is pending in Brazil. In the US, registration activity on flusilazole 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. 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 the EPA. For the purpose of this section 18 Quarantine Exemption request for flusilazole, the EPA has relied on studies reviewed by the European Union as well as internal study reviews. Therefore, the stated toxicological endpoints are applicable for this section 18 use only since upon detail review of the new and existing data the final conclusion may change.

## 2.0 Hazard Characterization and Assessment

### 2.1 Hazard characterization

Flusilazole was moderately acutely toxic by the oral, dermal and inhalation routes (Toxicity Category III). It was a mild dermal irritant (Toxicity Category IV) and not a dermal sensitizer. It was not an eye irritant. The primary skin irritation and eye irritation studies were conducted using a 25% emulsifiable-concentrate formulation of flusilazole.

Flusilazole is a fungicide that is a member of the triazole family of compounds. It is effective in controlling Australasian soybean rust in soybeans. Liver and bladder were identified as target organs. The critical effects were increased liver weight (relative and absolute) vacuolation, fatty changes, increased alanine aminotransferase (ALT), bladder hyperplasia, bladder transitional cell tumors and liver tumors. These effects were observed in both sexes in rats, mice and dogs; however, the dog was the most sensitive to flusilazole toxicity. Flusilazole exhibited a negative response to the variety of genotoxicity screening assays. Thus, it appears that flusilazole is not a genotoxic chemical. This chemical has not been evaluated by the Cancer Peer Review Committee. However, for the purpose of this **Section 18 Emergency Exemption**, a conservative Q1\* was calculated based on female mouse liver adenoma and/or carcinoma combined tumor rates. For risk characterization, a low-dose extrapolation model was applied to the animal data for the quantification of human risk (Q1\*). The unit risk Q1\* (mg/kg/day), for flusilazole is  $2.84 \times 10^{-3}$  in human equivalents based on female mouse liver adenoma and/or carcinoma combined tumor rates.

Flusilazole produced increased resorptions, increased partial supernumerary ribs in the cervical and lumbar regions, bipartite centra, partially ossified sternbrae and vertebral arches, small renal papillae, large renal pelvis, renal pelvic dilation, dilated ureter, stunted fetuses, fetal death at birth and decreased neonatal survival at doses lower than doses that produced minimal or no maternal toxicity. Flusilazole caused an increase in the length of gestation and angiectasis labyrinth, trophoblast necrosis and/or mineralization in the placenta in rats. In rabbits, flusilazole caused a decrease in the number of pregnant does and increased the number of resorptions. All of these reproductive effects were observed in the presence of marginal maternal toxicity.

Flusilazole is extensively metabolized in the rat. The absorption and metabolism of flusilazole was investigated with the molecule labeled on either the phenyl (silane molecule) or the triazole group (see figure 1 for structures). Total excretion of the phenyl-labeled flusilazole was 78-96% by 168 hours. The primary routes of elimination were the feces and urine. Males excreted up to 94% and females up to 67% of the administered dose in the feces. Females excreted up to 27% and males only 10% of the dose in the urine. Total excretion of the triazole moiety was 93-99%. Tissue retention was 1.3-2.6% of the silane molecule and 3.5% of the triazole labeled group. The primary route of elimination was urine (72-81%). The parent molecule and 8 metabolites were identified & isolated. The primary step in the metabolism of flusilazole is the cleavage and rapid excretion of the 1*H*-1,2,4 triazole moiety. The silane moiety is then excreted or further metabolized to non-polar fatty acid conjugates (higher in males),  $\beta$ -D-glucopyranuronic acid conjugates (higher in females) and more polar molecules.

<b>Guideline No.</b>	<b>Study Type</b>	<b>Results</b>	<b>Toxicity Category</b>
870.1100 (81-1)	Acute Oral (rat)	LD <sub>50</sub> 1110 mg/kg (M) 674 mg/kg (F)	III
870.1200 (81-2)	Acute Dermal (rat)	LD <sub>50</sub> > 2000 mg/kg	III
870.1300 (81-3)	Acute Inhalation (rat)	LC <sub>50</sub> > 5 mg/L	III
870.2400 (81-4)	Primary Eye Irritation* (rabbit)	Not an eye irritant	IV
870.2500 (81-5)	Primary Skin Irritation* (rabbit)	Not a dermal irritant	IV
87.2600 (81-6)	Dermal Sensitization* (guinea pig)	Not a dermal sensitizer	N/A

\*Studies conducted with a 25 % emulsifiable-concentrate formulation.

<b>Guideline No./ Study type</b>	<b>MRID No.(year)/ classification/Doses</b>	<b>Results</b>
870.3100 90-Day Oral [mouse]	40042111 (1983)0, 4, 14, 40, 90, and 193 mg/kg/day  <b>Core-Supplementary</b>	<b>NOAEL = 4 mg/kg/day, LOAEL = 14 mg/kg/day</b> based on increased relative liver weight and hepatocellular vacuolation in females.
870.3100 90-Day Oral [mouse]	41519401 (1990) M/F: 0/0, 161/239, 436/601 and 1004/1414 mg/kg/day  <b>Core-Supplementary</b>	The <b>NOAEL</b> was not established. <b>LOAEL = 161 mg/kg/day</b> based on cytoplasmic vacuolation, hypertrophy, focal necrosis and inflammation in the liver and urothelial hyperplasia, hypertrophy and vacuolation, inflammation of the lamina propria and lymphoid infiltrates in the urinary bladder lesions.
870.3100 90-Day Oral [rat]	00161400 (1983)M/F: 0/0, 2/2, 9/11, 27/31, and 55/70 mg/kg/day  <b>Core-Minimum</b>	<b>NOAEL =M/F: 9/11 mg/kg/day, LOAEL = M/F: 27/31 mg/kg/day</b> , based on urinary bladder hyperplasia, elevated cholesterol
870.3150 90-Day [dog]	00161168 (1983) 0, 0.9, 4.3, and 13.2 mg/kg  <b>Core-Minimum</b>	<b>NOAEL = 0.9 mg/kg/day, LOAEL = 4.3 mg/kg/day</b> , based on mucosal hyperplasia of the urinary bladder and increase in absolute and relative liver weight, increased alanine aminotransferase, uric acid and cholesterol(females); decrease in total protein, calcium, albumin, and cholesterol (males).
870.3200 21-Day Dermal [rabbit]	40042119 (1986), 0, 1, 5, 25, and 200 mg/kg/day  <b>Core-Minimum</b>	Systemic <b>NOAEL ≥ 200 mg/kg/day, LOAEL was not observed.</b> <b>Dermal NOAEL = 5 mg/kg/day, Dermal LOAEL = 25 mg/kg/day</b> based on slight to mild diffuse hyperplasia and thickening of the epidermis.

<b>Table 2.2. Toxicity Profile of Flusilazole (128835)</b>		
<b>Guideline No./ Study type</b>	<b>MRID No.(year)/ classification/Doses</b>	<b>Results</b>
870.4100 Chronic Toxicity [rat]	40042112 (1986) 0, 0.46, 2.3, and 11.5 mg/kg/day  <b>Core-Minimum</b>	<b>NOAEL = 0.46 mg/kg/day, LOAEL = 2.3 mg/kg/day</b> , based on increased relative liver weight and hepatocellular hypertrophy in females
870.4100b Chronic Oral [dog]	40042113 (1985), 0, 0.2, 0.7, and 2.5 mg/kg  <b>Core-Minimum</b>	<b>NOAEL = 0.2 mg/kg/day, LOAEL = 0.7 mg/kg/day</b> , based on increased liver weights & hypertrophy of centrilobular hepatocytes in both sexes, hepatocytic vacuolation, increased alkaline phosphatase, decreased cholesterol and total serum protein, and increased white blood cells in males.
870.4200 Carcinogenicity [mouse]	42613201 (1992) M/F: 0/0, 14.3/19.4, 73.1/200 and 144/384 mg/kg/day  <b>Core-Minimum</b>	systemic <b>NOAEL = M/F: 14.3/19.4 mg/kg/day, LOAEL = M: 73.1 mg/kg/day</b> , based on increased absolute liver weights and liver to body weight ratios, decreased absolute kidney weights and kidney to body weight ratios and increased incidence of stained fur. An increase was observed in hepatocellular carcinomas at 384 mg/kg/day and hepatocellular adenomas at 200 and 384 mg/kg/day in females
870.3700 Developmental Toxicity [rat-gavage]	00161169 (1983) 0, 10, 50, and 250 mg/kg/day  <b>Supplementary</b>	<b>Maternal NOAEL = 10 mg/kg/day, Maternal LOAEL = 50 mg/kg/day</b> , based on decreased food consumption, body weight gain and food efficiency. <b>Developmental NOAEL was not established, Developmental LOAEL = 10 mg/kg/day</b> based on cleft palate, no renal papilla, distended ureters, large renal pelvis, decreased fetal weight, increased resorption, misaligned sternbra, extra ossification center of ribs (lumbar #1, cervical #7), supernumerary rib (lumbar #1), and rudimentary ribs (lumbar #1 and cervical #7).
870.3700 Developmental Toxicity [rat-diet]	00148513 (1984) 0, 5.0, 9.0, 30 and 73 mg/kg/day  <b>Guideline</b>	<b>Maternal NOAEL = 9.0 mg/kg/day, Maternal LOAEL = 30 mg/kg/day</b> , based on decreased food consumption, and weight gain; <b>Developmental NOAEL = 9.0 mg/kg/day, Developmental LOAEL = 30 mg/kg/day</b> based on stunting, resorption, increased extra ossification center of lumbar and cervical #7 ribs, and rudimentary lumbar rib.
870.3700 Developmental Toxicity [rat-gavage]	00143542 (1984) 0, 0.4, 2, 10, 50, and 250 mg/kg/day  <b>Supplementary</b>	<b>Maternal NOAEL = 50 mg/kg/day, Maternal LOAEL = 250 mg/kg/day</b> based on decreased food consumption, weight gain and increased relative liver weight; <b>Developmental NOAEL was not established; Developmental LOAEL = 0.4 mg/kg/day</b> based on the absence of renal papilla.

