UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 27-FEB-2008

SUBJECT: Petition No: 6F7072. Cyproconazole: **Revised** Human-Health Risk Assessment for Proposed Uses on Corn, Soybean and Wheat.

PC Code: 128993
DP No: 349841 Decision No: 367588
Chemical Class: Triazole Fungicide

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NOTE: This document supersedes "Petition No: 6F7072. Cyproconazole: Human-Health Risk Assessment for Proposed Uses on Corn, Soybean and Wheat," M. Clock-Rust, *et al*., D330274, dated 16-NOV-2007. This assessment has been revised to correct inconsistencies in the recommended tolerance levels.

Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, Syngenta has requested registration of the fungicide cyproconazole. The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of cyproconazole in/on corn, soybean and wheat.

A summary of the findings and an assessment of human-health risk resulting from the proposed and registered uses of cyproconazole are provided in this document. The residue chemistry review was provided by George Kramer (RAB1); the dietary exposure assessment was provided by Mohsen Sahafeyan (RAB1); the occupational/residential exposure assessment was provided by Kelly Lowe (RAB1); the hazard assessment and dose-response assessment were provided by William Greear (RAB1), the risk assessment was provided by Mary Clock-Rust (RAB1) and the drinking water assessment was provided by James Hetrick of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Cyproconazole is a broad-spectrum triazole fungicide (Group 3) that is a mixture of two distereoisomers (2RS,3RS:2RS,3SR; ~1:1). Cyproconazole is currently registered to Syngenta Crop Protection for use on greenhouse- and field-grown roses and as a wood preservative. The use on turf is no longer being supported (personal communication with C. Grable, 10/31/07). Aside from a Section 18 Emergency Exemption for use on soybeans, there are currently no food/feed uses for cyproconazole in the U.S. A permanent tolerance is established for the residues of cyproconazole, (2RS,3RS)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol, on imported green coffee beans at 0.1 ppm [40 CFR §180.485(a)], and a temporary tolerance, set to expire on 12/31/09, is established for cyproconazole in/on soybean seed at 0.10 ppm.

The last HED risk assessment for cyproconazole was performed in 2005 (Memo, G. Kramer, D318617, 9/27/2005 on a Section 18 Emergency Exemption for use on soybean.

Proposed Uses
In the current action, Syngenta proposes new food/feed uses of cyproconazole on corn (field and seed), soybeans and wheat. Application rates are 0.036 lb ai/A for application to corn, soybean and wheat at the first signs of disease development. The maximum seasonal use rate is 0.036 lb ai/A for corn and wheat and 0.072 lb ai/A for soybeans, and the specified minimum retreatment intervals (RTIs) are 7 days for corn and 14 days for soybeans and wheat. Based on the proposed uses, dietary and occupational exposures are expected.

Hazard Characterization
Cyproconazole was moderately acutely toxic by the oral, dermal and inhalation routes (Toxicity Category III). It was neither an eye nor dermal irritant (Toxicity Category IV). Cyproconazole did not cause dermal sensitization in the guinea pig.

The critical toxicological effects in mammals appeared to be indicative of hepatotoxicity. These included elevated LDH ((lactic dehydrogenase) and AST (aspartate transaminate), increased liver weight (relative and absolute), vacuolation, fatty changes, hepatocytomegaly, hypertrophy and single-cell necrosis. Adenomas and carcinomas were only observed in mice. Hepatotoxicity was observed in rats, mice and dogs; all of these species appeared to be equally sensitive to cyproconazole toxicity. The chemical has been classified by The Cancer Peer Review Committee as "Not Likely to be Carcinogenic to Humans," based on the weight of evidence that supports a non-genotoxic mitogenic mode of action for cyproconazole. Except for the one of three *in vitro* chromosomal-aberration assays, cyproconazole exhibited a negative response in all other genotoxicity screening assays. Thus, it appears that cyproconazole is not genotoxic.

Cyproconazole is a developmental toxicant. Rabbits appeared to be more sensitive for developmental effects than the rat. Cyproconazole produced increased incidences of malformed fetuses (hydrocephale and kidney agenesis) and litters with malformed fetuses at doses lower than the doses that produced maternal toxicity in rabbits. Cyproconazole increased the incidences of supernumerary ribs in offspring in rats at the same doses at which maternal adverse effects were observed. There was no evidence of reproductive toxicity in the 2-generation

reproduction toxicity study. The maternal toxicity in a 2-generation reproduction study was manifested as fatty changes and increased lipid storage in the liver. No offspring toxicity was observed at any doses tested in the 2-generation reproduction study.

The dermal-penetration study indicated that for cyproconazole, the percent absorbed increased with duration of exposure and decreased with dose. The quantity absorbed increased with dose and duration of exposure. At the 10-hour exposure time point, 10.81% of the low dose was absorbed. For risk assessment, since an oral study was selected for the short- and intermediate-term dermal exposure assessment, an 11% dermal-absorption factor was applied.

Food Quality Protection Act (FQPA)
The cyproconazole risk assessment team evaluated the quality of the hazard and exposure data and determined that based on the hazard and exposure data, the FQPA safety factor (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.

Dose-Response Assessment
The acute dietary endpoint for child-bearing females (females 13+years old) was based on the developmental toxicity in New Zealand white rabbits; the lowest-adverse effect level (LOAEL) = 10 mg/kg/day. The no-observed adverse effect level (NOAEL) is 2 mg/kg/day. An uncertainty factor (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 acute reference dose (aRfD). The FQPA safety factor of 1X is applicable for acute dietary risk assessment. Therefore, the acute population-adjusted dose (aPAD) is 0.02 mg/kg/day. In a recent section 18 risk assessment (D318617, dated 8/27/05), the acute dietary endpoint for child-bearing females (females 13+years old) was based on the developmental toxicity study in Chinchilla rabbits; the lowest-adverse effect level (LOAEL) = 2.0 mg/kg/day. In this study, the no-observed adverse effect level (NOAEL) was not established. The FQPA SF of 3X was applied for the use of LOAEL instead of the NOAEL. Up on detailed review of the cyproconazole toxicological database for this action, RAB1 toxicologists concluded that the developmental toxicity in New Zealand white rabbits is more appropriate for this exposure scenario (details provided under section 3.3.5.1 Determination of Susceptibility).

The 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.

The chronic RfD (cRfD) of 0.01 mg/kg/day was determined on the basis of the chronic oral-toxicity study in dogs. The LOAEL of 3.2 mg/kg/day is based on liver effects manifested as increased in liver weights (absolute and relative) , elevated alkaline phosphatase and ALT levels (males), decreased total protein, albumin and cholesterol levels. This study provided the lowest NOAEL (1.0 mg/kg/day) in the database (most sensitive endpoint) and 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 1 mg/kg/day to derive the cRfD. Therefore, the chronic population-adjusted dose (cPAD) is 0.01 mg/kg/day.

Endpoints for short- and intermediate-term incidental oral risk assessment are based on the 90-

day oral rat study with a LOAEL of 27.3 mg/kg/day based on decreased body-weight gain in males and increased liver weight in females (NOAEL 1.5 mg/kg/day).

Endpoints for short and intermediate-term dermal and inhalation risk assessments were based on the developmental toxicity study in New Zealand white rabbits with a LOAEL of 10 mg/kg/day. The NOAEL is 2 mg/kg/day.

