United States Environmental Protection Agency

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

Pesticide Fact Sheet

Name of Chemical: **Metconazole**
Reason for Issuance: **New Chemical Tolerances Established**
Date Issued: **August 2006**

Description of Chemical

Generic Name:	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazole-1-ylmethyl)cyclopentanol
Common Name:	Metconazole
Trade Names Used In Foreign Countries:	Metconazole 90 SL (Caramba™ Fungicide)
Chemical Class:	Triazole
EPA Chemical Code:	125619
Chemical Abstracts Service (CAS) Number:	125116-23-6
Registration Status:	Not Registered, Import Tolerance Established
Pesticide Type:	Fungicide
U.S. Agent:	BASF Corporation Agricultural Product Division 26 Davis Drive, P.O. Box 13528 Research Triangle Park, NC 27709
International Producer:	Kureha Corporation 3-3-2, Nihonbashi-Hamacho, Chuo-ku Tokyo 103-8552, Japan

Tolerance Established

Tolerances were established in the 40 CFR §180.617 for imported bananas at 0.1 ppm.

Foreign Use Pattern and Formulations

Metconazole is a systemic triazole fungicide proposed for control of Black Sigatoka disease (*Mycosphaerella fijiensis*) on bananas grown outside the United States (U.S.). Metconazole acts primarily as an inhibitor of ergosterol biosynthesis, and interferes with synthesis of fungal cell membranes. The formulation proposed for use on bananas is Metconazole 90 SL (Caramba™ Fungicide), a soluble liquid concentrate formulation containing 9% active ingredient (a.i.). There are currently no registered uses of metconazole in the United States.

Table 1 Summary of Directions for Proposed Uses of Metconazole on Bananas.

Formulation	Single Application Rate	Maximum Number of Applications/Season	Maximum Seasonal Application Rate	PHI (days)
Metconazole 90 SL Foliar broadcast spray; ground or aerial equipment	0.089 lb a.i./Acre	7 (12 day minimum re-treatment interval)	0.62 lb a.i./Acre	0

Science Findings

Available product chemistry, toxicology, and residue data supporting the proposed use on bananas are summarized below.

Table 2 Physical/Chemical Structure

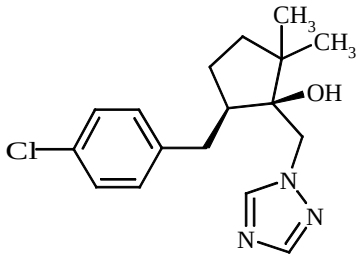	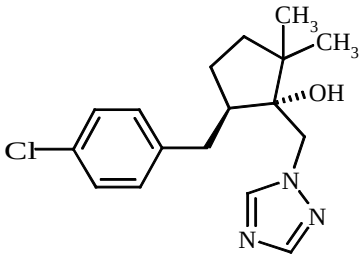
Cis-isomer	*Trans*-isomer

Table 3 Physicochemical Properties of the Technical Grade Metconazole	
Parameter	**Value**
Molecular Weight	319.837
Melting point/range	100.0-108.4°C (using Electrothermal Digital Melting Point Apparatus) (AC900,768 technical grade)
pH	No data were submitted.
Relative density (20°C)	1.14 (relative density to water at 4°C, using capillary-stoppered, density-specific gravity bottle) (Lot No. AC 8879-140B)
Water solubility (20°C)	Using shake flask method: 18.7±1.0 mg/L (*cis*-isomer, WL148271, KNF-S-474m) 13.6±1.7 mg/L (*trans*-isomer, WL148271, KNF-S-474m)
Solvent solubility (g/L) at 20°C	hexane: 1.40 toluene: 103 2-propanol: 132 ethyl acetate: 260 dichloromethane:481 methanol: 403 acetone: 363
Vapor pressure (20°C)	Using gas-saturation method at 20°C: $< 1.23 \times 10^{-5}$ Pa or 9.23×10^{-8} mm Hg (AC 900,768) $< 1.04 \times 10^{-5}$ Pa or 7.80×10^{-8} mm Hg (*cis*-isomer, CL 354,801) $< 1.96 \times 10^{-6}$ Pa or 1.47×10^{-8} mm Hg (*trans*-isomer, CL 354,802)
Dissociation constant (pK_a)	11.38±0.03 and 1.06±0.03 (in water using spectrophotometric method) (Lot No. AC 8879-140B)
Octanol/water partition coefficient Log (K_{ow})	K_{ow} (log K_{ow}) = 7090±989 (3.85) (using flask shaking method) (Lot No. AC 8879-140B) (TGAI) K_{ow} (log K_{ow}) = 7150±803 (3.85) (using flask shaking method) (*cis*-isomer, CL 354,801) K_{ow} (log K_{ow}) = 6800±1700 (3.8) (using flask shaking method) (*trans*-isomer, CL 354,802)
UV/visible absorption spectrum	Not required for TGAI; required for pure active ingredient

Table 4 Acute Toxicity Profile				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral mouse (cis:trans)	44721512	LD_{50} = 566 mg/kg M/F	III
870.1100	Acute oral rat (cis:trans)	44721512	LD_{50} = 660 mg/kg M/F	III
870.1100	Acute oral rat (cis only)	44721513	LD_{50} = 1459 mg/kg M/F	III
870.1200	Acute dermal rat (cis only)	44721513	LD_{50} > 2000 mg/kg M/F	III
870.1200	Acute dermal rat (cis:trans)	44721512	LD_{50} > 2000 mg/kg M/F	III
870.1200	Acute dermal rabbit (cis:trans)	44721512	LD_{50} > 2000 mg/kg M/F	III

Table 4 Acute Toxicity Profile				
870.2400	Acute eye irritation rat (cis only)	44721513	moderate irritant	III
870.2500	Acute dermal irritation rabbit (cis only)	44721513	non irritant	IV
870.2600	Skin sensitization guinea pig (cis only)	44721513	non sensitizer	-