<b>Table 2.2. Toxicity Profile of Flusilazole (128835)</b>		
<b>Guideline No./ Study type</b>	<b>MRID No.(year)/ classification/Doses</b>	<b>Results</b>
870.3700 Developmental Toxicity [rat-gavage]	00154928 (1985) 0, 0.2, 0.4, 2, 10, and 100 mg/kg/day  <b>Core-Supplementary</b>	<b>Maternal NOAEL = 10 mg/kg/day, Maternal LOAEL = 100 mg/kg/day</b> , based on increased mortality, prolonged gestation, decreased food consumption and weight gain, increased relative and absolute liver weight; <b>Developmental NOAEL = 2 mg/kg/day, Developmental LOAEL = 10 mg/kg/day</b> , based on distended ureter, small renal papilla, dilated renal pelvis, decrease survivability.
Dermal Prenatal Developmental [rat] Non-guideline study*	(1998) 0, 2, 10, 50 or 250 mg/kg bw/day  <b>Acceptable</b>	<b>Maternal NOAEL was not established, Maternal LOAEL = 2 mg/kg/day</b> , based on angiectasis labyrinth, trophoblast necrosis and/or mineralization in the placenta; <b>Developmental NOAEL = 2 mg/kg/day, Developmental LOAEL = 10 mg/kg/day</b> based on 14th rudimentary ribs, 14th full ribs, 7th cervical ribs and unossified sternbrae.
870.3700(b) Developmental Toxicity [New Zealand White rabbit-gavage]	00148512 (1984) 0, 2, 5 and 12 mg/kg/day	<b>Maternal NOAEL = 12 mg/kg/day, Maternal LOAEL was not observed; Developmental NOAEL = 12 mg/kg/day, Developmental LOAEL was not observed.</b>
870.3700(b) Developmental Toxicity [New Zealand White rabbit-gavage]	00154929 (1985) 0, 2, 12 and 35 mg/kg/day  <b>Core-Supplementary</b>	<b>Maternal NOAEL = 12 mg/kg/day, Maternal LOAEL = 35 mg/kg/day</b> , based on decreased food consumption and final body weight; <b>Developmental NOAEL = 12 mg/kg/day, Developmental LOAEL = 35 mg/kg/day</b> , based on increased resorptions, abortion and decreased fetal weight.
870.3700(b) Developmental Toxicity [New Zealand White rabbit-diet]	00154930 (1985) 0, 0.9, 3.0, 8.0, 21.21 and 37.78 mg/kg/day  <b>Core-Minimum</b>	<b>Maternal NOAEL = 21.21 mg/kg/day, Maternal LOAEL = 37.78 mg/kg/day</b> , based on decreased food consumption and body weight gain; <b>Developmental NOAEL = 8 mg/kg/day, Developmental LOAEL = 21.21 mg/kg/day</b> , based on increased total resorptions.
870.3800 2-generation reproduction- 1 generation[rat]	00161400 (1983) M/F: 0, 2/2, 9/11, and 27/31 mg/kg/day  <b>Core-Supplementary</b>	<b>Parental NOAEL = M/F: 9/11 mg/kg/day, Parental LOAEL = M/F: 27/31 mg/kg/day</b> , based on urinary bladder hyperplasia, elevated cholesterol; <b>Reproduction NOAEL and LOAEL were not determined due to abnormally low fertility in the control group; Offspring NOAEL = 9/11 mg/kg/day. Offspring LOAEL = 27/31 mg/kg/day</b> based on percentage of pups born alive and mean pup weights at days 4 and 21.

**Table 2.2. Toxicity Profile of Flusilazole (128835)**

Guideline No./ Study type	MRID No.(year)/ classification/Doses	Results
870.3800 2-generation reproduction [rat]	40042112 (1986) 0, 0.85, 3.5, and 19 mg/kg/day  <b>Core-Minimum</b>	<b>Parental NOAEL = 3.5 mg/kg/day, Parental LOAEL = 19 mg/kg/day</b> based on decreased body weight and weight gain in F <sub>1</sub> males; <b>Reproductive NOAEL was not established; LOAEL was 0.85 mg/kg/day; Offspring NOAEL was not established. Offspring LOAEL = 0.85 mg/kg/day</b> based on a slight increase in hydronephrosis in all treatment groups at weaning of the F <sub>2b</sub> pups.
870.3800 2-generation reproduction [rat]	41684601 (1990) 0, 0.35, 3.5, and 17.5 mg/kg/day  <b>Minimum</b>	<b>Parental NOAEL = 0.35 mg/kg/day, Parental LOAEL = 3.5 mg/kg/day</b> , based on hepatocellular hypertrophy in P <sub>1</sub> females, cytoplasmic glycogen pooling in P <sub>1</sub> and F <sub>1</sub> males, lower final body weights in F <sub>1</sub> females, and the presence of periportal hepatocytes with irregularly shaped eosinophilic inclusion in F <sub>1</sub> males <b>Reproductive NOAEL = 3.5 mg/kg/day; Reproductive LOAEL = 17.5 mg/kg/day</b> based on prolonged gestation length and decreased number of pups born alive; <b>Offspring NOAEL = 3.5 mg/kg/day; Offspring LOAEL = 17.5 mg/kg/day</b> based on mean lower pup weights on days 14 and 21 of lactation.
870.3800 2-generation reproduction [rat]*	(1990) M/F: 1/0, 1/1, 2.85/3.51, 18/22 mg/kg/day  <b>Acceptable</b>	<b>Parental NOAEL ≥ 18 mg/kg/day, Parental LOAEL was not observed; Reproductive NOAEL = 2.85 mg/kg/day; Reproductive LOAEL = 18 mg/kg/day</b> based on a decrease in the number of pups born alive; <b>Offspring NOAEL = 2.85 mg/kg/day; Offspring LOAEL = 18 mg/kg/day</b> based on failure to thrive and decreased postnatal survival on day four.
870.4300 Combined Chronic Toxicity/ Carcinogenicity [rat]	42613202 (1992)M/F: 0/0, 5.0/6.8, 14.8/20.5, and 30.8/43.6 mg/kg/day  <b>Core Minimum</b>	<b>NOAEL = 5.0 mg/kg/day, LOAEL = 14.8 mg/kg/day</b> , based on decreased mean body weight in females and increased incidence of transitional cell carcinoma of the urinary bladder, and mucosal hyperplasia in both sexes.
870.5265 Gene mutation - Ames	00161171  <b>Acceptable/guideline</b>	Not mutagenic
870.5375 <u>In vitro</u> chromosome aberration assay [CHO cells]	00161172 (1983) <b>Acceptable/guideline</b>	Not mutagenic
870.5550 Unscheduled DNA synthesis assay rat primary hepatocyte	00161174 <b>Acceptable/guideline</b>	Not mutagenic

<b>Guideline No./ Study type</b>	<b>MRID No.(year)/ classification/Doses</b>	<b>Results</b>
870.5385 <i>In Vivo</i> Mammalian Cytogenetics - Bone Marrow Chromosome Aberration Test	00161173 (1983) 0, 40, 50, 150, and 500 mg/kg  <b>Acceptable/guideline</b>	Not mutagenic
870.7585 Metabolism Study in Rats	40042115 (1986)  <b>Acceptable/non-guideline</b>	DPX-H6573 is rapidly absorbed and metabolized. There is little to no difference in absorption, distribution and elimination with respect to dose, dosing schedule or sex. Total excretion of the phenyl-labeled flusilazole was 78-96% by 168 hours. The primary routes of elimination were the feces and urine. Males excreted up to 94% and females up to 67% of the administered dose in the feces. Females excreted up to 27% and males only 10% of the dose in the urine. . Total excretion of the triazole moiety was 93-99%. Tissue retention was 1.3-2.6 % of the silane molecule and 3.5% of the triazole labeled group. The primary route of elimination was urine (72-81%). Less than 0.2% of the dose remained in the tissues, with the highest residue levels in the liver, GI tract, muscle and skin.
870.7600 Dermal penetration	00152932 (1983),  <b>Unacceptable/guideline</b>	The compound absorbed by skin, enters blood, is excreted by the kidneys and in feces (more by kidneys) and gauze ties 70 to 80 % of dose regardless of time.

\*Data extracted from study summaries prepared by the European Union.