Endpoints for long-term dermal and inhalation risk assessments are based on the chronic oral toxicity study in dogs with a LOAEL of 3.2 mg/kg/day based on liver effects (NOAEL = 1.0 mg/kg/day). The endpoint is appropriate for the duration of exposure.
Since oral studies were selected for the dermal-exposure assessment, a dermal-penetration factor of 11% (based on a dermal-penetration study in rats) should be used. Since oral NOAELs were selected for the inhalation-exposure assessment, an inhalation-absorption factor of 100% oral equivalent should be used.

HED's level of concern (LOC) for cyproconazole occupational and residential dermal and inhalation exposures is 100 [i.e., a margin of exposure (MOE) greater than 100 is not of concern to HED]. The LOC is based on a 10X uncertainty factor (UF) to account for interspecies extrapolation to humans from the animal test species and 10X UF to account for intra-species sensitivity.

Environmental Fate and Drinking Water Assessment
Although cyproconazole is a triazole fungicide, laboratory environmental fate studies do not show formation of 1,2,4-triazole and triazole conjugates [i.e., triazole alanine (TA) and triazole acetic acid (TAA)] in soil or aquatic environments. Therefore, the drinking water assessment was conducted for the parent compound.

The drinking water assessment for parent cyproconazole is based on Tier I modeling. Tier I FQPA Index Reservoir Screening Tool (FIRST) modeling indicate percent crop area corrected (PCA-corrected) cyproconazole concentrations in surface source drinking water are not expected to exceed 1.14 µg/L for the annual peak concentration and 0.11 µg/L for the annual average concentration. Tier I Screening Concentration In Ground Water (SCI-GROW) modeling indicates the peak and average cyproconazole concentration in shallow groundwater is not expected to exceed 0.05 µg/L. These estimates were used in the dietary risk analysis.

Dietary Risk
Tier I acute and chronic aggregate (food + water) dietary risk assessments to support Section 3 registration of cyproconazole on soybean, wheat and corn were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, ver. 2.03) model and assumed tolerance-level residues, 100% crop treated (CT), and DEEM™ default processing factors. Drinking water was included in the dietary assessments. The resulting acute and chronic aggregate exposure estimates were not of concern to HED; therefore, acute and chronic dietary risks are not of concern to HED. An acute dietary exposure analysis was conducted only for females 13-49 years old since an endpoint of concern attributable to a single dose for general population was not identified. The acute food exposure risk estimate for female 13-49 years old was 3% aPAD at the 95th percentile of the exposure distribution. The highest chronic food exposure estimate was for children 1-2 years old at 13%

of the cPAD. A chronic cancer dietary assessment was not conducted since it was determined that cyproconazole is not likely to be a human carcinogen.

Residential Risk
All residential uses of cyproconazole have been withdrawn and are no longer being supported. Therefore, residential risk assessments were not performed.

Aggregate Risk
Acute and chronic aggregate risks were assessed based on dietary exposure from food and drinking water sources. Since there are no residential uses, short- and intermediate-term aggregate risks were not assessed. Cancer aggregate risk was not assessed since a cancer risk assessment is not needed.

Acute aggregate risk is made up of food and water exposure and is the same as reported for acute dietary exposure for females 13-49 years old. The risk estimate was 3% aPAD at the 95th percentile of the exposure distribution, and is not of concern to HED.

Chronic aggregate risk is made up of food and water exposure and is the same as reported for chronic dietary exposure (<100% cPAD for U.S. general population and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 13% cPAD). Therefore, the chronic aggregate risk to cyproconazole is not of concern to HED.

HED has also determined that 1,2,4-triazole, triazole alanine (TA) and triazole acetic acid (TAA) are also potential residues of concern in plants and livestock for all triazole fungicides. However, these triazole-related residues will not be regulated for specific triazole pesticides, but will be evaluated for the entire class of triazole compounds. HED has recently completed a comprehensive risk assessments considering 1,2,4-triazole and TA + TAA based on established and proposed uses of triazole fungicides. These risk assessments were last updated in October 2007 (DP#: 341803 and DP#: 344298, M. Sahafeyan, 10/30/07; note: separate memorandums). Along with other uses, these risk assessments considered the use of cyproconazole on soybeans and the use of related triazole fungicides on wheat and corn. Triazole-related residues from the application of cyproconazole to the subject crops will not be sufficiently different from those used in the in the previous risk assessment. Therefore, a separate risk assessment for these triazole-related residues will not be required for the current petition.

Occupational Handler Risk
Based on the proposed uses in corn, wheat and soybean crops, handlers may be potentially exposed to cyproconazole. Handlers include mixer/loaders who handle concentrated liquid cyproconazole and applicators using aerial or groundboom equipment, and flaggers for aerial applications. Based upon the proposed use pattern, HED expects the *most highly* exposed occupational pesticide handlers are likely to be mixer/loaders handling liquids for aerial applications and applicators applying sprays using aerial equipment.

Short- and intermediate-term dermal and inhalation risks were assessed for the two representative exposure scenarios at baseline, and with additional personal protective equipment (PPE). Chemical-specific data were not available, so surrogate data from the Pesticide Handlers

Exposure Database (PHED) were used. The combined dermal and inhalation exposure risks for mixer/loaders are not of concern (i.e., MOEs>100), **provided the mixer/loaders wear protective gloves as directed on the label.** For aerial applicators, risks were assessed using the engineering controls (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); pilots are not required to wear protective gloves. With this level of protection, there are no risks of concern for applicators.

Occupational Post-application Risk
Following cyproconazole application to corn, wheat and soybean, occupational exposure is possible. Post-application activities may include scouting, maneuvering irrigation equipment, hand weeding and hand harvesting. HED assessed short-term post-application dermal risk for workers using dermal transfer coefficients (TCs) from the Science Advisory Council for Exposure (ExpoSAC) Policy Number 3.1: Agricultural TCs, August 2000. Risks are not of concern (i.e., MOE>100) on day 0 (restricted-entry interval (REI) = 12 hours) for all of the exposure activities.

Regulatory Recommendations and Residue Chemistry Deficiencies
Provided the petitioner submits revised Sections B and F and independent laboratory validations (ILVs) of the high-performance liquid chromatography/mass spectrometry (HPLC/MS) method for metabolite M14 in liver and the HPLC/UV method for M36 in milk, HED concludes that the residue chemistry database is sufficient for conditional registration and establishment of permanent tolerances for free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] in or on the following commodities:

Aspirated Grain Fractions	2.5
Corn, field, forage	0.60
Corn, field, grain	0.01
Corn, field, stover	1.2
Soybean, seed	0.05
Soybean, forage	1.0
Soybean hay	3.0
Soybean, oil	0.10
Wheat, forage	0.80
Wheat, hay	1.3
Wheat, straw	0.90
Wheat, grain	0.05
Wheat, grain, milled byproducts	0.10
Fat of cattle, goat, horse and sheep	0.01
Meat byproducts (except liver) of cattle, goat, horse and sheep	0.01

Additionally, HED has determined that a tolerance is required for the combined free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] and its metabolite M36 [δ-(4-chlorophenyl)-β,δ-dihydroxy-γ-methyl-1H-1,2,4-triazole-1-hexenoic acid] in or on the following commodity:

Milk	0.02

and that tolerances are required for the combined free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] and its metabolite M14 [2-(4-chlorophenyl)-3-cyclopropyl-1-[1,2,4]triazol-1-yl-butane-2,3-diol] in or on the following commodities:

Liver of cattle, goat, horse, and sheep	0.50
Hog liver	0.01

Registration of these tolerances should be made conditionally until the remaining residue chemistry deficiencies described in Section 9.0 are satisfied.