Table 5 Toxicity Profile for Cis/Trans[1] Metconazole Technical

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 28-Day oral toxicity rodents (rat)	44721515 (1990) M/F: 0, 30, 100, 1000, 3000 ppm M: 0, 2.7, 9.1, 90.5, 261.1 mg/kg/day F: 0, 3.1, 10.1, 97, 287.4 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 9.1/10.1 mg/kg/day LOAEL (M/F) = 90.5/97 mg/kg/day based on depression of body weight in M, liver and kidney weight increases with associated histopathological effects (hypertrophy and fatty vacuolation) in liver only.
870.3100 90-Day oral toxicity rodents (rat)	44721517 (1991) M/F: 0, 30, 100, 300, 1000, 3000 ppm M: 0, 1.94, 6.4, 19.2, 64.3, 192.7 mg/kg/day F: 0, 2.1, 7.2, 22.1, 71.4, 208.0 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 6.4/7.2 mg/kg/day LOAEL (M/F) = 19.2/22.1 mg/kg/day based on increased spleen weight in females and hepatic vacuolation in males.
870.3100 90-Day oral toxicity rodents (mouse)	44721519 (1991) M/F: 0, 30, 300, 3000 (wk 1)/2000(wk 2-13) ppm M: 0, 9.58, 50.5, 341.1 mg/kg/day F: 0, 6.94, 60.7, 438.5 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 9.58/6.94 mg/kg/day LOAEL (M/F) = 50.5/60.7 mg/kg/day based on increase in absolute and relative liver weights, hepatocellular hypertrophy and vacuolation, and increase in relative spleen weight (F), elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) activity.
870.3150 28-Day oral toxicity non-rodents (dog)	44721520 (1991) M/F: 0, 100, 1000, and 7000-10000 ppm in diet Unacceptable/non-guideline (some preliminary test data provided)	NOAEL (M/F) = 100 ppm in diet LOAEL (M/F) = 1000 ppm in diet (increase in relative and absolute thyroid wt. in one/two females) Deficiencies: low n (2M/2F per dose); decrease in food consumption means low exposure to test compound; actual dose received per dose group not provided.
870.3150 90-Day oral toxicity non-rodents (dog)	44721521 (1991) M/F: 0, 60, 600, 6000 ppm in diet M: 0, 2.5, 24.4, 225.2 mg/kg/day F: 0, 2.6, 24.3, 206.6 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 2.5/2.6 mg/kg/day LOAEL (M/F) = 24.4/24.3 mg/kg/day based on decreased food consumption and body weight gain in females and elevated platelets and reticulocytes in males.

Table 5 Toxicity Profile for Cis/Trans[1] Metconazole Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700 Prenatal developmental in rodents	44721522 (1991) 0, 12, 30, 75 mg/kg/day gavage Acceptable/Guideline	**Maternal** NOAEL = 12 mg/kg/day LOAEL = 30 mg/kg/day based on decrease in body weight gain. **Developmental** NOAEL = 12 mg/kg/day LOAEL = 30 mg/kg/day based on increased incidence of skeletal variations (predominantly lumbar ribs).
870.3700 Prenatal developmental in non-rodents (rabbits) Definitive Study	44721602 (1997) 0, 5, 10, 20, 40 mg/kg/day gavage Acceptable/Guideline	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on reductions in body weight gain, food consumption, and changes in various hematology parameters (reductions in hematocrit, hemoglobin, mean corpuscular volume and increases in platelet counts and alkaline phosphatase activity). **Developmental** NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on increases in post-implantation losses and reduction in fetal body weight.
870.3700 Prenatal developmental in nonrodents (rabbits)	44721603 (1991) 0, 4, 10, 25, 62.5 mg/kg/day (Exp. #1) 0, 2, 4, 10 mg/kg/day (Exp. #2) Acceptable/Guideline	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 62.5 mg/kg/day based on body weight changes and slight clinical signs (anorexia/reduced or altered fecal output, cold ears). **Developmental** NOAEL = 4 mg/kg/day LOAEL = 10 mg/kg/day based on examining data from the two experiments. Effects at 62.5 mg/kg/day show total litter loss, decreased. live fetuses, increased early and late resorptions. Effects at 25 mg/kg/day show some malformations: hydrocephaly (4 fetuses from 4 different litters, but NOT seen at 62.5 mg/kg/day) and limb effects (2 fetuses from 2 different litters, with one fetus with same effect at 62.5 mg/kg/d). Hydrocephaly and limb effects were observed at 10 mg/kg/day in Experiment #2, but not at that same dose in Experiment #1.
870.3800 Reproduction and fertility effects One-generation rat (cis/trans - Part I; and a comparative study between cis/trans and cis-only Part II)	44721607 (1991) Dose-range finding study in two parts. PART I: 0, 50, 500, and 1500 ppm in diet (M/F: 0, 2.9/3.6, 28.0/35.8, and 89.9/116 mg/kg/day) PART II: Comparative study. Both test groups received 0, 500, 750 ppm in diet. Conversions to mg/kg/day not provided. Not Acceptable/ Non-Guideline	**PART I:** **Parental/Systemic** NOAEL (M/F) =2.9/3.6 mg/kg/day LOAEL (M/F) = 28.0/35.8 mg/kg/day based on decreases in food/water consumption and body wt. gain (F0). **Reproductive** NOAEL (M/F) = 2.9/3.6 mg/kg/day LOAEL (M/F) = 28.0/35.8 mg/kg/d based on increased gestation length (1/10 animals). **Offspring** NOAEL (M/F) = not established LOAEL (M/F) = 2.9/3.6 mg/kg/day based on lower weight gain. **PART II:** **Parental/systemic/reproductive/offspring** NOAEL: < 500 ppm in diet (LDT). Mixed isomer appeared to be more toxic to dams and cis isomer appeared to be more toxic to offspring.
870.3800 Reproduction and fertility effects 2-generation rat (WL136184)* ***cis* only isomer**	44721608 (1993) 0, 13, 50, 220, 340 ppm M/F: 0, 2, 8, 32, 48 mg/kg/day Acceptable/Guideline	**Parental/Systemic** NOAEL (M/F) = 8 mg/kg/day LOAEL (M/F) = 32 mg/kg/day based on increase in absolute and relative ovarian weight in F1 females. **Reproductive** NOAEL (M/F) = 48 mg/kg/day No LOAEL established. **Offspring** NOAEL (M/F) =32 mg/kg/day LOAEL (M/F) = 48 mg/kg/d based on decreased body weight in both F1 and F2 offspring.