M - Male; F - Female

## **2.2 FQPA HAZARD CONSIDERATIONS**

### **2.2.1. Adequacy of the Toxicity Data Base**

The toxicology database for flusilazole is complete. The following acceptable studies are available:

- Developmental toxicity in rats and rabbits (7)
- Dermal Prenatal Developmental study in rats (1)
- Two-generation reproduction study in rats (4)

### **2.2.2. Evidence of Neurotoxicity**

There is not a concern for neurotoxicity resulting from exposure to flusilazole; however, acute and subchronic neurotoxicity studies were not performed. Based on the available data from multiple studies, the chemical is not considered neurotoxic.



### 2.2.3. Developmental Toxicity Studies

#### Teratology Study in rats (MRID 00161169)

In a developmental toxicity study [MRID 00161169], INH-6573 [96.6% a.i. in corn oil] was administered to 25 mated Crl:CD (BR rats via gavage at dose levels of 0, 10, 50, and 250 mg/kg/day from days 7 - 16 of gestation. Dams were sacrificed on GD 21.

**The maternal NOAEL = 10 mg/kg/day, maternal LOAEL = 50 mg/kg/day**, based on decreased food consumption, death and clinical signs. **Developmental NOAEL was not established, Developmental LOAEL = 10 mg/kg/day**, based on cleft palate, no renal papilla distended ureters, large renal pelvis, decreased fetal weight, increased resorption, misaligned sternbra, extra ossification center of ribs (lumbar #1, cervical #7), supernumerary rib (lumbar #1), and rudimentary ribs (lumbar #1 and cervical #7).

#### Teratology Study in rats (MRID 00148513)

In a developmental toxicity study [MRID 00148513], INH-6573-66 [94.8% a.i.] was administered to 24/dose pregnant Crl:CD(BR) rats in the diet at dose levels of 0, 50, 100, 300 and 900 ppm (0, 5.0, 9.0, 30 and 73 mg/kg/day) from days 7 - 16 of gestation. Dams were sacrificed on GD 21.

**The maternal NOAEL = 9.0 mg/kg/day , LOAEL = 30 mg/kg/day**, based on decreased food consumption, and weight gain; **Developmental NOAEL = 9.0 mg/kg/day; Developmental LOAEL = 30 mg/kg/day** based on stunting, resorption, increased extra ossification center of lumbar and cervical #7 ribs, and rudimentary lumbar rib.

#### Teratology Study in rats (MRID 00143542)

In a developmental toxicity study [MRID 00143542], INH-6573-39 [95.6% a.i. in corn oil] was administered to 24/dose pregnant Crl:CD<sup>®</sup>(SD) rats (except the high dose group which had 10 animals) via gavage at dose levels of 0, 0.4, 2, 10, 50, and 250 mg/kg/day from days 7 - 16 of gestation. Dams were sacrificed on GD 21.

**Maternal NOAEL = 50 mg/kg/day, Maternal LOAEL = 250 mg/kg/day** based on decreased food consumption, weight gain and increased relative liver weight; **Developmental NOAEL was not established; Developmental LOAEL was 0.4 mg/kg/day** based on the absence of renal papilla.

#### Teratology Study in rats (MRID 00154928)

A developmental toxicity study in rats was conducted in two phases [MRID 00154928]. INH-6573-39 [95.6% a.i.] was administered to 24/dose pregnant Crl:CD<sup>®</sup>(SD) rats via gavage at dose levels of 0, 0.2, 0.4, 2, 10 and 100 mg/kg/day from days 7 - 16 of gestation in both phases. In phase I, dams were sacrificed on GD 21/22. In phase 2, dams were allowed to deliver and raise the young to weaning.

**The maternal NOAEL = 10 mg/kg/day, LOAEL = 100 mg/kg/day**, based on increased mortality, prolonged gestation, decreased food consumption and weight gain, increased relative and absolute liver weight; **Developmental NOAEL = 2 mg/kg/day, Developmental LOAEL = 10 mg/kg/day**, based on distended ureter, small renal papilla, dilated renal pelvis, distended ureter and decrease survivability.

#### **Dermal Prenatal Developmental Study in rats (European Union study review summary)**

In a developmental toxicity study, flusilazole (95% *a.i*) was administered to 25 female CrI:CD (SD)BR rats by topical application at dose levels of 0, 2, 10, 50 or 250 mg/kg bw/day from days 6 through 19 of gestation. The test substance in 0.5% aqueous methylcellulose, was applied to the clipped intact dorsal skin (10% area) of each rat, for a period of six hours per day. There were no treatment-related mortalities. A single female died in the 50 mg/kg bw/day, the death was not considered treatment-related. Clear maternal toxicity was demonstrated at the high-dose level by greatly reduced body weight gains during gestation days 18-19 and 19-20.

Food consumption was slightly reduced from days 12-20 at  $\geq 50$  mg/kg bw/day. An increased incidence of minimal to mild hepatocellular hypertrophy from  $\geq 10$  mg/kg bw/day was considered treatment-related. No evidence of a treatment-related effect was seen at 2 mg/kg bw/day. Compound-related microscopic changes in the placenta (angiectasis labyrinth, trophoblast necrosis and/or mineralization) were observed at all treatment levels. The maternal LOEL was not identified, due to placental alterations at all doses. There was an increased incidence of postimplantation losses from  $\geq 10$  mg/kg bw/day. Mean fetal body weights were increased from 50 mg/kg bw/day. There was no treatment-related increase in malformations. A number of treatment-related increases in skeletal variants occurred in treatment groups from  $\geq 10$  mg/kg bw/day and included 14th rudimentary ribs, 14th full ribs, 7th cervical ribs and unossified sternbrae 5 and/or 6. Enlarged and swollen livers were also noted at these dose levels.

The **Maternal NOAEL was not established, Maternal LOAEL = 2 mg/kg/day**, based on angiectasis labyrinth, trophoblast necrosis and/or mineralization in the placenta; **Developmental NOAEL = 2 mg/kg/day, Developmental LOAEL = 10 mg/kg/day** based on 14th rudimentary ribs, 14th full ribs, 7th cervical ribs and unossified sternbrae.

#### **Developmental Study in rabbits (MRID 00148512)**

In a developmental toxicity study [MRID 00148512], INH-6573-66 [94.8% *a.i.*] was administered to 18/dose level mated Hra(NZW)SPF rabbits via gavage at dose levels of 0, 2, 5, and 12 mg/kg/day from days 7-19 of gestation. Dams were sacrificed on GD 29.

**Maternal NOAEL = 12 mg/kg/day, Maternal LOAEL was not established; Developmental NOAEL = 12 mg/kg/day, Developmental LOAEL was not established.**

### **Developmental Study in rabbits (MRID 00154929)**

In a developmental toxicity study [MRID 00154929], INH-6573-66 [94.8% a.i.] was administered to 20/dose level mated Hra(NZW)SPF rabbits via gavage at dose levels of 0, 2, 12, and 35 mg/kg/day from days 7-19 of gestation. Dams were sacrificed on GD 29.

**The Maternal NOAEL = 12 mg/kg/day, Maternal LOAEL = 35 mg/kg/day**, based on decreased food consumption and final body weight; **Developmental NOAEL = 12 mg/kg/day, Developmental LOAEL = 35 mg/kg/day**, based on increased resorptions, abortion and decreased fetal weight.

### **Developmental Study in rabbits (MRID 00154930)**

A developmental toxicity study in rabbits was conducted in two phases [MRID 00154930]. INH-6573-66 [94.8% a.i.] was administered to 20/dose level mated Hra(NZW)SPF rabbits in the diet at dose levels of 0, 300, 600 and 1200 ppm (0, ~8.0, 21.21, 37.78 mg/kg/day) from days 7 - 19 of gestation. Dams were sacrificed on GD 29. Since no NOEL could be established, phase 2 was initiated in which 18/pregnant Hra(NZW)SPF rabbits/dose were offered diets containing 0, 30, and 100 ppm (0, 0.9, 3.0 mg/kg/day) and 25 Hra(NZW)SPF rabbits were offered 300 ppm.

**The Maternal NOAEL = 600 ppm (21.21 mg/kg/day; Maternal LOAEL = 1200 ppm (37.78 mg/kg/day)**, based on decreased food consumption and body weight gain; **Developmental NOAEL = 300 ppm (8 mg/kg/day), Developmental LOAEL = 600 ppm (21.21 mg/kg/day)**, based on increased total resorptions.

### **1-Generation Reproduction Study in rats (MRID 00161400)**

In a single-generation reproduction study with a recovery phase (a substudy of a 90 day oral study, MRID 00161400), INH-6573-21 [94.8% a.i.] was administered in the diet for approximately 5 months to CD<sup>®</sup> rats (6/sex/dose) at dose levels of 0, 25, 125, and 375 ppm (0/0, 2/2, 9/11, 27/31 mg/kg/day). Pairs of animals were mated for 15 days after which the pregnant female was housed separately. Pups were raised to weaning (day 21 post-partum). Litters were weighed and no other examination was carried out either in premature decedents or scheduled sacrifice. The parental animals were retained on a control diet for four weeks (recovery phase) then sacrificed.

**Parental NOAEL = M/F: 9/11 mg/kg/day, Parental LOAEL = M/F: 27/31 mg/kg/day**, based on urinary bladder hyperplasia, elevated cholesterol; **Reproduction NOAEL and LOAEL were not determined due to abnormally low fertility in the control group; Offspring NOAEL = 9/11 mg/kg/day, Offspring LOAEL = 27/31 mg/kg/day** based on percentage of pups born alive and mean pup weights at days 4 and 21.