Note to RD: The preferred chemical name for cyproconazole is "α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol." 40 CFR §180.485(a) should be revised to use this terminology. Also, the time-limited tolerance established for soybean seed under 40 CFR §180.485(b) should be deleted once a tolerance is established in section (a).

2.0 Ingredient Profile

Cyproconazole is a broad-spectrum triazole fungicide (Group 3) that is a mixture of two distereoisomers (2RS,3RS:2RS,3SR; ~1:1). Cyproconazole acts by inhibiting sterol biosynthesis in fungi. It is effective for the control of several plant diseases, such as yellow Sigatoka (*Mycosphaerella musicola*) and black Sigatoka (*Mycosphaerella fijiensis* var. *difformis*) in bananas, early leaf spot (*Cercospora arachidicola*) and stem rot (*Sclerotitum rolfsii*) in peanuts, and rust (*Puccinia spp.*) and powdery mildew (*Erysiphe spp.*) in wheat and soybean.

Cyproconazole is currently registered to Syngenta Crop Protection for use on greenhouse- and field-grown roses, and as a wood preservative. The wood preservative products are labeled for industrial and commercial use only. The use on turf is no longer being supported. Aside from a Section 18 Emergency Exemption for use on soybeans, there are currently no food/feed uses for cyproconazole in the U.S. A permanent tolerance is established for the residues of cyproconazole, (2RS,3RS)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol, on imported green coffee beans at 0.1 ppm [40 CFR §180.485(a)], and a temporary tolerance, set to expire on 12/31/09, is established for cyproconazole in/on soybean seed at 0.10 ppm.

2.1 Cyproconazole Structure and Nomenclature

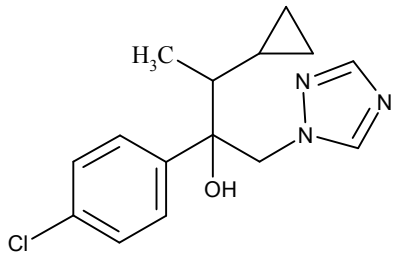
Table 2.1a. Cyproconazole Nomenclature.	
Chemical structure	
Common name	Cyproconazole
Company experimental name	SAN619
IUPAC name	(2RS,3RS)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol
CAS name	α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol
CAS registry number	94361-06-5
End-use products (EP)	0.67 lb/gal SC (Quadris Xtra™ Fungicide, EPA Reg. No 100-1225) 0.83 lb/gal SC/L (Alto® 100SL Fungicide; EPA Reg. No. 100-1226)

TABLE 2.1b. Physicochemical Properties of Cyproconazole.			
Parameter	Value		Reference
Melting range	99-106°C		D179678, R. Lascola, 9/24/91
pH at 22ºC	6.7 ± 0.2		
Bulk Density at 20ºC	0.5 ± 0.1 g/mL		
Water solubility at 25ºC	108 mg/L at pH 4.1 93 mg/L at pH 7 109 mg/L at pH 10		MRID 46840803
Solvent solubility (g/100 mL at 25°C)	n-Hexane Diisopropyl ether Toluene Xylene Acetone	0.2 2.2 10.9 11.2 >20	D179678, R. Lascola, 9/24/91
Vapor pressure at 25ºC	2.6 x 10^{-5} Pa		MRID 46840803
Dissociation constant, pK_a	Compound does not dissociate		D179678, R. Lascola, 9/24/91
Octanol/water partition coefficient, $Log(K_{OW})$	2.91 ± 0.12		
UV/visible absorption spectrum	Not reported		

2.2 Summary of Proposed and Registered Uses

Cyproconazole is currently registered to Syngenta Crop Protection for use on greenhouse- and field-grown roses and as a wood preservative. All cyproconazole uses are commercial or industrial in nature; there are no residential uses. The use on turf is no longer supported (personal communication with C. Grable, 10/31/07).

In the current petition, Syngenta proposes new food/feed uses for two formulations of cyproconazole on corn (field and seed), soybeans and wheat. One formulation is a 0.83 lb/gal soluble concentrate/liquid (SC/L; Alto® 100SL Fungicide; EPA Reg. No. 100-1226). The second formulation is a 0.67 lb/gal SC (Quadris Xtra™ Fungicide, EPA Reg. No 100-1225); this

product is a multiple-active-ingredient (MAI) formulation, which also contains 1.67 lb/gal of azoxystrobin. The current review pertains to issues related to cyproconazole only. Syngenta is proposing to use these formulations for broadcast foliar applications at up to 0.036 lb ai/A/application to corn, soybean and wheat at the first signs of disease development. The maximum seasonal use rate is 0.036 lb ai/A for corn and wheat and 0.072 lb ai/A for soybeans, and the specified minimum retreatment intervals (RTIs) are 7 days for corn and 14 days for soybeans and wheat.

Aside from a Section 18 Emergency Exemption for use on soybeans, there are currently no food/feed uses for cyproconazole in the U.S.

Table 2.2 summarizes the proposed use pattern and formulations specified in the end-use products containing cyproconazole.

Table 2.2. Summary of Directions for Use of Cyproconazole.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations[1]
Wheat/Triticale						
Broadcast foliar application(s) at Feekes Stage 5-10.5 using ground, air or chemigation equipment	0.83 lb/gal SC/L [100-1226] 0.67 lb/gal SC [100-1225][2]	0.036	2	0.036	30 - grain 21 - forage/ hay	The minimum RTI is 14 days.
Field or Seed Corn						
Broadcast foliar application at first sign of disease using ground, air or chemigation equipment	0.83 lb/gal SC/L [100-1226] 0.67 lb/gal SC [100-1225][2]	0.036	2	0.036	30 - grain 21 - silage	The minimum RTI is 7 days.
Soybean						
Broadcast foliar application prior to disease using ground, air or chemigation equipment	0.83 lb/gal SC/L [100-1226] 0.67 lb/gal SC [100-1225][2]	0.036	2	0.072	30 - seed	The minimum RTI is 14 days. Do not graze forage within 14 days of application.

[1] Both labels specify the following rotational crop restrictions: no PBI for corn, soybean and wheat; a 60-day PBI for leafy vegetables and cereal grains other than wheat; and a 365-day PBI for all other crops.

[2] This MAI formulation also contains azoxystrobin at 1.67 lb/gal.

3.0 Hazard Assessment

References:

Memo, P. Terse, TXR 0053768, 11/17/2005.

Toxicology Endpoint Selection Document, L. Taylor *et. Al.,* HED Doc. No. 013148, 06/18/1997.

Cyproconazole was moderately acutely toxic by the oral, dermal and inhalation routes (Toxicity Category III). It was neither an eye nor dermal irritant (Toxicity Category IV). Cyproconazole

did not cause dermal sensitization in the guinea pig.

The critical toxicological effects in mammals appeared to be indicative of hepatotoxicity. These included elevated LDH and AST, increased liver weight (relative and absolute), vacuolation, fatty changes, hepatocytomegaly, hypertrophy and single cell necrosis. Adenomas and carcinomas were only observed in mice. Hepatotoxicity was observed in rats, mice and dogs; all of these species appeared to be equally sensitive to cyproconazole toxicity. The chemical has been classified by The Cancer Peer Review Committee as "Not Likely to be Carcinogenic to Humans", based on the weight of evidence that supports a non-genotoxic mitogenic mode of action for cyproconazole. Except for one of three *in vitro* chromosomal-aberration assays, cyproconazole exhibited a negative response in all other genotoxicity screening assays. Thus, it appears that cyproconazole is not genotoxic.