Table 5 Toxicity Profile for Cis/Trans[1] Metconazole Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800 Reproduction and fertility effects 2-generation rat **(cis/trans isomer)**	**No MRID (submission expected 2006) - The following information is based on a registrant submitted executive summary received on 12/13/05:** **0, 30, 150 (~10 mg/kg/d), and 750 (~50 mg/kg/d) ppm in diet**	**Parental/Systemic** NOAEL (M/F) = ~10 mg/kg/day LOAEL (M/F) = ~ 50 mg/kg/day based on: reduced body weight gains and food consumption (P and F1 males and females); increases in relative liver (P and F1 males and females), relative spleen (F1 females), and absolute and relative ovarian (P and F1 females) weights. Liver (centrilobular fatty changes and hypertrophy) and spleen (congestion) histopathology was observed, but there were no ovarian histopathology changes in the ovaries. **Reproductive** NOAEL (M/F) = ~10 mg/kg/day LOAEL (M/F) = ~ 50 mg/kg/day based on prolonged estrous cycle length (P females); prolonged gestation duration (P and F1 females), maternal deaths during delivery (P and F1), and significant decreases in gestation index (P and F1 females). **Offspring** NOAEL (M/F) = ~10 mg/kg/day LOAEL (M/F) =~ 50 mg/kg/day based on decreased viability index (F2); decreased body weights (F1 and F2 males and females); increased relative spleen weights without corresponding histopathological alterations (F1 and F2 males and females).
870.4100a Chronic toxicity rodents (rat)	44721609 (1992) 0, 10, 100, 300, 1000 ppm M: 0, 0.44, 4.3, 13.1, 43.9 mg/kg/day F: 0, 0.52, 5.3, 16.0, 53.8 mg/kg/day Acceptable/Guideline	NOAEL = (M/F) = 4.3/16.0 mg/kg/day LOAEL = (M/F) = 13.1/ 53.8 mg/kg/day based on an increase in mean adjusted liver weights at 12 months (M) and 24 months (F), increase in spleen weights at 24 months (F), and increased hepatocellular lipid vacuolation (M/F) and centrilobular hypertrophy (M/F).
870.4100b Chronic toxicity dogs	44721610 0, 30, 300, 1000, 3000 ppm in diet M: 0, 1.1, 12.0, 38.5, 110.0 mg/kg/day F: 0, 1.1, 10.3, 36.8, 113.7 mg/kg/day Acceptable/Guideline	NOAEL (M/F) = 12.0/10.3 mg/kg/day LOAEL (M/F) = 38.5/36.8 mg/kg/day based on decreased body weight gain weeks 1-13 (males), increased alkaline phosphatase activity (both sexes) and increased incidence of Kupffer cell pigmentation (females).
870.4200 Carcinogenicity rats	44721611 (1992) 0, 100, 300, 1000 ppm M: 0, 4.6, 13.8, 46.5 mg/kg/day F: 0, 5.5, 16.6, 56.2 mg/kg/day Acceptable/Guideline	Non-neoplastic findings at (M/F) 13.8/56.2 mg/kg/day: increased incidence of hepatocellular lipid vacuolation (M/F), centrilobular hypertrophy (M/F), liver pigment deposition (M), histiocytic foci in the spleen (M/F),and increase in severity of chronic renal nephropathy (M). Evidence of mononuclear cell leukemia (F).
870.4300 Carcinogenicity mice	44721612 (1992) 0, 30, 300, 1000 ppm M: 0, 4.5, 39.5, 166.9 mg/kg/day F: 0, 5.9, 58.1, 195.5 mg/kg/day Acceptable/Guideline	Non-neoplastic findings at (M/F) 166.9/58.1 mg/kg/day: increase in vacuolation, hypertrophy, splenic atrophy and adrenal corticomedullary pigmentation, sinusoidal hypercellularity/single cell necrosis. Neoplastic findings: increase in liver cell tumors at high dose (M/F): Increased incidence of hepatocellular adenomas in males and hepatocellular carcinomas in females.