### **2-Generation Reproduction Study in rats (MRID 40042112)**

In a multigeneration reproduction study conducted as a sub-study of a two year feeding study (MRID 40042112), INH-6573-39 [95.6% a.i.] was administered in the diet to

Crl:CD(BR rats (90/sex/dose) at dose levels of 0, 10, 50 and 250 ppm (0, 0.85, 3.5, and 19 mg/kg/day). After 90 days on this diet 20/sex/dose were mated (F<sub>0</sub>) twice to produce F1<sub>a</sub> and F1<sub>b</sub> offspring and then returned to the feeding study. F1 mating pairs were selected from the F1<sub>b</sub> offspring and mated to produce two F2 litters (F2<sub>a</sub> and F2<sub>b</sub>). Premature decedents and 10/sex of the F2<sub>b</sub> weanlings were sacrificed and examined.

**The Parental NOAEL = 50 ppm [3.5 mg/kg/day], Parental LOAEL = 250 ppm [19 mg/kg/day]** based on decreased body weight and weight gain in F1 males;  
**Reproductive NOAEL was not established, Reproductive LOAEL was <10 ppm (0.85 mg/kg/day); Offspring NOAEL was not established, Offspring LOAEL = 0.85 mg/kg/day** based on a slight increase in hydronephrosis in all treatment groups at weaning of the F<sub>2b</sub> pups.

## **2-Generation Reproduction Study in rats (MRID 41684601)**

In a multigeneration reproduction study (MRID 41684601), DPX 6573-193 [94% a.i.] was administered in the diet to Crl:CD®BR rats (30/sex/dose) at dose levels of 0, 5, 50 and 250 ppm (0, 0.35, 3.5, and 17.5 mg/kg/day) beginning 73 days prior to mating and throughout gestation, lactation, weaning and breeding of the second generation litters. A single litter was bred from the P1 parents and two litters from the F1 parents (30/sex/dose selected from the F1 weanlings). 20 F1 weanlings/sex/dose not selected as parents were sacrificed and gross examination carried out, the remaining weanlings were sacrificed without examination. Gross examination was carried out on all P1 and F1 parents at sacrifice and histopathological examinations made of all premature decedents.

**Parental NOAEL = 5 ppm [0.35 mg/kg/day], Parental LOAEL = 50 ppm [3.5 mg/kg/day]**, based on hepatocellular hypertrophy in P<sub>1</sub> females, cytoplasmic glycogen pooling in P<sub>1</sub> and F<sub>1</sub> males, lower final body weights in F<sub>1</sub> females, and the presence of periportal hepatocytes with irregularly shaped eosinophilic inclusion in F<sub>1</sub> males;  
**Reproductive NOAEL = 50 ppm [3.5 mg/kg/day]; Reproductive LOAEL = 250 ppm [17.5 mg/kg/day]** based on prolonged gestation length and decreased number of pups born alive; **Offspring NOAEL = 50 ppm [3.5 mg/kg/day]; Offspring LOAEL = 250 ppm [17.5 mg/kg/day]** based on mean lower pup weights on days 14 and 21 of lactation.

## **2-Generation Reproduction Study in rats (European Union study review summary)**

In a multigeneration reproduction study, DPX 6573-39 [95.6% a.i.] was administered in the diet to Crl:CD®BR rats (90/sex/dose) at dose levels of 0, 10, 50 and 250 ppm (M/F: 1/0, 1/1, 2.85/3.51, and 18/22 mg/kg/day). After 90 days on this diet, 20/sex/dose were removed and used as the F0 generation in a multigeneration study. The F0 parents were mated twice to produce the F1a and F1b offspring and then returned to the feeding study. The F1 mating pairs were selected from the F1b offspring and mated to produce two F2 litters. Pathology was carried out on premature decedents and 10/sex of the F2b weanlings.

**Parental NOAEL 18 mg/kg/day, Parental LOAEL was not observed.**  
**Reproductive NOAEL = 2.85 mg/kg/day; Reproductive LOAEL = 18 mg/kg/day**

based on a decrease in the number of pups born alive; **Offspring NOAEL = 2.85 mg/kg/day**; **Offspring LOAEL = 18 mg/kg/day** based on failure to thrive and decreased postnatal survival on day four.

## **2.2.5. Pre-and/or Postnatal Toxicity**

### **2.2.5.1. Determination of Susceptibility:**

There are several developmental and 2-generation reproduction studies in rats and rabbits that provide evidence of increased susceptibility to in utero and/or pre-, postnatal exposure to flusilazole. Developmental effects such as cleft palate, resorption and skeletal malformations were observed in rats. In rabbits, increased resorptions were observed. In both species, these effects occurred either in the absence of maternal toxicity and/or at a dose that caused marginal maternal toxicity (decreased food consumption, body weight gain).

In a multi-generation reproduction study in rats a decrease in pup viability at birth and decreased post-natal survival were observed either in the absence of maternal toxicity and/or at a dose that caused marginal maternal toxicity.

### **2.2.5.2. Degree of Concern Analysis and Residual Uncertainties**

The degree of concern is low for the susceptibility observed in rats and rabbits since there are well established NOAELs in most of the developmental and 2-generation reproduction studies. The NOAELs were not established in some developmental and 2-generation reproduction studies, however, the concern for these increased susceptibility is low since the acute (0.02 mg/kg) and chronic (0.002 mg/kg) RfDs are set at values equal or lower than the dose at which these developmental effects were observed and are therefore protective of these effects. Based upon the above-described data, no FQPA safety factor is warranted (*i.e.*, 1X).

### **2.2.5.3. Special FQPA Safety Factor**

The flusilazole risk assessment team evaluated the quality of the hazard and exposure data and determined that based on the hazard and exposure data, the special FQPA SF is reduced to 1X. In terms of hazard, there are low concerns and no residual uncertainties with regard to pre- and/or post-natal toxicity. The recommendation is based on the following:

1. The dietary food exposure assessment utilizes proposed tolerance-level or higher residues and 100% CT information for all commodities. By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated.
2. The dietary drinking water assessment (Tier 2 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.
3. There are no residential uses of flusilazole.

### **2.3. Recommendation for a Developmental Neurotoxicity Study**

There is not a concern for developmental neurotoxicity resulting from exposure to flusilazole.

**A. Evidence that suggest requiring a Developmental Neurotoxicity study:**

None

**B. Evidence that do not support a Developmental Neurotoxicity Study:**

There is no indication of neurotoxicity observed in any subchronic or chronic toxicity study.

Based on the available data from multiple studies, the chemical is not considered neurotoxic; thus, a developmental neurotoxicity study is not required for flusilazole.

### **2.4 Hazard Identification and Toxicity Endpoint Selection**

#### **2.1.3. Dose-response**

***Acute Dietary Endpoint:*** Acute dietary endpoint for child bearing females (females 13+) was determined from the developmental toxicity study in rat; LOAEL= 10 mg/kg/day based on distended ureter, and small renal papilla. An UF of 100X (10-fold for interspecies extrapolation and 10-fold for intra species variability) was applied to the NOAEL of 2 mg/kg/day to derive the aRfD. The FQPA safety factor of 1X is applicable for acute dietary risk assessment. Therefore, the aPAD is 0.02 mg/kg/day.

The acute oral reference dose (aRfD) for the general population, including infants and children, was not established since an endpoint of concern attributable to a single dose was not identified.

***Chronic Dietary Endpoint:*** The chronic reference dose (cRfD) of 0.002 mg/kg/day was determined on the basis of the chronic oral toxicity study in dog. This study provided the lowest NOAEL in the database (most sensitive endpoint) and that will also provide the most protective limits for human effects. An UF of 100X (10-fold for interspecies extrapolation and 10-fold for intra species variability) was applied to the NOAEL of 0.2 mg/kg/day to derive the cRfD. The LOAEL of 0.7 mg/kg/day was based on increased liver weights & hypertrophy of centrilobular hepatocytes in both sexes, hepatocytic vacuolation, increased alkaline phosphatase, decreased cholesterol and total serum protein, and increased white blood cells in males. The FQPA safety factor of 1X is applicable for chronic dietary risk assessment. Therefore, the cPAD is 0.002 mg/kg/day.

***Short- and Intermediate-Term Incidental Oral, dermal and inhalation Endpoints:*** Short- and intermediate-term incidental oral and inhalation endpoints are based on a 2-generation reproduction study in the rat. A LOAEL of 18 mg/kg/day was based on failure to thrive and decreased postnatal survival on day four (NOAEL = 2.85 mg/kg/day). A 2-generation reproduction study in the rat is selected for these scenarios because it protects the developmental effects and is also appropriate for duration of exposures and population of concern.

Short- and intermediate-term dermal endpoints are based on a dermal prenatal developmental

study in rats. The NOAEL of 2 mg/kg/day was based on 14th rudimentary ribs, 14th full ribs, 7th cervical ribs and unossified sternbrae at the LOAEL of 10 mg/kg/day. The dermal prenatal developmental study is selected for these scenarios because it is route specific, protects the developmental effects and is also appropriate for duration of exposures and population of concern.

Note: NOAELs and LOAELs for these toxicological endpoints were selected based on study review summaries prepared by the European Union. Upon further detailed review of all existing and new data, these NOAELs and LOAELs are subject to change.