The chemical is a developmental toxicant. Rabbits appeared to be more sensitive for developmental effects than the rat. Cyproconazole produced increased incidences of malformed fetuses and litters with malformed fetuses (hydrocephale and kidney agenesis) at doses lower than the doses that produced maternal toxicity in rabbit. Cyproconazole increased the incidences of supernumerary ribs in rats at the same doses at which maternal adverse effects were observed. There was no evidence of reproductive toxicity in the 2-generation reproduction toxicity study. The maternal toxicity in a 2-generation reproduction study was manifested as fatty changes and increased lipid storage in the liver. No offspring toxicity was observed at any doses tested in the 2-generation reproduction study.

The dermal-penetration study indicated that for cyproconazole, the percent absorbed increased with duration of exposure and decreased with dose. The quantity absorbed increased with dose and duration of exposure. At the 10-hour exposure time point, 11% of the low dose was absorbed.

3.1 Hazard and Dose-Response Assessment

3.2 Absorption, Distribution, Metabolism and Excretion in Rats

Cyproconazole was almost completely absorbed in males (84%) and females (100%). The majority of the total administered dose (96.5%) was recovered in the feces (56.3%) and urine (40.2%). It is extensively metabolized; diastereomers A & B of parent + 13 metabolites were identified and isolated; 35 metabolites were detected; metabolic profiles for urine, feces and bile were similar; major metabolic reactions include oxidative elimination of triazole ring; hydroxylation of the C bearing CH_3 group; oxidation of CH_3 group to carbinol and further oxidation to carboxylic acid; rapid excretion occurred with the majority of the total administered dose appearing in feces (biliary excretion). Three days after final dosing, radioactivity was almost completely excreted. The calculated half-life for the depletion of radioactivity (assuming mono-phasic first-order kinetics) from the tissues ranged from one to three days. The greater persistence and longer half-life of radioactivity in blood compared to plasma indicated some partitioning of radioactivity into the red blood cells. The highest concentrations of radioactivity were observed in the liver (1.37 ppm cyproconazole equivalents), adrenals (0.93 ppm), lungs (0.56 ppm), fat (0.49 ppm), kidneys (0.25 ppm), pancreas, (0.22 ppm), and ovaries (0.16 ppm) seven days after the start of dosing. The results also indicated a potential for accumulation in the

liver during long-term studies.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for cyproconazole is adequate. The following acceptable studies are available:

One developmental toxicity study in rats
Two developmental toxicity studies in rabbits
One 2-generation reproduction study in rats

3.3.2 Evidence of Neurotoxicity

There is not a concern for neurotoxicity resulting from exposure to cyproconazole. Acute and subchronic neurotoxicity studies were not performed. Based on the available data (clinical signs and neuropathology) from multiple studies, the chemical is not considered to be neurotoxic.

3.3.3 Developmental Toxicity Studies

3.3.3.1 Developmental Toxicity Study in the New Zealand White Rabbit

In a developmental toxicity study (MRID 42175401), cyproconazole (95% a.i. Batch # 8507)) was administered to pregnant New Zealand White rabbits (18/dose) in 1% aqueous methyl cellulose by gavage at dose levels of 0, 2, 10, or 50 mg/kg bw/day from days 6 through 18 of gestation.

Maternal toxicity as indicated by decreased body weight gain and food consumption was observed at the high dose level. The pregnancy rate was 88.9% in the control, low-, and mid-dose groups and 77.8% in the high dose group. The number of litters with viable young was 16, 11, 14, and 10 for the control, low , mid , and high dose groups, respectively. There was no effect noted on the numbers of implants or live fetuses per doe, on the number of resorptions or fetal deaths, and overall mean fetal weight and mean fetal weight/sex were comparable among the groups. Pre- and post-implantation losses were comparable among the groups.

There was an increased incidence of total external/visceral or skeletal malformations at the high dose level, which was statistically significant when compared to the concurrent control group. The incidence in external/visceral and skeletal variations was increased in a dose-related manner in some instances. It is concluded that the highest dose level resulted in a slight increase in the incidence of several malformations and variations. This is based on the facts that (1) several of the malformations were not observed in either the concurrent control or historical control data; (2) each of these malformations occurred in more than one fetus and in more than one litter; (3) the malformation, malrotated hindlimbs, was also observed at the mid-dose but at a lower incidence than in the high dose group (dose-related); (4) of the twenty three skeletal malformations observed in the study, all but 4 were observed only at the high dose level [one

control fetus had one malformation, one mid-dose fetus displayed 3 malformations, and one additional mid dose fetus displayed 1 malformation (2 different litters)]; and (5) the mid and high dose fetuses displayed more malformations/variations per fetus than the low-dose, concurrent, and historical control groups. Also to be considered are the facts that (1) the high-dose had the highest number of non-pregnant does and, were these does to have been pregnant, the number of fetal findings might have been greater for this group; and (2) both the mid- and high dose groups had fewer fetuses/litter than the low-dose and control groups [5.O and 5.5 vs 6.9 and 6.4, respectively).

The maternal NOAEL was 10 mg/kg, the LOAEL was 50 mg/kg, based on decreased body-weight gains and food consumption.

The developmental toxicity NOAEL was 2 mg/kg, the LOAEL was 10 mg/kg, based on the increased incidence of malformed fetuses and litters with malformed fetuses.

This developmental toxicity study is classified acceptable/Guideline and satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

3.3.3.2 Developmental Toxicity Study in the Chinchilla Rabbit

In a developmental toxicity study (MRID 40607720), SAN 619F (95.6 % a.i. Lot # 8507)) was administered to pregnant Chinchilla rabbits (16/group) in 4% aqueous methyl cellulose by gavage at dose levels of 0, 2, 10, or 50 mg/kg bw/day from days 6 through 18 of gestation.

Evidence of maternal toxicity included reduced body weight gain (-26%) during treatment and decreased food consumption during the initial phase of treatment, both at 50 mg/kg. However, corrected body weight changes between groups were comparable indicating maternal changes in body weight gain could be due to increased resorptions.

Developmental toxicity, observed at 50 mg/kg, was evident from the decreased number of live fetuses/dam and an increased incidence of non-ossification in certain forelimb and hindlimb digits. Evidence of Developmental toxicity at dosages of 10 and 50 mg/kg was indicated by an increased incidence of embryonic and fetal resorptions.

Evidence of developmental toxicity included hydrocephalus internus, observed in 1 fetus at each dosage level, and agenesia of the left kidney and ureter in 1 high-dose fetus. The incidence of hydrocephalus internus was 0.85, 0.83 and 0.93 for the low-, mid- and high-dose fetuses and 0.08 for the historical control incidence. Hydrocephaly was also seen at 2 dosage levels in a developmental toxicity study in rats with this test material, however, this anomaly did not occur in the concurrent controls of either study. In the another developmental toxicity study in New Zealand White rabbits, Hydrocephaly was not seen.

The maternal NOAEL was 10 mg/kg, the LOAEL was 50 mg/kg, based on decreased body-weight gains and food consumption.

Developmental toxicity NOAEL was not attained; Developmental LOAEL was 2 mg/kg, based

on incidence of hydrocephalus internus.

This developmental toxicity study is classified Unacceptable/Guideline and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit because: 1) a NOAEL for developmental toxicity apparently was not attained and 2) the concentrations of test material were not within the acceptable range (± 15% of nominal concentration) for the mid- and high dose suspensions immediately after preparation.