Table 5 Toxicity Profile for Cis/Trans[1] Metconazole Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300 *in vitro* Mouse Lymphoma Mutagenesis Assay WL136184* **cis* **only** isomer	44721615 (1991) Two experiments: 12.5, 25, 50, 75, 100 and 125 µg/ml and 20, 30, 40, 50, 60, and 70 µg/ml in the presence and absence of metabolic activation (±S9). Acceptable/Guideline	There was no evidence of biologically significant induction of mutant colonies. Negative up to cytotoxic levels (125 µg/ml) ± S9.
870.5375 *in vitro* Cytogenetics Test	44721616 (1991) From 6.25 to 400 µg /ml, with and without metabolic activation (± S9) Acceptable/Guideline	Weakly positive (induced chromosome aberrations in Chinese hamster ovary (CHO-K1) cells) in the presence of S9 activation at 24 hr at µg/ml in the absence of cytotoxicity; negative in the absence of S9 activation. Negative at 48 hr ± S9.
870.5395 *in vivo* Mammalian Erythrocyte Micronucleus Test: Mouse	44721618 (1995) 400, 1000 and 2000 mg/kg bw Acceptable/Guideline	There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or collection time. The highest dose tested was 2000 mg/kg bw.
870.5500 *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay	44721613 (1990) Up to limit dose of 5000 µg/ plate (*S. typhimurium*) and (*E. coli*) in the presence and absence of metabolic activation (± S9) Acceptable/Guideline	Was not cytotoxic with or without S9 activation in five *S. typhimurium* strains and one strain of *E. coli*, and did not induce a genotoxic response in any strain. Negative up to maximum test concentration (5000 µg/plate, ± S9).
870.5550 *in vivo*/*in vitro* Mammalian UDS test Rat	44721620 (1995) 400, 1000 and 2000 mg/kg bw Acceptable/Guideline	Negative up to 2000 mg/kg bw.
870.7485 Metabolism and pharmacokinetics: rat	44721622 (1992) single high dose: 164 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after five days: feces (males - 81.3%, females - 65.5%) and urine (males - 13.6%, females - 28.4%)
870.7485 Metabolism and pharmacokinetics: rat	44721622 (1992) single high dose: 164 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after five days: feces (males - 81.3%, females - 65.5%) and urine (males - 13.6%, females - 28.4%)
870.7485 Metabolism and pharmacokinetics: rat	44721623 (1991) single low dose: 2 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after 72 hrs: feces (males - 80%, females - 67%) and urine (males - 14.8%, females - 26%). Metabolite information presented.

Table 5 Toxicity Profile for Cis/Trans[1] Metconazole Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism and pharmacokinetics: rat WL136184* *_cis_ **only** isomer	44721624 (1991) single high dose: 200 mg/kg (males only) Radiolabel: (Triazole - ^{14}C) Acceptable/Guideline	Approximately 96% of radioactivity in excreta after seven days: feces (76%) and urine (20%). Metabolite information presented.
870.7485 Metabolism and pharmacokinetics: rat WL136184* *_cis_ **only** isomer	44721625 (1991) single low dose: 2 mg/kg Radiolabel: (Cyclopentyl - ^{14}C) Acceptable/Guideline	Excretion/retention in bile-duct cannulated rats. Approximately 80% of radioactivity were excreted in the bile after 48 hrs: males (78.7%) and females (83.3%).
870.7485 Effects on rat/mice liver enzymes WL136184* *_cis_ **only** isomer	44721626 (1991) 0, 300 ppm in diet (mice) and 0, 1000 ppm in diet (rats) for seven or 28 days Acceptable/*Non-guideline*	Increased liver weight, cytochrome P450, ethoxycoumarin O-deethylase, ethylmorphine N-demethylase, and lauric acid 11-hydroxylase in both rats and mice. No effect on ethoxyresorufin O-deethylase, palmitoyl-CoA oxidation, or peroxisome proliferation (in terms of peroxisome number or morphology).
14-day Mechanistic Study	46665402 (2005) 0, 30, 300, 1000 ppm in diet (mice) for 14 days. F: 4.5, 48, 151 mg/kg/day Acceptable/*Non-guideline*	Increased liver weight (300 and 1000 ppm); increased hepatic drug metabolizing enzymes (300 and 1000 ppm) after 7 days; enlarged livers (1000 ppm) at days 3, 7 and 14; hepatic hypertrophy and vacuolation (300 and 1000 ppm) at day 14; increased ALT and AST activities at 1000 ppm (day 14); increased lipid peroxide (300 and 1000) at day 14; increased PCNA labeling at 1000 ppm at day 3 and 7.
[1] Assuming 94% purity of product, the cis/trans ratio is 85:15. All studies used cis/trans mixture unless otherwise noted.		

TOXICOLOGICAL ENDPOINTS

Table 6 Summary of Toxicological Doses and Endpoints for Metconazole for Use in Human Risk Assessments			
Exposure/ Scenario	**Dose Used in Risk Assessment, Interspecies, Intraspecies and any Traditional UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49 years of age)	NOAEL= 12 mg/kg/day UF = 100 Acute RfD = 0.12 mg/kg/day	Special FQPA SF = 1X aPAD = Acute RfD Special FQPA SF = 0.12 mg/kg/day	**Developmental toxicity study in rats**: LOAEL= 30 mg/kg/day based on increases in skeletal variations.

Table 6 Summary of Toxicological Doses and Endpoints for Metconazole for Use in Human Risk Assessments			
Exposure/ Scenario	**Dose Used in Risk Assessment, Interspecies, Intraspecies and any Traditional UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General population including infants and children)	An appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed.		
Chronic Dietary (All populations)	NOAEL= 4.3 mg/kg/day UF = 100 Chronic RfD = 0.04 mg/kg/day	Special FQPA SF = 1X cPAD = Chronic RfD / Special FQPA SF = 0.04 mg/kg/day	**Chronic oral toxicity study in rats**: LOAEL = 13.1 mg/kg/day based on increased liver (M) weights and associated hepatocellular lipid vacuolation (M) and centrilobular hypertrophy(M). Same effects seen in F at 54 mg/kg/day, plus increased spleen wt.
Cancer (oral, dermal, inhalation)	**Classification: "Not Likely to be Carcinogenic to Humans"**		

Food Quality Protection Act Considerations

FQPA Safety Factor:

There are adequate data in the metconazole database to characterize the potential for pre-natal or post-natal risks to infants and children. Metconazole did not exhibit neurotoxicity in any of the submitted data. The effects seen in the developmental toxicity studies do not indicate that pups are more susceptible: pup effects were only seen in the presence of maternal toxicity and, in general, were of comparable or less severity to the effects observed in adults. Thus, there are no residual uncertainties and the FQPA factor was reduced to 1X.