**Long-Term Dermal and Inhalation Endpoints:** Long-term dermal and inhalation endpoints are based on the chronic oral toxicity study in dog; LOAEL = 0.7 mg/kg/day based on increased liver weights and hypertrophy of centrilobular hepatocytes (NOAEL 0.2 mg/kg/day).

Since oral studies were selected for dermal exposure assessment and a dermal penetration study is not available, a dermal-absorption factor (DAF) of 30% should be used. The DAF was estimated by using an oral LOAEL of 30 mg/kg/day from a developmental toxicity study in rats (MRID 00148513) and dividing by a dermal LOAEL of 10 mg/kg/day from a dermal prenatal developmental study in rats (European Union Study) based on similar effects (resorption, stunting, skeletal variation) in oral and dermal prenatal developmental study in rats. Since oral NOAELs were selected for inhalation exposure assessment, an inhalation absorption factor of 100% oral equivalent should be used. The level of concern for residential exposure is for margins of exposure (MOEs) <100 and for occupational exposure is for MOEs <100.

**Carcinogenicity:** This chemical has not been evaluated by the Cancer Peer Review Committee. However, for the purpose of this **Section 18 Emergency Exemption**, a conservative Q1\* was calculated based on female mouse liver adenoma and/or carcinoma combined tumor rates. For risk characterization, a low-dose extrapolation model was applied to the animal data for the quantification of human risk (Q1\*). The unit risk Q1\* (mg/kg/day), for flusilazole is  $2.84 \times 10^{-3}$  in human equivalents based on female mouse liver adenoma and/or carcinoma combined tumor rates.

<b>Exposure Scenario</b>	<b>Dose Used in Risk Assessment, UF</b>	<b>Special FQPA SF* and Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Acute Dietary (general population)	Not applicable	None	An endpoint of concern attributable to a single dose for general population was not identified.
Acute Dietary (Females 13+)	NOAEL = 2.0 mg/kg/day  UF = 100X Acute RfD = 0.02 mg/kg	FQPA SF = 1X  aPAD = 0.02 mg/kg (aRfD)/1X (FQPA SF)  = 0.02 mg/kg	Developmental toxicity - rat; LOAEL = 10 mg/kg/day based on distended ureter, small renal papilla, large renal pelvis, increased skeletal variations.

**Table 2.3. Summary of Toxicological Dose and Endpoints for Flusilazole Used in Human Risk Assessment**

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	NOAEL= 0.2 mg/kg/day UF = 100X Chronic Rfd = <b>0.002 mg/kg/day</b>	FQPA SF = <b>1X</b>  cPAD = 0.002mg/kg/day (c Rfd)/1X (FQPA SF) = <b>0.002 mg/kg/day</b>	Chronic oral toxicity - dog; LOAEL = 0.7 mg/kg/day, based on increased increased liver weights & hypertrophy of centrilobular hepatocytes.
Short-Term Incidental Oral (1-30 days)	NOAEL = 2.85 mg/kg/day	Residential LOC for MOE = 100	2-gen. repro. - rat; LOAEL = 18 mg/kg/day, based on failure to thrive and decreased postnatal survival on day four.
Intermediate-Term Incidental Oral (1-6 months)		Occupational LOC for MOE = 100	
Short-Term Dermal (1 to 30 days)	NOAEL = 2.0 mg/kg/day	Residential LOC for MOE = 100	Dermal Prenatal Developmental-rat LOAEL = 10 mg/kg/day based on 14th rudimentary ribs, 14th full ribs, 7th cervical ribs and unossified sternbrae.
Intermediate-Term Dermal (1 to 6 months)		Occupational LOC for MOE = 100	
Long-Term Dermal (>6 months)	NOAEL= 0.2 mg/kg/day  (Dermal absorption= 30%)	Residential LOC for MOE = 100  Occupational LOC for MOE = 100	Chronic oral toxicity - dog; LOAEL = 0.7 mg/kg/day, based on increased increased liver weights & hypertrophy of centrilobular hepatocytes.
Short-Term Inhalation (1 to 30 days)	NOAEL = 2.85 mg/kg/day  (inhalation absorption rate = 100% oral equivalent)	Residential LOC for MOE = 100	2-gen. repro. - rat; LOAEL = 18 mg/kg/day, based on decreased pup viability at birth and decreased postnatal survival
Intermediate-Term Inhalation (1 to 6 months)		Occupational LOC for MOE = 100	
Long-Term Inhalation (>6 months)	NOAEL = 0.2 mg/kg/day  (inhalation absorption rate = 100% oral equivalent)	Residential LOC for MOE = 100; Occupational LOC for MOE = 100	Chronic oral toxicity - dog; LOAEL = 0.7 mg/kg/day, based on increased increased liver weights & hypertrophy of centrilobular hepatocytes.
Cancer	Q1* (mg/kg/day) <sup>-1</sup> is 2.84 X 10 <sup>-3</sup> in human based on female mouse liver adenoma and/or carcinoma combined tumor rates.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOEL = no observed adverse effect level, LEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) Rfd = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable



**NOTE:** The Special FQPA Safety Factor was reduced to 1X because the hazard and exposure databases (dietary food, drinking water, and residential) are complete and the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

## **2.4 Endocrine Disruption**

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on flusilazole, there was evidence of potential estrogen and/or androgen mediated toxicity. Effects were observed in developmental studies in rats (MRIDs 00161169, 00148513, 00154928) and rabbits (MRIDs 0015429, 00154930), and in a dermal prenatal developmental study in rats (European Union report) which indicated potential estrogen and/or androgen mediated toxicity manifested as increase in gestation in rats and a decrease in the number of pregnant does in rabbits.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flusilazole may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

## **3.0 Registered/Proposed Application Scenarios**

*Registered Uses:* None

*Proposed Use:* The state of MN is requesting application of Charisma™ (9.7% flusilazole + 9.1% famoxadone) and Punch™ (37.8% flusilazole) to soybeans. Two applications are requested at 1.0-1.75 oz ai/acre with a 14- to 21-day retreatment interval (RTI) and a preharvest interval (PHI) of 30 days. Rotational crops may be planted 30 days after the last application.

***HED's Conclusions:* The labels should be amended to specify that use of soybean hay and forage for livestock feed is prohibited and to specify PBIs of 30 days for root and leafy vegetables and 40 days for small grains and all other crops.**

#### 4.0 Residue Chemistry Considerations

*Nature of the Residue in Plants:* Plant metabolism studies conducted with apples, grapes, and wheat show qualitatively similar metabolism among the crops. A major metabolic route in plants is cleavage of the Si-CH<sub>2</sub> bond to form IN-H7169 or the silanol (INF7321) 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 triazole alanine, which is subsequently metabolized to triazole acetic acid. With the exception of triazole alanine and triazole acetic acid, individual metabolites generally account for less than 14% of the total radioactivity in the plants. The metabolic pathway for flusilazole in plants is shown in Figure 1.

HED has reviewed apple, grape, and wheat metabolism studies (see Memos C. Trichilo, 2/12/88; W. Hazel, 1/3/90; S. Funk, 10/4/90; and F. Griffith, 12/20/90). The total toxic residue (TTR) was tentatively identified as flusilazole plus IN-F7321 and IN-H7169; the parent compound was deemed adequate to serve as a marker for the TTR in the tolerance expression (Memo W. Hazel, 8/21/90). The wheat metabolism study was reviewed subsequently to this decision (S. Funk, 10/4/90). In wheat straw, metabolites IN-37722 and IN-37738 (and their conjugates) comprised a significant portion of the identified residue. As these metabolites are also closely related to the parent, HED will include them in the TTR. For the purposes of this Section 18 request only, HED concludes that the nature of the residue in plants is adequately understood and the residue of concern for tolerance expression is flusilazole *per se* and the residues of concern for this risk assessment are flusilazole plus IN-F7321, IN-H7169, IN-37722 and IN-37738 (and their conjugates). The smallest portion of the TTR comprised of flusilazole was 31% in wheat straw. Using these data and since soybean metabolism data are not available, HED concludes that a factor of 3.2X should be used to adjust residue data on flusilazole *per se* to account for potential metabolite residues. Additionally, the Agency does have concern about potential toxicity to 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, metabolites common to most of the triazole fungicides. To support the extension of existing and granting of new parent triazole-derivative fungicide tolerances, EPA has conducted a human-health assessment for aggregate exposure to 1,2,4-triazole in a separate document (Memo Doherty, *et al.*, 12/22/05; DP# 322215).

*Nature of the Residue 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. Residues in goats and hens were similar. Generally, flusilazole *per se* was present at levels lower than the metabolites. 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 poultry tissues and eggs. The proposed metabolic pathway for flusilazole in livestock is shown in Figure 2.

HED has reviewed the livestock metabolism studies (see Memos C. Trichilo, 2/12/88; and W. Hazel, 1/3/90). The residues of concern for the tolerance expression and risk assessment were tentatively identified as flusilazole plus IN-F7321 (Memo W. Hazel, 8/21/90). For the purposes of this Section 18 request only, HED concludes that the nature of the residue in livestock is adequately understood. The residues of concern for the tolerance expression and risk assessment are flusilazole plus IN-F7321. Additionally, the Agency does have concern about potential toxicity to 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, metabolites common to most of the triazole fungicides. To support the extension of existing and granting of new parent triazole-derivative fungicide tolerances, EPA has conducted a human-health assessment for aggregate exposure to 1,2,4-triazole in a separate document (Memo Doherty, *et al.*, 12/22/05; DP# 322215).