3.3.3.3 Developmental Toxicity Study in Rats

In a developmental toxicity study (MRID 40607721), SAN 619F (95% a.i. Lot # 8507)) was administered to pregnant Wistar/Han rats (25/dose) in 4% aqueous methyl cellulose by gavage at dose levels of 0, 6, 12, 24 or 48 mg/kg bw/day from days 6 through 15 of gestation.

Evidence of maternal toxicity included inhibited body weight gain (11.4%) during treatment at dosage levels of 12 mg/kg and above and decreased body weight and food consumption among females in the 24 and 48 mg/kg dosage groups. These differences in maternal body weights could have been influenced by treatment-related intrauterine effects (e.g., increased number of resorptions, decreased fetal weight). Evidence of fetal toxicity was apparent from observed dose-related increases in the number of litters with supernumerary ribs at dosages 12 mg/kg and above. Developmental toxicity was apparent at 24 and 48 mg/kg from the following observations: decreased total number of fetuses/dam, decreased number of live fetuses/dam, increased percentage and number of fetal resorptions, decreased body weight and incomplete ossification in phalangeal nuclei and the absence of ossification in calcanea. There was evidence of developmental toxicity in the 24 and 48 mg/kg groups. Hydrocephaly was observed in 1 fetus in the 24 mg/kg and 2 fetuses in the 48 mg/kg groups. Cleft palate was observed in 2 fetuses in the 48 mg/kg group.

The maternal NOAEL was 6 mg/kg, the LOAEL at 12 mg/kg based on decreased body weight gain during treatment. The developmental toxicity NOAEL was 6 mg/kg, the LOAEL at 12 mg/kg based on increased incidence of supernumerary ribs.

This developmental toxicity study is classified acceptable/Guideline and satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

3.3.4 Reproductive Toxicity

In a 2-generation reproduction study (MRID 40607723) cyproconazole (purity, 95.6% a.i.; lot # 8507) was administered to groups of 26/sex KFM-Wistar albino rats/dose, in the diet, at concentrations of 0, 4, 20, or 120 ppm (F0, M/F: 0, 0.28/0.33, 1.39/1.67, 8.29/9.88 mg/kg/day, respectively) during the pre-mating (10 wks and 12 wks, for the F0 and F1 generation, respectively), mating, pregnancy and lactation periods.

Two of the reproductive parameters investigated in parental animals were affected by treatment in F0 animals only: the duration of gestation at the mid- and high doses was increased and a lower number of implantation sites was seen in high-dose females, both in comparison to

respective concurrent control values. However, the HED/Peer Review committee (TXR # 0053466, Nov 15, 1993) concluded that the effects noted (increased gestation length and litter size) were not treatment related. Evidence of liver toxicity was seen in high dose F0 males (increased lipid storage and relative weight) and females (increased relative weight).

Parameters examined among the offspring which showed treatment-related effects included decreased litter sizes in both the F1 and F2 high-dose groups and the F1 mid-dose group during the early phase of lactation (litters were standardized at day 4 post partum), decreased live birth index in the high-dose F1 offspring and decreased viability index in the high-dose F1 and F2 offspring. However, the HED/Peer Review committee (TXR # 0053466, Nov 15, 1993) concluded that the effects noted (litter size) were not treatment related.

The parental LOAEL for the systemic toxicity is 120 ppm (8.29 mg/kg/day), based on liver effects ((increased lipid storage and relative weight). The parental NOAEL for systemic toxicity is 20 ppm (1.39 mg/kg/day).

The offspring toxicity NOAEL is > 120 ppm (8.29 mg/kg/day), LOAEL is not established.

The reproductive toxicity NOAEL is > 120 ppm (8.29 mg/kg/day), LOAEL is not established.

This study is classified Acceptable/Guideline and satisfies the guideline requirement (It was noted that although dose levels were not adequate, study need not be repeated since similar effects (increased resorptions, decreased litter size) were observed in the rat developmental study at dose levels of 24 and 48 mg/kg and a NOAEL for these effects was established in that study.

3.3.5 Pre- and Post-Natal Toxicity

3.3.5.1 Determination of Susceptibility

There is no quantitative or qualitative evidence of increased susceptibility of rats fetuses to cyproconazole in utero exposure in developmental toxicity study in rats. There is no quantitative or qualitative evidence of increased susceptibility of rats fetuses following pre/post-natal exposure to cyproconazole in a 2-generation reproduction study in rats. In the developmental toxicity study in rats, maternal (decreased body weight gain) and fetal toxicity (increased incidence of supernumerary ribs) was observed at the same dose (NOAEL=6 mg/kg/day. In this study, hydrocephaly was observed in 1 fetus in the 24 mg/kg and 2 fetuses in the 48 mg/kg groups. Cleft palate was observed in 2 fetuses in the 48 mg/kg group. In the 2-generation reproduction study in rats, no offspring toxicity was observed including highest dose tested and in the presence of maternal toxicity. Therefore, it is concluded that there is no evidence of increased susceptibility of rats fetuses to pre/post natal exposure to cyproconazole.

There is evidence of increased susceptibility for cyproconazole from *in utero* exposure in rabbits. Cyproconazole produced developmental toxicity at doses lower than the doses that produced maternal toxicity in two developmental toxicity studies in rabbits.

Cyproconazole was evaluated by the HED Developmental and Reproductive Toxicity Peer Review Committee on July 21, 1993. The deliberations of the Committee are detailed in the memorandum dated November 15, 1993. The Committee concluded that developmental toxicity was induced following cyproconazole exposure in rats and rabbits by the oral route and established the NOAELs and LOAELs (as discussed above). Hydrocephalus and cleft palate were observed in the rat study at higher doses (24 and 48 mg/kg/day) than the dose that produced marginal maternal toxicity. (12 mg/kg/day). These findings were not observed in the concurrent control animals. The incidence of these observations in the treated animals exceeded the values reported in the historical control data. There is a well defined NOAEL for the developmental toxicity of cyproconazole in the rat of 6 mg/kg/day.

Hydrocephalus was also observed in the cyproconazole Chinchilla rabbit developmental toxicity study in one fetus of each treatment group (not including control). The incidence was 0.85, 0.83, and 0.93% for the low, mid, and high dose fetuses and 0.09% for the historical control. While the hydrocephaly does appear to be treatment related, a dose response relationship does not exist for this finding. Therefore, in the Chinchilla rabbit developmental toxicity study a NOAEL was not achieved. The LOAEL is < 2.0 mg/kg/day. The available hazard database for the other triazole fungicides does not identify hydrocephaly as a developmental outcome or concern.

When side by side comparison of the developmental toxicity studies was performed, it was noted that hydrocephaly was seen in the rat and the Chinchilla rabbit study when 4% CMC was used as the vehicle. However, when 1% CMC was used as the vehicle in the NZW rabbit study hydrocephaly was not observed. The influence of CMC concentration in the induction of hydrocephaly in these studies is unknown.

The cyproconazole hazard database contains a second developmental toxicity study conducted in New Zealand White rabbits which is the preferred strain. In the second study, the exact same doses were evaluated (i.e., 0, 2, 10, or 50 mg/kg/day) and hydrocephaly was not observed. However, the New Zealand White rabbits treated with cyproconazole did exhibit an increased incidence of malformed fetuses and litters with malformed fetuses. Malrotated hindlimbs were observed at the mid and high dose levels in the main study, and at the high dose in the range-finding study. This malformation was not observed in the concurrent or relevant historical control data. The New Zealand White rabbit study does have a well defined NOAEL of 2 mg/kg/day for developmental toxicity.