Exposure Assessments

Risk assessments included dietary exposure (food only) from use of metconazole on imported bananas and dietary exposure (food and water) resulting from the potential use of metconazole on soybeans to control soybean rust. Use of metconazole on soybeans was authorized under Section 18 of FIFRA.

Acute: The acute dietary exposure assessment assumed 100% crop treated and tolerance level residues on bananas (food only) and on soybeans (food and water). A drinking water assessment provided an estimated metconazole concentration of 1.57 ppb which was incorporated directly into the acute dietary assessment. The acute exposure estimate for the only population subgroup

of concern, females ages 13-49, was <1% of the aPAD which is below the Agency's level of concern.

Chronic: The chronic dietary exposure assessment assumed 100% crop treated and tolerance level residues on bananas (food only) and on soybeans (food and water). A drinking water assessment provided an estimated metconazole concentration of 0.4 ppb which was incorporated directly into the chronic dietary assessment. The chronic exposure estimate for the general U.S. population was 2% of the cPAD, and for the most highly exposed population subgroup, children 1-2 years old, the chronic exposure estimate was 5 % of the cPAD which is below the Agency's level of concern.

Cancer**:** The Agency has classified metconazole as "not likely to be carcinogenic to humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range and that carcinogenic effects were seen in animals only at higher doses. A non-genotoxic mode of action for mouse liver tumors was established. Given that metconazole's cancer effects is a threshold effect and that the threshold is well above other chronic effects, the chronic RfD is protective against any cancer risk.

Summary of Data Gaps

1. A confirmatory two-generation reproduction study with the metconazole 85:15 (*cis:trans*) isomer mixture. The two-generation reproduction study submitted for review used the *cis*-only isomer. However, the database for metconazole contains a sufficient number of subchronic and developmental studies with the *cis/trans* isomer mixture to adequately assess *cis/trans* metconazole toxicity and to bridge the data gap.

2. An FDA multiresidue method using metconazole.

3. Three side-by-side crop field trials using an older 200 EC formulation which was used as the test material in some residue trials and will not be marketed and the newer 90 SL formulation which replaces the older formulation.

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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.

APPENDIX I:

GLOSSARY OF TERMS AND ABBREVIATIONS

ADNT	Acute delayed neurotoxicity
a.i.	Active Ingredient
aPAD	Acute Population Adjusted Dose
ARI	Aggregate Risk Index
BCF	Bioconcentration Factor
CAS	Chemical Abstracts Service
ChE	Cholinesterase
ChEI	Cholinesterase inhibition
cPAD	Chronic Population Adjusted Dose
%CT	Percent crop treated
DAT	Days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model - Food Consumption Intake Database
DNA	Deoxyribonucleic acid
DNT	Developmental neurotoxicity
DIT	Developmental immunotoxicity
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
GLC	Gas Liquid Chromatography
GLN	Guideline Number
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal (e.g., mg/kg).
LOAEL	Lowest Observed Adverse Effect Level
LOAEC	Lowest Observed Adverse Effect Concentration
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of quantitation
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number), EPA's system of recording and tracking

	studies submitted
MTD	Maximum tolerated dose
NA	Not Applicable
NOEC	No Observable Effect Concentration
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
NOAEC	No Observed Adverse Effect Concentration
NPDES	National Pollutant Discharge Elimination System
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/ EXAMS	Tier II Surface Water Computer Model
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
TGAI	Technical Grade Active Ingredient
UF	Uncertainty Factor
µg	micrograms
µg/L	Micrograms Per Liter
µL/g	Microliter per gram
USDA	United States Department of Agriculture
WPS	Worker Protection Standard

Appendix II

Data Citations Considered to Support the Import Tolerance for Use of Metconazole on Bananas (Pesticide Petition # 9E5052)

MRID	Citation
44721500	Kureha Chemical Industry Co., Ltd. (1998) Submission of Product Chemistry, Toxicity, and Residue Data in Support of the Petition for Tolerances for Metconazole on Bananas. Transmittal of 22 Studies.
44721501	Kureha Chemical Industry Co., Ltd. (1998) Reduced Risk Pesticide Rationale for Metaconazole: Lab Project Number: CY228. Unpublished study. 117 p.
44721502	Overholt, J. (1998) Metconazole on Bananas: Summary Volume and FQPA Evaluation: Lab Project Number: CY226. Unpublished study prepared by Kureha Chemical Industry Co., Ltd. and Argus International Inc. 436 p.
44721503	Overholt, J.; Searfass, M.; Liu, W. (1998) Metconazole Technical: Product Identity and Composition, Description of Starting Materials, Production and Formulation Processes, and Discussion of Formulation of Impurities: Lab Project Number: CY224. Unpublished study prepared by American Cyanamid Company. 86 p. {OPPTS 830.1550, 830.1600, 830.1620, 830.1650, 830.1670}.
44721504	Ahuja, E.; Yang, H. (1997) Metconazole Technical: Preliminary Analysis, Ceritified Limits, and Enforcement Analytical Method: Lab Project Number: CY209: APBR 670.01: APBR 693. Unpublished study prepared by American Cyanamid Company. 169 p. {OPPTS 830.1700, 830.1750, 830.1800}.
44721505	Kramer, H.; Mangels, G.; Bashir, M. et al. (1998) Metconazole Technical: Physical and Chemical Characteristics: Lab Project Number: CY227: CHW 6123-224: ENV 95-05. Unpublished study prepared by Corning Hazleton, Inc., American Cyanamid Company and Hazleton Wisconsin, Inc. 365 p. {OPPTS 830.6302, 830.6303, 830.6304, 830.6313, 830.7200, 830.7300, 830.7370, 830.7550, 830.7840, 830.7950}.
44721506	Cartin, J.; Overholt, J. (1998) Metconazole (AC 900768): Directions for Use on Bananas: Lab Project Number: CY222. Unpublished study prepared by Kureha Chemical Industry Co., Ltd. 7 p. {OPPTS 860.1200}.
44721507	Kao, L. (1998) CL 900768 (Metconazole): Metabolism of CL 900768 in Banana Under Greenhouse Conditions: Lab Project Number: MET 98-009: MET 98-009.01: 97.105. Unpublished study prepared by American Cyanamid Company and Plant Sciences, Incorporated. 289 p. {OPPTS 860.1300}.
44721508	Khunachak, A.; Sweeney, R. (1998) Independent Laboratory Validation of GC/NP Determinative Method M 2722 for the Determination of CL 354,801 (cis-isomer) and CL 354,802 (trans-isomer) of Metconazole (CL 900,768) Residues in Whole Bananas and Banana Pulp and CL 900768 (Metconazole): Verification of the Extraction Efficiency and Accountability of American Cyanamid Company Method M 2722 Used for the Determination of CL 354801 (cis-isomer) and CL 354802 (trans-isomer) Residues in Whole Banana and Banana Pulp: Lab Project Number: RES 98-080: RES 98-181: CY215.