*Nature of the Residue - Rotational Crops:* Two confined <sup>14</sup>C-flusilazole rotational crop studies were conducted. Neither of these studies have been reviewed by HED. 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. In the initial study, sandy loam soil was treated with phenyl-labeled flusilazole at rates of 0.257 (1.3X) or 0.483 (2.4X) lb a.i./A. 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. In the second study, two radiolabeled forms of the test substance were used. Silt loam soil was treated at 1.00 lb a.i./A (4.9X). 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). Residue levels in mature crops from the initial study with phenyl-labeled flusilazole ranged from 0.02 ppm (soybean seeds and barley grain) to 2.16 ppm (barley straw). 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 ppm flusilazole equivalents (wheat straw). 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 the silanol (IN F7321), the silanediol (IN-V5571), and high levels of bound residues. Quantifiable residues of flusilazole were observed in 360-day wheat grain (0.03 ppm); and IN-V5571 in 120-day wheat straw (0.16 ppm) and 360-day wheat straw (0.10 ppm). 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). Triazole alanine and an unidentified polar metabolite were the major plant metabolites from the triazole label in addition to high levels of bound residues. Since triazole alanine was identified in wheat grain in the crop rotation study, it is likely that the unidentified polar residues consist primarily of triazole acetic acid.

For the purposes of this Section 18 request only, HED concludes that the nature of the residue in rotational crops is adequately understood and the residues of concern for this risk assessment are flusilazole, IN F7321 and IN-V5571.

*Magnitude of the Residue 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 (0.6-

1.6X), 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. A decline study was conducted in Brazil for three different flusilazole formulations. The average half-life for residues of flusilazole *per se* in soybeans following 3 applications was 7 days (range 6.8-7.3 days). In all trials, there were no quantifiable flusilazole residues in/on soybean seed at a 30-day PHI or later except for 1 trial in France (0.01 ppm, 2 x 2.86 oz flusilazole/A (1.6X), 48-day PHI). However, DuPont has reported preliminary results from 21 sites in the U.S. have been analyzed, with a PHI of 30 days. All but one sample showed residues of parent flusilazole in the ~0.01 - ~0.02 ppm range, with one site showing a residue of ~0.03 ppm. **Based on these data, the appropriate tolerance for soybean, seed is 0.04 ppm.** DuPont has also submitted preliminary results residues of flusilazole in soybean aspirated grain fractions which result in a concentration factor of 65X (e-mail from L. Palmer to C. Rodia, 3/27/06). Thus, for the purposes of this Section 18 request only, HED concludes that **the appropriate tolerance for aspirated grain fractions is 2.6 ppm** (0.04 ppm x 65). No residue data for soybean hay and forage were submitted. Therefore, the labels should be amended to specify that use of soybean hay and forage for livestock feed is prohibited

*Magnitude of the Residue in Processed Commodities:* 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. For the purposes of this Section 18 request only, HED concludes that **the appropriate tolerance for soybean, oil is 0.10 ppm.**

*Magnitude of the Residue in Livestock - Ruminants:* A dairy cattle feeding study has been previously reviewed by HED (Memo C. Trichilo, 2/12/88). Dairy cows were orally dosed daily with flusilazole at levels equivalent to 2 ppm (16X), 10 ppm (80X), and 50 ppm (400X). The animals were sacrificed after 28 days of dosing. The milk and tissue samples were analyzed for residues of flusilazole plus IN-F7321, IN-H7169 and IN-G7072. At the lowest dose level (2 ppm, 16X), quantifiable residues of flusilazole and its metabolites were found only in kidney (0.25 ppm) and liver (0.29 ppm). Extrapolation to a 1X feeding level results in values of <0.02 ppm. Based on the expected dietary burden for beef and dairy cattle (0.125 ppm, Table 4.1), HED concludes that tolerances are not required for residues of flusilazole and its metabolites in ruminant commodities for the purposes of this Section 18 request only.

Feed Commodity	Anticipated Residue (ppm)	% Dry Matter <sup>a</sup>	Beef Cattle		Dairy Cattle	
			% of Diet <sup>a</sup>	Burden, ppm	% of Diet <sup>a</sup>	Burden, ppm
Soybean, seed	0.048 <sup>b</sup>	89	15	0.0080	15	0.0080
Aspirated grain fractions	0.499 <sup>c</sup>	85	20	0.117	20	0.117
<b>TOTAL</b>			<b>35</b>	<b>0.125</b>	<b>35</b>	<b>0.125</b>

<sup>a</sup> Table 1, OPPTS GLN 860.1000.

<sup>b</sup> Average residue (0.015 ppm) x the factor (3.2) used to adjust the flusilazole residues in order to account for potential metabolite residues

<sup>c</sup> The maximum expected flusilazole residues in soybean aspirated grain fractions would be 0.975 ppm based on the average residue (0.015 ppm) in/on soybean seed and a 64X concentration factor. However, soybeans comprise only 16% of commercial aspirated grain fractions. The expected residue of flusilazole + potential metabolites in aspirated grain fractions is 0.499 ppm (0.975 ppm x 0.16 x 3.2).

**Poultry:** A poultry feeding study has been previously reviewed by HED (Memo C. Trichilo, 2/12/88). Laying hens were orally dosed daily with flusilazole at levels equivalent to 2 ppm (210X), 10 ppm (1040X), and 50 ppm (5210X). The animals were sacrificed after 28 days of dosing. The egg and tissue samples were analyzed for residues flusilazole plus IN-F7321, IN-H7169 and IN-G7072. At the lowest dose level (2 ppm, 210X), quantifiable residues of flusilazole and its metabolites were found only in eggs (0.17 ppm), fat (0.15 ppm) and liver (0.16 ppm). Extrapolation to a 1X feeding level results in values of <0.001 ppm. Based on the maximum theoretical dietary burden (MTDB) for poultry (0.0096 ppm, Table 4.2), HED concludes that tolerances are not required for residues of flusilazole and its metabolites in poultry and/or eggs for the purposes of this Section 18 request only.

Table 4.2. Calculation of the MTDB of Flusilazole in Poultry			
Feed Commodity	Anticipated Residue (ppm)	Poultry	
		% of Diet <sup>a</sup>	Burden, ppm
Soybean, seed	0.048 <sup>b</sup>	20	0.0096
<b>TOTAL</b>		20	0.0096

<sup>a</sup> Table 1, OPPTS GLN 860.1000.

<sup>b</sup> Average residue (0.015 ppm) X the factor (3.2) used to adjust the flusilazole residues in order to account for potential metabolite residues+

**Magnitude of the Residue in Rotational Crops:** DuPont has submitted preliminary results of field rotation studies conducted at 4 locations in the U.S. (e-mail from L. Palmer to C. Rodia, 3/27/06). Wheat, lettuce, and turnips were planted in soil shortly after flusilazole application to the soil (lettuce and turnips) or soybeans (wheat) at a 1X treatment rate. The results demonstrated little or no uptake ( $\leq 0.003$  ppm) of flusilazole or its metabolite IN F7321. Data were not provided for residues of the silanediol metabolite (IN-V5771). However, for the purposes of this Section 18 request only, these data will not be required as the residues of flusilazole and IN F7321 were significantly lower in the field study than the confined study and IN-V5771 is a major metabolite only in wheat straw. The results of this study thus support PBIs of 30 days for root and leafy vegetables and 40 days for small grains and all other crops.

**Multiresidue Methods (MRMs):** Data pertaining to multiresidue testing of flusilazole have been submitted previously (MRIDs 408047-09 to -011) (Memo W. Hazel, 10/20/89). The Food and Drug Administration (FDA) Pestrak Database indicates that flusilazole is completely recovered through Method Sec. 302 no. C.

**Analytical Enforcement Method:** Gas chromatography/nitrogen-phosphorus detector (GC/NPD) Method AMR-604-86 is available for enforcement of the previously-proposed plant tolerances on wheat (Memo F. Griffith, 12/20/90). Gas chromatography/mass-selective detector (GC/MSD) Method 15737 was employed in the soybean residue trials and processing studied (e-mail from L. Palmer to C. Rodia, 3/27/06). Based on these methods and the complete recovery of flusilazole through MRM Sec. 302 no. C, HED concludes that adequate methodology is available to enforce the recommended tolerances.

## 5.0 Drinking Water Considerations

EFED memo - DP# 324127, C. Sutton, 11/30/05

*Environmental Fate Assessment:* Based on the submitted flusilazole environmental fate data, its physical-chemical properties, and the proposed use patterns, flusilazole is expected to be persistent and to have low mobility in soil. Flusilazole is stable to hydrolysis and to aqueous photolysis, but undergoes relatively slow degradation via microbially-mediated metabolism, with much of the apparent loss of the compound attributed to the formation of non-extractable residues. Microbially-mediated cleavage of the parent at the methylene bridge yields the minor degradates [bis(4-fluorophenyl)methyl]silanol (silanol) and 1H-1,2,4-triazole (triazole); there are no major degradates (*i.e.*, >10%). In anaerobic flooded sediments, flusilazole undergoes very slow transformation, with relatively rapid dissipation from the water column to the sediment phase, where it remains as parent and bound residues. In aerobic flooded sediments, flusilazole is essentially stable to degradation, but partitions predominantly to the sediment phase. While the silanol degradate has low to moderate mobility in soil, the triazole has very high mobility. However, both of the degradates appear to degrade more rapidly than they are formed, and do not reach major degradate levels (*i.e.*, >10%) in the laboratory studies. Based on these data and for the purposes of this Section 18 request only, HED concludes that the residue of concern for drinking water is flusilazole *per se*.