3.3.5.2 Degree of Concern

There is no evidence of increased susceptibility in the developmental study in rats or in the two-generation reproduction study in rat. There is no concern for the increased susceptibility in the NZW rabbit study since clear NOAELs/LOAELs were established for maternal and developmental toxicities and malformations were observed at a doses higher than the dose that produced marginal maternal toxicity. The concern is low for the increased susceptibility in the Chinchilla rabbit study since the incidences of hydrocephaly were low, there was no dose response, high concentration of the vehicle (CMC) used, and the hydrocephaly was not seen at

the same doses in the New Zealand White strain of rabbit. Therefore, there is no residual uncertainty for pre- and/or post natal toxicity.

3.3.6 Recommendation for a Developmental Neurotoxicity Toxicity (DNT) Study

Acute and subchronic neurotoxicity studies were not performed for cyproconazole. The liver appears to be the primary target organ for cyproconazole. Based on the available data (clinical signs and neuropathology) from multiple studies, the chemical is not considered to be neurotoxic. However, cyproconazole produced hydrocephaly in one fetus in each treatment group in the Chinchilla rabbit developmental toxicity study [the finding was observed in one fetus at 2 mg/kg/day (lowest dose tested, LDT)]. Cyproconazole did not produce hydrocephaly in the NZW rabbit. Hydrocephaly was observed in the cyproconazole rat developmental toxicity study at 24 and 48 mg/kg/day. In the rat developmental toxicity study, there was a well defined NOAEL of 6 mg/kg/day for hydrocephaly. Therefore, the Chinchilla rabbit appears to be the most sensitive species/strain.

Because the doses are well characterized at which hydrocephaly was observed in the developmental toxicity study in the rat, a developmental neurotoxicity study in this species will not provide additional toxicological data. Although hydrocephaly was also observed in the chinchilla at lower doses than in the rat, DNT studies are performed only in the rat. Therefore, a DNT study is not required for cyproconazole.

3.4 FQPA Safety Factor

The cyproconazole risk assessment team evaluated the quality of the hazard and exposure data and determined that based on the hazard and exposure data, the 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:

- The acute dietary food exposure assessment utilizes proposed tolerance-level residues and 100% CT information for all commodities. The chronic dietary food exposure estimate is conservative since it assumed average residues based on field-trial data (maximum application rate; minimum pre-harvest interval; frozen immediately after harvest) and assumed that 100% of the imported coffee was treated By using these screening-level assessments, acute and chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.
- There are no residential uses.

3.5 Hazard Identification and Endpoint Selection

3.5.1 Acute Dietary Endpoint

The acute dietary endpoint for child bearing females (females 13+years old) was determined

from the developmental toxicity in New Zealand white rabbits; LOAEL = 10 mg/kg/day. The NOAEL is 2 mg/kg/day. 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.

Note: In the previous section 18 risk assessment (Memo, G. Kramer, D318617, 9/27/2005), the dose and endpoint selected for acute dietary risk assessment was based on the study in chinchilla rabbits described above with a total FQPA SF of 300. The FQPA SF of 3X was applied for the use of LOAEL instead of the NOAEL. Up on detailed review of the cyproconazole toxicological database for this action, RAB1 toxicologists concluded that the developmental toxicity in New Zealand white rabbits is more appropriate for this exposure scenario (details provided above under section 3.3.5.1 Determination of Susceptibility).

The 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.

3.5.2 Chronic Dietary Endpoint

The cRfD of 0.01 mg/kg/day was determined on the basis of the chronic oral-toxicity study in dogs. The LOAEL of 3.2 mg/kg/day is based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intrahepatocytic bodies in males). This study provided the lowest NOAEL (1.0 mg/kg/day) in the database (most sensitive endpoint) and also provides the most protective limits for human effects. In addition, hepatotoxicity was seen in rats, mice and dog; all of these species were appeared to be equally sensitive to cyproconazole toxicity with very close NOAELs (range between 1-2 mg/kg/day). An UF of 100X (10-fold for interspecies extrapolation and 10-fold for intra species variability) was applied to the NOAEL of 1 mg/kg/day to derive the cRfD.

3.5.3 Short- and Intermediate-Term Incidental Oral Endpoints

Endpoints for these scenarios are based on a 90-day oral rat study; LOAEL = 27.3 mg/kg/day based on decreased body weight gain in males and increased liver weight in females (NOAEL = 1.5 mg/kg/day). This endpoint is appropriate for the route, duration of exposure (1-30 days) and population of concern (infants and children). The subchronic dog study was not considered for these scenarios because the NOAEL from the subchronic dog study (0.8 mg/kg/day) appears to be artificially lower than the NOAEL of the chronic dog study (1.0 mg/kg/day) and subchronic rat study (1.5 mg/kg/day) due to dose-spread effect.

HED's LOC for cyproconazole residential incidental oral exposure is 100 (i.e., MOE greater than 100 is not of concern to HED). The level of concern is based on a 10X UF to account for interspecies extrapolation to humans from the animal test species and 10X UF to account for intra-species sensitivity.

3.5.4 Short and Intermediate-Term Dermal and Inhalation Endpoints

Endpoints for these scenarios were determined from the developmental toxicity study in New Zealand white rabbits; LOAEL = 10 mg/kg/day. The NOAEL is 2 mg/kg/day. The endpoint is appropriate for the duration of exposure. Since oral studies were selected for dermal exposure assessment, a dermal-penetration factor of 11% (based on a dermal-penetration study in rats) should be used. Since oral NOAELs were selected for inhalation exposure assessment, an inhalation-absorption factor of 100% oral equivalent should be used.

HED's LOC for cyproconazole residential incidental oral exposure is 100 (i.e., MOE greater than 100 is not of concern to HED). The level of concern is based on a 10X UF to account for interspecies extrapolation to humans from the animal test species and 10X UF to account for intra-species sensitivity.

3.5.5 Long-Term Dermal and Inhalation Endpoints

Endpoints for these scenarios are based on the chronic oral toxicity study in dog; LOAEL = 3.2 mg/kg/day based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intra-hepatocytic bodies in males) (NOAEL = 1.0 mg/kg/day). The endpoint is appropriate for the duration of exposure (> 6 months).

Since oral studies were selected for dermal exposure assessment, a dermal-penetration factor of 11% (based on a dermal-penetration study in rats) should be used. Since oral NOAELs were selected for inhalation exposure assessment, an inhalation-absorption factor of 100% oral equivalent should be used. The LOC for residential exposure is for MOEs = 100 and for occupational exposure is for MOEs =100.

HED's LOC for cyproconazole residential incidental oral exposure is 100 (i.e., MOE greater than 100 is not of concern to HED). The level of concern is based on a 10X UF to account for interspecies extrapolation to humans from the animal test species and 10X UF to account for intra-species sensitivity.

3.5.6 Carcinogenicity

Cyproconazole has been classified by the Cancer Peer Review Committee as Not Likely to be Carcinogenic to Humans (Report in Process; W. Greear, Meeting date: 8/22/2007, TXR 054777). The decision was based on the weight of evidence that supports a non-genotoxic mitogenic mode of action for cyproconazole.

Note: Previously, cyproconazole was considered a carcinogen (TXR 052586, 06/03/2004). HED has since re-evaluated cyproconazole with respect to carcinogenicity based on toxicity studies submitted by the registrant describing cyproconazole's mechanistic mode of action. The Cancer Peer Review Committee re-evaluated the studies and concluded that cyproconazole is not likely to be carcinogenic to humans at doses that do not perturb the liver in rats. Further, HED concluded that the cRfD of 0.01 mg/kg/day is low enough to be protective of any liver effects.