	Unpublished study prepared by ABC Laboratories, Inc. and American Cyanamid Company. 135 p. {OPPTS 860.1340}.
44721509	Steller, W.; Highman, J. (1998) Metconazole (CL 900768): Characteristics of the cis-isomer (CL 354801) and the trans-isomer (CL 354802) of Metconazole through FDA Multiresidue Methods: Lab Project Number: CY 223. Unpublished study prepared by American Cyanamid Company. 26 p. {OPPTS 860.1360}.
44721510	Khunachak, A.; Sweeney, R. (1998) Freezer Storage Stabilities of CL 354,801 (cis-isomer) and CL 354,802 (trans-isomer) of Metconazole (CL 900,768) Residues in Whole Banana and Banana Pulp: Lab Project Number: RES 98-146. Unpublished study prepared by ABC Laboratories, Inc. 45 p. {OPPTS 860.1380}.
44721511	Kleiner, A.; Garrett, A. (1998) Field Residue Trials with Metconazole on Bananas: Lab Project Number: RES 97-085: RES 97-086: RES 97-087. Unpublished study prepared by ABC Laboratories, Inc. and American Cyanamid Company. 973 p. {OPPTS 860.1500}.
44721512	Gardner, J. (1990) WL 148271: Acute Oral and Dermal Toxicity: Metconazole (in Rats, Mice and Rabbits): Lab Project Number: SBGR. 89.214. Unpublished study prepared by Shell Research Limited. 59 p. {OPPTS 870.1100, 870.1200}.
44721513	Gardner, J. (1991) WL 136184: Acute Oral and Dermal Toxicity in Rat, Skin and Eye Irritancy in Rabbit and Skin Sensitization Potential in Guinea Pig: Lab Project Number: SBGR.91.103. Unpublished study prepared by Sittingbourne Research Centre. 54 p. {OPPTS 870.1100, 870.1200, 870.2400, 870.2500, 870.2600}.
44721514	Lowe, C.; Bradley, D. (1994) Oral LD 50 Study in Albino Rats with AC 382390: Lab Project Number: T-0959: A97-25. Unpublished study prepared by American Cyanamid Company. 18 p. {OPPTS 870.1100}.
44721515	Esdaile, D. (1990) WL 148271 (KNF-S-474m): A 28 Day Feeding Study in Rats: Metconazole: Lab Project Number: SBGR.89.054. Unpublished study prepared by Sittingbourne Research Centre. 281 p. {OPPTS 870.1300}.
44721516	Esdaile, D. (1991) WL 136184: A 28 Day Feeding Study in Rats: Metconazole: Lab Project Number: SBGR.88.013. Unpublished study prepared by Sittingbourne Research Centre. 281 p. {OPPTS 870.3100}.
44721517	Esdaile, D. (1991) KNF-S-474m/WL 148271: A 90 Day Feeding Study in Rats: Metconazole: Lab Project Number: SBGR.89.186. Unpublished study prepared by Sittingbourne Research Centre. 693 p. {OPPTS 870.3100}.
44721518	Fokkema, G. (1992) KNF-S-474c/WL 136184: A 90 Day Feeding Study in Rats: Metconazole: Lab Project Number: SBGR.88.214. Unpublished study prepared by Sittingbourne Research Centre. 598 p. {OPPTS 870.3100}.
44721519	Clay, H. (1991) WL 148271: A 90 Day Oral (Dietary Administration) Toxicity Study in the Mouse: Metconazole: Lab Project Number: 579/25: 6418-579/25. Unpublished study prepared by Hazleton UK. 280 p. {OPPTS 870.3100}.
44721520	Pickersgill, N. (1991) WL 148271: A 28 Day Oral (Dietary Administration) Toxicity Study in the Beagle: Metconazole: Lab Project Number: 579/22: 6303-579/22. Unpublished study prepared by Hazleton UK. 174 p. {OPPTS 870.3150}.