*Ground and Surface Water Estimated Environmental Concentrations (EECs):* A Tier II water assessment was conducted for the proposed use of flusilazole on soybeans using the proposed maximum application rate for soybean; 0.206 lbs ai/acre with two applications at a 21-day interval. The estimated drinking-water concentrations (EDWCs) of flusilazole in surface water from the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) are presented in Table 5.1. The Screening Concentration in Ground Water (SCI-GROW) model version 2.3 was used to estimate the concentration of flusilazole in ground water. SCI-GROW estimated the concentration of flusilazole in shallow ground water sources to be 0.05 µg/L.

Table 5.1. Tier II PRZM/EXAMS Fusilazole <sup>1</sup> EDWCs in Index Reservoir corrected for percent crop area (PCA = 0.41 for soybeans).			
Conditions	EDWC (ug/L)		
	1-in-10-Year Peak	1-in-10-Year Average Annual	30-Year Average Annual
Ground Spray	1.73	0.87	0.66
Aerial Spray	1.81	0.92	0.72

<sup>1</sup> Two applications, by ground spray (gs) and aerial spray (as) at 0.206 lb ai/ac with a 21-day interval and first application on June 1.

## 6.0 Dietary Risks (Food and Water)

DP# 325950, George Kramer, 30-JAN-2006

### Acute Dietary Exposure Results and Characterization

The Tier 1 acute analysis assumed 100% crop treated (%CT), Dietary Exposure Evaluation Model (DEEM™ version 7.81) default processing factors and tolerance-level residues. A factor of 3.2X was used to adjust the flusilazole residues in order to account for potential metabolite residues. Drinking water was incorporated directly in the dietary assessment using the 1-in-10 year annual peak concentration for surface water generated by the PRZM-EXAMS model. As an appropriate endpoint attributable to a single dose was not identified for the general population (including infants and children), the acute analysis was performed only for females 13-49 years of age. The resulting acute dietary exposure and risk estimates using the DEEM-FCID™ model at the 95<sup>th</sup> percentile were 0.000326 mg/kg/day and 1.6% of the aPAD, respectively. The risk estimate is thus below HED's level of concern (100% aPAD).

### Chronic Dietary Exposure Results and Characterization

The Tier 1 chronic analysis assumed 100% CT, DEEM™ 7.81 default processing factors and tolerance-level residues. A factor of 3.2X was used to adjust the flusilazole residues in order to account for potential metabolite residues. Drinking water was incorporated directly into the dietary assessment using the 1-in-10 year annual average concentration for surface water generated by the PRZM-EXAMS model as a high-end estimate. The resulting chronic food risk estimates (<22% chronic population adjusted dose (cPAD); all infants <1 year old were the most highly exposed population subgroup) were less than HED's level of concern (100% cPAD).

### Cancer Dietary Exposure Results and Characterization

The cancer analysis assumed 100% CT, DEEM™ 7.81 default processing factors and tolerance-level residues. Drinking water was incorporated directly into the dietary assessment using the 30-year average annual concentration for surface water generated by the PRZM-EXAMS model as a high-end estimate. The resulting cancer risk for the general U.S. population ( $4.5 \times 10^{-7}$ ) was less than HED's level of concern (generally  $1 \times 10^{-6}$ ).

Table 6.1. Summary of Dietary Exposure and Risk for Fusilazole						
Population Subgroup*	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A	N/A	0.000162	8.1	0.000158	4.5 x 10 <sup>-7</sup>
All Infants (< 1 year old)			<b>0.000429</b>	21	N/A	N/A
Children 1-2 years old			0.000334	17		
Children 3-5 years old			0.000338	17		
Children 6-12 years old			0.000243	12		
Youth 13-19 years old			0.000161	8.0		
Adults 20-49 years old			0.000143	6.7		
Adults 50+ years old			0.000110	5.5		
Females 13-49 years old			0.000326	1.6		

### 7.0 Residential Exposure

No flusilazole uses in the residential market are allowed under the proposed labeling. Therefore, HED did not include exposure scenarios/populations for this setting in this assessment.

### 8.0 Aggregate Risk

Including all existing and proposed uses, human-health risk assessments have been conducted for the following exposure scenarios: acute, chronic and cancer dietary exposures (food + water only). **All aggregate exposure and risk estimates are below HED's level of concern.** Because there are no uses of flusilazole that are expected to result in residential exposures, this aggregate risk assessment takes into consideration dietary food + water exposure only; therefore, the acute, chronic and cancer aggregate estimates would be the same as the dietary exposure results shown in Table 6.1 above.

### 9.0 Cumulative

The Agency did not perform a cumulative risk assessment as part of this tolerance action for flusilazole. However, the Agency does have concern about potential toxicity to 1,2,4-triazole and two conjugates, triazole alanine and triazole acetic acid, metabolites common to most of the triazole fungicides. To support the extension of existing parent triazole-derivative fungicide tolerances, EPA conducted an interim human health assessment for aggregate exposure to 1,2,4-triazole (M. A. Doherty, "Interim Human Health Risk Assessment of 1,2,4-Triazole to Support Tolerance Extensions and New Section 18 Soybean Tolerances for Triazole-Derivative Fungicides," June 29, 2004, DP Barcode D304288). The exposure and risk estimates presented



in this assessment are overestimates of actual likely exposures and therefore, should be considered to be highly conservative. Based on this assessment the EPA concluded that for all exposure durations and population subgroups, aggregate exposures to 1,2,4-triazole are not expected to exceed its level of concern. This assessment should be considered interim due to the ongoing series of studies being conducted by the U.S. Triazole Task Force (USTTF). Those studies are designed to provide the Agency with more complete toxicological and residue information for free triazole and are expected to be submitted to the Agency in 2005. Upon completion of review of these data, EPA will prepare a more sophisticated assessment based on the revised toxicological and exposure databases.

## **10.0 Endocrine Disruption**

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on flusilazole, there was evidence of potential estrogen and/or androgen mediated toxicity. Effects were observed in developmental studies in rats (MRIDs 00161169, 00148513, 00154928) and rabbits (MRIDs 0015429, 00154930), and in a dermal prenatal developmental study in rats (European Union report) which indicated potential estrogen and/or androgen mediated toxicity manifested as increase in gestation in rats and a decrease in the number of pregnant does in rabbits.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, flusilazole may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

## **11.0 Occupational Exposure**

Occupational and Residential Risk Assessment memo - DP# 319403, J. Dawson, 10/26/05

Risks were calculated based on both noncancer and cancer endpoints. Noncancer dermal risks were based on a dermal prenatal developmental study in rats (NOAEL = 2.0 mg/kg/day) where the endpoint was rib (various) malformations and unossified sternbrae. Noncancer inhalation risks were calculated based on a 2-generation reproduction study in rats (NOAEL = 2.85

mg/kg/day) where the endpoint was decreased pup viability at birth and decreased post-natal survival. A linear, low-dose extrapolation approach (*i.e.*,  $Q_1^* = 2.84 \times 10^{-3}$ ) was used to assess cancer risks where the endpoint was based on female mouse liver adenoma and/or carcinoma tumor rates. A 30% dermal-absorption factor was used in the cancer risk calculations.

The occupational handler results indicate that the noncancer risks are generally not of concern at the levels of personal protection specified by the two proposed flusilazole labels. Two dermal-exposure scenarios have risks of concern associated with mixing/loading liquids for very high-acreage uses (*i.e.*, 1200 acres) where the MOEs are less than 100 (*i.e.*, 51 and 73 for Punch™ and Charisma™ labels, respectively). The risks for these two scenarios are not of concern if closed loading systems are employed (*i.e.*, MOEs = 136 and 194, respectively). Inhalation noncancer risks are not of concern for any scenario considered without respiratory protection as stipulated in the proposed labels. Cancer risks were also generally not of concern. Cancer risks for private applicators (*i.e.*, 10 days use per year) were not of concern for any scenario considered. The trend for commercial applicators (*i.e.*, 30 days use per year) are similar to those noted above for the dermal noncancer risks. For the high-acreage mixing/loading events, additional personal protection (*e.g.*, closed loading in one case) compared to the proposed label is needed to achieve cancer risk estimates that are less than  $1 \times 10^{-6}$ .

Both of the proposed flusilazole labels (*i.e.*, Punch™ 3.3 EC and Charisma™ 0.9 EC) specify 12-hour REIs. Noncancer risks (*i.e.*, MOEs) are of concern at the currently proposed REI as the MOEs are 52 for the Punch™ 3.3 EC and 74 for the Charisma™ 0.9 EC labels, respectively, on the day of application for scouting which is the only anticipated hand labor activity that would lead to routine exposures. The level of concern for noncancer risks is a total uncertainty factor (*i.e.*, target MOE) of 100. Noncancer risks exceed the target uncertainty factor (*i.e.*,  $MOE \geq 100$ ) at 7 or 3 days after application, respectively, for the Punch™ (*i.e.*, 0.10 lb ai/acre) and Charisma™ (0.07 lb ai/acre) labels. Cancer risks are not of concern for all scenarios considered on the day of application for both proposed label or population considered.