Table 3.5. Summary of Toxicological Dose and Endpoints for Cyproconazole 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
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 mg/kg/day UF = 100X **Acute RfD** = 0.02 mg/kg	FQPA SF = 1X **aPAD** = acute RfD FQPA SF = **0.02** mg/kg	Developmental toxicity – New Zealand white rabbits; LOAEL = 10 mg/kg/day based on increased incidence of malformed fetuses and litters with malformed fetuses.
Chronic Dietary (All populations)	NOAEL= **1.0** mg/kg/day UF = **100X** **Chronic RfD** = **0.01** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD FQPA SF = **0.01** mg/kg/day	Chronic oral toxicity - dog; LOAEL = 3.2 mg/kg/day based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intrahepatocytic bodies in males).
Short-Term Incidental Oral (1-30 days) Intermediate-Term Incidental Oral (1- 6 months)	NOAEL= **1.5** mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day oral toxicity - rat; LOAEL = 27.3 mg/kg/day based on decreased body weight gain in males and increased liver weight in females.
Short-Term Dermal (1 to 30 days) Intermediate-Term Dermal (1 to 6 months)	NOAEL =**2** mg/kg/day (dermal-absorption rate = **11**%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Developmental toxicity – New Zealand white rabbits; LOAEL = 10 mg/kg/day based on increased incidence of malformed fetuses and litters with malformed fetuses.
Long-Term Dermal (>6 months)	NOAEL= **1.0** mg/kg/day (dermal-absorption rate = **11**%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Chronic oral toxicity - dog; LOAEL = 3.2 mg/kg/day based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intrahepatocytic bodies in males).
Short-Term Inhalation (1 to 30 days) Intermediate-Term Inhalation (1 to 6 months)	NOAEL =**2** mg/kg/day (inhalation-absorption rate = 100% oral equivalent)	Residential LOC for MOE = 100; Occupational LOC for MOE = 100	Developmental toxicity – New Zealand white rabbits; LOAEL = 10 mg/kg/day based on increased incidence of malformed fetuses and litters with malformed fetuses.

Table 3.5. Summary of Toxicological Dose and Endpoints for Cyproconazole 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**
Long-Term Inhalation (>6 months)	NOAEL= **1.0** mg/kg/day (inhalation-absorption rate = 100% oral equivalent)	Residential LOC for MOE = 100; Occupational LOC for MOE = 100	Chronic oral toxicity - dog; LOAEL = 3.2 mg/kg/day based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intrahepatocytic bodies in males).
Cancer	"Not Likely to be Carcinogenic to Humans."		

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no-observed adverse-effect level, LOAEL = 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.

3.6 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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis 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 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.

4.0 Dietary Exposure/Risk Characterization

References:
Residue Chemistry Summary - D349906, G. Kramer, 27-FEB-2008
Dietary Exposure - D349907, M. Sahafeyan, 28-FEB-2008
Estimated Drinking Water Concentrations & Environmental Degradation - D343771, J. Hetrick, 11-SEP-2007

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1 Metabolism in Primary Crops

The nature of cyproconazole residues in plants is adequately understood for purposes of this petition, provided that questions are resolved pertaining to the stability of ^{14}C-residues in an earlier wheat metabolism study using [triazole-^{14}C]cyproconazole. Plant metabolism data are available from studies using [^{14}C]cyproconazole on coffee, apples, grapes, and wheat. Although several of the studies are not fully acceptable, their results have been relatively consistent with respect to the major residues identified in plants. The metabolism of cyproconazole in plants involves (i) hydroxylation of the methyl- and cyclopropyl-substituted carbon to form Metabolites M9/M14; (ii) oxidation of the methyl group to form Metabolites M11/M18; (iii) elimination of the cyclopropyl-substituted carbon to form the benzylic alcohol (M15) and further oxidation to the ketone (M16); (iv) hydroxylation of the cyclopropyl ring and the phenyl ring; (v) conjugation of parent and hydroxylated metabolites to form various glycosides; and (vi) oxidative elimination of the triazole ring and its subsequent conversion to triazole alanine.

4.1.2 Metabolism in Rotational Crops

Although the confined rotational crop study contained numerous deficiencies, the available data suggest that the primary route of metabolism for cyproconazole in rotated crops involves hydroxylation of either the carbon bearing the cyclopropyl group (Metabolites M9/M14) or hydroxylation of the methyl group (Metabolites M11/M18). These primary metabolites and parent also appeared to form conjugates. Although the data are tentative, the metabolism of cyproconazole in rotational crops appears to be similar to primary crops. The study also indicates that residues of parent may occur at levels >0.01 ppm in rotated crops planted up to 90 days following applications totaling 0.089 lb ai/A/season (1.2X the maximum seasonal rate for soybeans).

4.1.3 Metabolism in Livestock

The nature of cyproconazole residues in livestock is also adequately understood for purposes of this petition, provided that the outstanding deficiencies related to the goat metabolism study are adequately resolved. The submitted poultry metabolism study is adequate. Although incomplete, the available data indicate that the metabolism of cyproconazole is similar in ruminants and poultry. The major routes of metabolism involved either hydroxylation of the carbon bearing the cyclopropyl group to form M9 and M14 or elimination of the methyl-cyclopropyl side chain (M16) followed by reduction (M15). Hydroxylation of the methyl group (M11 and M18) was also a major route of metabolism, as was opening and modification of the cyclopropyl ring (M21, M36, M56, M57, and M59). The data indicate that there is only limited cleavage of the triazole ring and that the majority of residues retain the intact phenyl and triazole rings. See Appendix B for the proposed metabolic pathway in laying hens.

4.1.4 Analytical Methodology

An adequate gas chromatograph/nitrogen-phosphorus detection (GC/NPD) method is available for enforcing tolerances of cyproconazole (free and conjugated) on plant commodities (Method AM-8022-0994-3). An improved version of this method is also available, which includes mass-

selective detection (MSD). As the extraction and purification procedures for the two methods are identical, a copy of Method AM-0842-0790-0 will be forwarded to the Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Method Volume II (PAM II), as it is superior to the current enforcement method. In the current petition, the GC/MSD method (Method AM-0842-0790-0) was used to collect data on cyproconazole residues in corn, soybean and wheat commodities. In addition, a liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (Morse Method #Meth-160) was used in the corn, soybean, and wheat field trials and processing studies to collect data on residues of triazole, TA and TAA in plant commodities. Both of these methods were adequately validated in conjunction with the field trials and processing studies. The method limit of quantitation (LOQ) is 0.01 ppm for cyproconazole and each of the triazole residues.

For enforcing the proposed tolerances on livestock commodities, Syngenta provided a copy of a LC-MS/MS method (Syngenta Method RAM 499/01) for determining free and conjugated cyproconazole in milk, eggs and livestock tissues. For this method, free and conjugated cyproconazole residues are extracted with acetonitrile (ACN):water and hydrolyzed using either concentrated ammonia (eggs and tissues) or 2M HCl (milk). Cyproconazole residues are then determined by LC-MS/MS using external standards. The method LOQ is 0.01 ppm for cyproconazole in each livestock commodity. Method RAM 499/01 was used for collecting cyproconazole residue data in the submitted cattle and poultry feeding studies, and was adequately validated in conjunction with these studies. The method has also undergone a successful ILV trial and was radiovalidated using samples from a goat dosed with [^{14}C]cyproconazole. A copy of Method RAM 499/01 will be forwarded to the Analytical Chemistry Branch (ACB) for evaluation as an enforcement method. As M14 in ruminant liver and M36 in milk need to be included in the tolerance expression, enforcement methods will be required for these residues. HED thus requests that the petitioner submits ILVs of the HPLC/MS method for Metabolite M14 in liver and the high-performance liquid chromatography/ultraviolet (HPLC/UV) method for M36 in milk. Radiovalidation data should also be submitted. Once the ILVs and radiovalidation data are submitted, the methods will be forwarded to ACB for evaluation as enforcement methods.