44721521	Pickersgill, N. (1991) WL 148271: A 90 Day Oral (Dietary Administration) Toxicity Study in the Beagle: Metconazole: Lab Project Number: 579/23: 6396-579/23. Unpublished study prepared by Hazleton UK. 256 p. {OPPTS 870.3150}.
44721522	Masters, R. (1991) A Study of the Effect of WL 148271/KNF-S-474m on Pregnancy of the Rat (incorporating pilot and preliminary studies SLL 163/164) and Historical Data for Developmental Toxicity Studies on Sprague-Dawley Rats: Lab Project Number: SLL/163: SLL/164: SLL/165. Unpublished study prepared by Huntingdon Research Centre Ltd. 197 p. {OPPTS 870.3700}.
44721600	Kureha Chemical Industry Co. (1998) Submission of Toxicity Data in Support of the Petition for Tolerance of Metconazole in/on Bananas. Transmittal of 26 Studies.
44721601	Willoughby, C. (1992) WL 136184: Teratology Study in the Rat, Preliminary Teratology Study in the Rat, and Second Preliminary Teratology Study in the Rat: Lab Project Number: 92/0121: 92/0678: 91/1019. Unpublished study prepared by Life Science Research Limited. 244 p. {OPPTS 870.3700}
44721602	Hoberman, A. (1997) A Definitive Oral Developmental Toxicity (Embryo-Fetal Toxicity/Teratogenicity) Study with AC900768 in Rabbits: Lab Project Number: ARGUS 101-027: 971-96-120. Unpublished study prepared by Argus Research Laboratories, Inc. 449 p. {OPPTS 870.3700}
44721603	Masters, R. (1991) A Study of the Effect of WL148271/KNF-S-474m (Technical) on Pregnancy of the Rabbit: Lab Project Number: SLL/162: SLL/179: SLL/167. Unpublished study prepared by Huntingdon Research Centre, Ltd. 242 p. {OPPTS 870.3700}
44721604	Masters, R. (1990) A Preliminary Study of the Effect of Three Isomers of KNF-S-474 on Pregnancy of the Rabbit: Lab Project Number: SLL 178. Unpublished study prepared by Huntingdon Research Centre, Ltd. 100 p. {OPPTS 870.3700}
44721605	Masters, R. (1992) A Study of the Effect of WL 136184/KNF-S-474c on Pregnancy of the Rabbit: Lab Project Number: SLL/91408: SLL/212: SLL/205. Unpublished study prepared by Huntingdon Research Centre, Ltd. 176 p. {OPPTS 870.3700}
44721606	Masters, R. (1992) A Study of the Effect of WL 136184/KNF-S-474c on Pregnancy of the Rabbit: Lab Project Number: SLL 236/920867. Unpublished study prepared by Huntingdon Research Centre, Ltd. 108 p. {OPPTS 870.3700}
44721607	Masters, R. (1991) Dietary Range Finding Studies in Mature Rats and Their Offspring-KNF-S-474 (Technical): Lab Project Number: CY 205: SLL/166: SLL/182. Unpublished study prepared by Huntingdon Research Centre, Ltd. 187 p. {OPPTS 870.8300}
44721608	Willoughby, C. (1993) WL 136184: Reproductive Performance Study in Rats Treated Continuously Through Two Successive Generations: Lab Project Number: 92/0553: 92/SLK012/0553. Unpublished study prepared by Sittingbourne Research Centre. 1097 p.
44721609	Berry, P. (1992) WL 148271: A Two Year Chronic Toxicity Feeding Study in Rats: Lab Project Number: SBGR.91.193. Unpublished study prepared by Sittingbourne Research Centre. 2101 p. {OPPTS 870.4100}
44721610	Clay, H. (1992) WL 148271: 52 Week Oral (Dietary Administration) Toxicity Study in the Beagle: Lab Project Number: 579/24. Unpublished study prepared by Hazleton UK. 314 p.

	{OPPTS 870.4100}
44721611	Berry, P. (1992) WL 148271: A Two Year Oncogenicity Feeding Study in Rats: Lab Project Number: SBGR.91.192. Unpublished study prepared by Sittingbourne Research Centre. 1481 p. {OPPTS.4200}
44721612	Clay, H. (1992) WL 148271: 91 Week Oral (Dietary Administration) Carcinogenicity Study in the Mouse: Lab Project Number: 579/26: 35004D. Unpublished study prepared by Hazleton UK. 1595 p. {OPPTS 870.4200}
44721613	Brooks, T.; Wiggins, D. (1990) Bacterial Mutagenicity Studies WL 148271 (KNF-S-474M): Lab Project Number: SBGR.90.190. Unpublished study prepared by Sittingbourne Research Centre. 48 p. {OPPTS 870.5100}
44721614	Brooks, T.; Wiggins, D. (1991) WL 136184 (KNF-S-474c) Bacterial Mutagenicity Studies: Lab Project Number: SBGR.91.071. Unpublished study prepared by Sittingbourne Research Centre. 47 p. {OPPTS 870.5100}
44721615	Clements, J. (1991) Study to Determine the Ability of WL 136184 (KNF-S-474c) to Induce Mutations at the Thymidine Kinase (tk) Locus in Mouse Lymphoma L5178Y Cells Using a Fluctuation Assay: Lab Project Number: SRS 3/TK: 5144. Unpublished study prepared by Hazleton Microtest. 41 p. {OPPTS 870.5195}
44721616	Brooks, T.; Wiggins, D. (1991) WL148271 (KNF-S-474m) In Vitro Chromosome Studies: Lab Project Number: SBGR.90.290. Unpublished study prepared by Sittingbourne Research Centre. 45 p. {OPPTS 870.5375}
44721617	Brooks, T.; Wiggins, D. (1991) WL136184 (KNF-S-474c) In Vitro Chromosome Studies Using Human Lymphocytes: Lab Project Number: SBGR.91.170. Unpublished study prepared by Sittingbourne Research Centre. 37 p. {OPPTS 870.5375}
44721618	Xu, J. (1995) In Vivo Test for Chemical Induction of Micronucleated Polychromatic Erythrocytes in Mouse Bone Marrow Cells--CL 900,768: Lab Project Number: 0312-1521: TAN 94-055. Unpublished study prepared by SITEK Research Laboratories. 73 p.{OPPTS 870.5395}
44721619	Marshall, R. (1991) Study to Evaluate the Potential of WL136184 (KNF-s-474c) to Induce Micronuclei in the Polychromatic Erythrocytes of CD-1 Mice: Lab Project Number: SRS 3/MNT: 5145. Unpublished study prepared by Hazleton Microtest. 34 p. {OPPTS 870.5395}
44721620	Pant, K. (1995) Test for Chemical Induction of Unscheduled DNA Synthesis in Rat Primary Hepatocytes Obtained from Rats Treated in Vivo--CL 900,768: Lab Project Number: 0312-5220: TAN 94-056. Unpublished study prepared by SITEK Research Laboratories. 65 p. {OPPTS 870.5550}
44721621	Dean, S. (1991) Study to Evaluate the Potential of WL 136184 (KNF-S-474c) to Induce Unscheduled DNA Synthesis in Rat Liver Using In Vivo/In Vitro Procedure: Lab Project Number: SRS 3/ILU: 5146. Unpublished study prepared by Hazleton Microtest. 42 p. {OPPTS 870.5550}
44721622	Richardson, K. (1992) (Cyclopentyl-(carbon-14) WL148271 (KNF-S-474m): The Fate of a Single High Oral Dose of 164 mg per kg in the Fischer 344 Rat: Lab Project Number: SBGR.91.188. Unpublished study prepared by Sittingbourne Research Centre. 150 p.