All of the key exposure patterns that would be associated with the anticipated use patterns of flusilazole have been addressed in this assessment. Overall, the best available exposure monitoring data have been used to complete this assessment including the Pesticide Handlers Exposure Database (PHED) and data from the Agricultural Reentry Task Force (ARTF). Generally, the PHED exposure estimates are considered to be high quality data and the ARTF data are also considered high quality. Other factors used in this assessment were those commonly used by the Agency as more specific data were not available (*e.g.*, to calculate dislodgeable foliar residues). Chemical-specific data could potentially refine risk estimates (*e.g.*, a dislodgeable foliar residue for postapplication worker risks). Generally, the flusilazole occupational risks should be considered a highly quality assessment that results in upper percentile exposure estimates based on the inputs used.

#### Attachment 1: Figures

cc: G. Kramer (RAB1)  
RDI: RAB1 Branch (12/21/05), RAB1 Chemists (5/24/06), RAB1 Toxicologists (10/17/05)  
G.F. Kramer:806T:CM#2:(703)305-5079:7509C:RAB1

Figure 1: Metabolic Pathways for Flusilazole in Plants

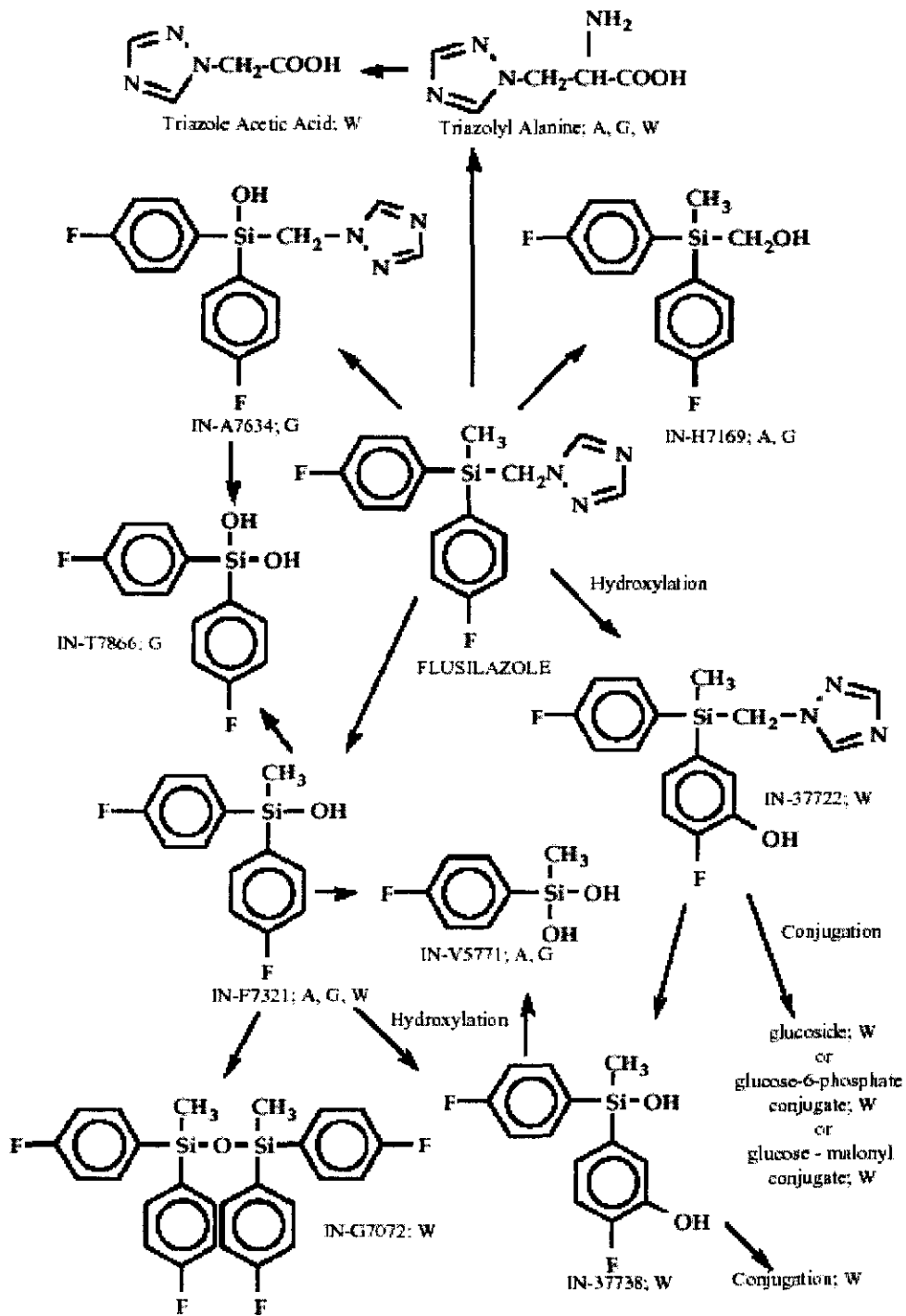
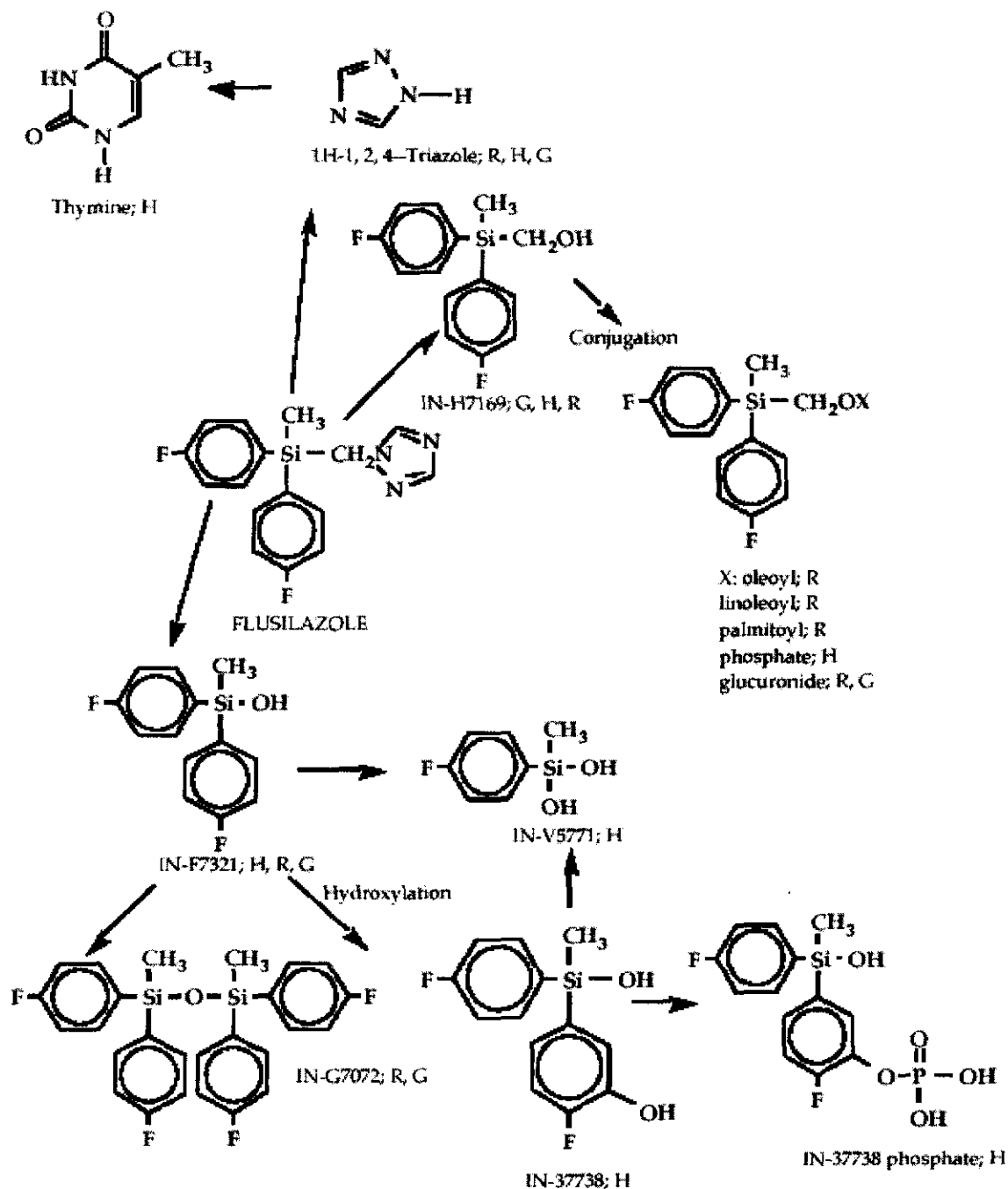


Figure 2: Metabolic Pathways for Flusilazole in Livestock





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**R128885**

**Chemical: Flusilazole**

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