	{OPPTS 870.7485}
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44721624	Richardson, K. (1991) (Triazole-(carbon-14)) WL136184 (KNF-s-474c): The Isolation and Identification of Metabolites Following a Single Oral Dose (200 mg kg-1) to the Rat: Lab Project Number: SBGR.90.108. Unpublished study prepared by Sittingbourne Research Centre. 185 p. {OPPTS 870.7485}
44721625	Elsom, L. (1991) The Excretion of (carbon 14)-WL 136184 in Bile-Duct Cannulated Rats: Lab Project Number: HRC/SLL 204/91719: SLL/204. Unpublished study prepared by Huntingdon Research Centre Ltd. 34 p. {OPPTS 870.7485}
44721626	Worrell, N. (1991) Study to Investigate the Effects of WL 136184 on Rat and Hepatic Xenobiotic Metabolizing Enzymes: Lab Project Number: 3.0980. Unpublished study prepared by BIBRA Toxicology International. 160 p. {OPPTS 870.7485}
46665400	BASF Corporation (2005) Submission of Product Chemistry, Toxicity, Exposure, Risk and Residue Data in Support of the Petition for Tolerance of Metconazole on Bananas. Transmittal of 7 Studies.
46665401	Akkari, K. (2005) Response to the Request from the French Authorities Concerning Clarification on the Purity and Isomer Ratios for Metconazole Technical. Project Number: 2005/7003402, 20057003402. Unpublished study prepared by BASF Corporation. 5 p.
46665402	Hess, F. (2005) Metaconazole: Hypothesized Non-Linear Mode of Action for Mouse Live Tumors with a Review of the Mechanistic Study: Metconazole: 2-Week Hepatic Drug-Metabolizing Enzyme Induction, Cell Proliferation, and Reactive Oxygen Species Production Study in Mice. Project Number: 2005/7003406. Unpublished study prepared by BASF Corporation. 25 p.
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46665404	Christian, M.; Hess, F. (2005) BASF Document ID #MK-432-012 -- "Expert Report: Effect of Metconazole on Pregnancy of the Rabbit." Dr. Mildred S. Christian. November 26, 1996 (67 Pages): With Preceding Cover Letter (3 Pages). Project Number: 2005/7003347, MK/432/012. Unpublished study prepared by BASF Corporation and Argus Research Laboratories, Inc. 73 p.
46665405	Pelz, S.; Weeren, R. (1999) Metconazole (CL 900768): Validation of DFG Method S 19 for the Determination of Residues on Metconazole (CL 900768) as CIS-(CL 354801) and TRANS-Isomer (CL 354802) in Plant Material, Foodstuff of Animal Origin and Soil. Project Number: MK/240/003, CYA/9907V, AZ/M8995/99. Unpublished study prepared by Dr. Specht and Partner, R-VEE-R Distributing Company and Landesuntersuchungsamt fuer das Gesundheitswesen Nordbayern. 127 p.
46665406	Veit, P.; Weber, S. (2003) Validation of the Analytical Method 536/0: Determination of Triazole, Triazolyl-Alanine and Triazolyl-Acetic Acid in Banana (Pulp, Peel and Fruit).

	Project Number: 141823, 2003/1009779. Unpublished study prepared by BASF Ag Research Station (Basf Aktieng.). 75 p.
46665407	Class, T. (2003) Metconazole (CL 900768): Assessment and Validation of the Multi-Residue Enforcement Method DFG S19 with Modified Extraction (and with SDF Cleanup Method 5 for Fatty/Oily Matrices) for the Determination of Metconazole (CL 900768) in Plant Material (Wheat Grain, Grape, Pea and Oilseed Rape Seed) and in Foodstuff of Animal Origin (Milk, Egg, Bovine Muscle and Fat). Project Number: P/349/G, CFS/1999/127, 2003/7007238. Unpublished study prepared by PTRL Europe Gmbh. 180 p.
46756900	BASF Corporation (2005) Submission of Residue and Toxicity Data in Support of the Petition for Tolerance of Metconazole on Bananas. Transmittal of 2 Studies.
46756901	Akkari, K. (2006) Metconazole: Response to Residue Chemistry Database Scope for Import Tolerance Petition for Bananas: Final Report. Project Number: 2006/7006110. Unpublished study prepared by BASF Corporation and Kureha Chemical Industry Co., Ltd. 66 p.
46756902	Little, E. (1992) WL 136184 (KNF-S-474C): A Study of Absorption and Excretion Following Dermal Application to the Rat. Project Number: 579/93, 6915/579/93, MK/440/008. Unpublished study prepared by Hazleton Uk. 132 p.