4.1.5 Environmental Degradation

Probable cyproconazole dissipation pathways are microbial-mediated degradation, leaching, surface water runoff, and spray drift. Cyproconazole is stable to hydrolysis and photodegradation. It slowly degrades in aerobic soil ($t_{1/2}$=329 days) and aerobic/anaerobic aquatic environments ($t_{1/2}$= 2,895 days). Degradation products include 2-amino-3-(1-*H*-1,1,2,4-triazol-tyl) propanoic acid and CO_2. Triazole acetic acid, triazole aniline and triazole were not identified as environmental degradation products of cyproconazole.

4.1.6 Comparative Metabolic Profile

The metabolism of cyproconazole in plants and livestock involves (i) hydroxylation of the methyl- and cyclopropyl-substituted carbon to form Metabolites M9/M14; (ii) oxidation of the methyl group to form Metabolites M11/M18; (iii) elimination of the cyclopropyl-substituted carbon to form the benzylic alcohol (M15) and further oxidation to the ketone (M16). Further

metabolism of cyproconazole in plants involves (i) hydroxylation of the cyclopropyl ring and the phenyl ring; (ii) conjugation of parent and hydroxylated metabolites to form various glycosides; and (iii) oxidative elimination of the triazole ring and its subsequent conversion to triazole alanine. Further metabolism of cyproconazole in livestock involves opening and modification of the cyclopropyl ring (M21, M36, M56, M57, and M59). In rats, cyproconazole is extensively metabolized; parent + 13 metabolites were identified and isolated; 35 metabolites were detected; metabolic profiles for urine, feces and bile were similar; major metabolic reactions include oxidative elimination of triazole ring; hydroxylation of the C bearing CH_3 group (M9/M14); oxidation of CH_3 group to carbinol and further oxidation to carboxylic acid; rapid excretion occurred with the majority of the total administered dose appearing in feces (biliary excretion). The primary residue in urine and feces was the parent compound and a metabolite identified as M9/M14 (a diol metabolite of cyproconazole).

4.1.7 Toxicity Profile of Major Metabolites and Degradates

Rat metabolism studies indicate that urine was found to contain at least 21 metabolite fractions by two-dimensional TLC (thin layer chromatography). Feces were found to contain at least 13 metabolite fractions by two- dimensional TLC. The primary residue in urine and feces was the parent compound and a metabolite identified as NOA 421153 (a diol metabolite of cyproconazole). Toxicity data are only available on Metabolite M-36. M-36 is not acutely toxic by the oral route of exposure. In 4-week subchronic toxicity studies in rats, the only toxic effects were attributed to malnutrition. M-36 was not mutagenic in a bacterial reverse mutation (Ames) test. It is unlikely that cyproconazole metabolites are more toxic than the parent compound since they would probably be conjugated and/or hydroxylated (polar) products which are likely to be excreted rapidly.

Table 4.1.7. Toxicity Profile of Cyproconazole Metabolites.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.1100	Acute oral toxicity (rat)	43674701 (1992) Acceptable/guideline M-36 Metabolite	LD_{50} = 2054 mg/kg in males and females
870.1100	Acute oral toxicity (mouse)	43674732 (1995) Acceptable/guideline M-36 Metabolite	LD_{50} > 2000 mg/kg in males and females
870.3100	4-Week oral toxicity (rat)	43674702 (1994) Supplementary/non-guideline 0, 20, 200, 800 or 2800 ppm 0, 2.5, 25, 99 and 366 mg/kg/d M-36 Metabolite	NOAEL = 2800 ppm (366 mg/kg/day) LOAEL was not determined.
870.3100	4-Week oral toxicity (rat)	43674703 (1995) Supplementary/non-guideline 0, 1500, 5000 or 20000 ppm M: 0, 155, 527 and 2008 mg/kg/d F: 0, 176, 528 and 2126 mg/kg/d M-36 Metabolite	NOAEL = 1500 ppm (M/F: 155/176 mg/kg/day) LOAEL = 5000 ppm (M/F: 527/528 mg/kg/day) base on malnutrition as indicated by various changes; i.e., decreased food efficiency and body weight gains in females, clinical chemistry changes, decreased organ weights, small seminal vesicles, uteri and thymus, and microscopic lesions in most organs examined.
870.5100	Bacterial Reverse Mutation Test	43692601 (1990) Acceptable/guideline 8-5000 µg/plate (+/- S9) 312.5-5000 µg/plate (+/- S9) M-36 Metabolite	Negative

4.1.8 Pesticide Metabolites and Degradates of Concern

Plants

Cyproconazole (free and conjugated) was the only significant (>10%) residue identified in the plant metabolism studies (other than the triazole-related metabolites). HED has also determined that 1,2,4-triazole, TA and TAA are also potential residues of concern in plants and livestock for all triazole fungicides. However, these triazole-related residues will not be regulated for specific triazole pesticides, but will be evaluated for the entire class of triazole compounds. HED has recently completed a comprehensive risk assessment considering triazole, TA and TAA based on established and proposed uses of triazole fungicides as of September 2005 (DP# 322215, M. Doherty *et al.*, 2/7/06). Along with other uses, this risk assessment considered the use of cyproconazole on soybeans and the use of related triazole fungicides on wheat and corn. Triazole-related residues from the application of cyproconazole to the subject crops will not be sufficiently different from those used in the previous risk assessment. Therefore, a separate risk assessment for these triazole-related residues will not be required for the current petition.

Livestock

The available toxicity data for M36 (the major metabolite in milk) show that the metabolite is less acutely toxic than the parent. However, as the metabolite is closely related to the parent and

no data addressing chronic toxicity are available, the M36 metabolite is considered as toxic as the parent in this risk assessment. As there are no toxicity data for M14 and M15, they are considered as toxic as the parent. These metabolites will thus be included in the tolerance expression for tissues in which they comprise a significant portion of the toxic residue (i.e., M36 in milk, M14 in ruminant liver, and M14 + M15 in poultry commodities).

Water
As no major environmental degradates were identified, the residue of concern in the risk assessment for drinking water is cyproconazole only.

Table 4.1.8. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crops	Cyproconazole (free and conjugated)	Cyproconazole (free and conjugated)
	Rotational Crops	Cyproconazole (free and conjugated)	Not Applicable
Livestock	Ruminant, milk	Cyproconazole (free and conjugated) + M36	Cyproconazole (free and conjugated) + M36
	Ruminant, liver	Cyproconazole (free and conjugated) + M14	Cyproconazole (free and conjugated) + M14
	Ruminant, meat, meat byproducts (except liver), and fat	Cyproconazole (free and conjugated)	Cyproconazole (free and conjugated)
	Poultry	Cyproconazole (free and conjugated) + M14 and M15	Cyproconazole (free and conjugated) + M14 and M15
Drinking Water		Cyproconazole	Not Applicable

4.1.9 Drinking Water Residue Profile

Probable cyproconazole dissipation pathways are microbial-mediated degradation, leaching, surface water runoff, and spray drift. Cyproconazole is stable to hydrolysis and photodegradation. It slowly degrades in aerobic soil ($t_{1/2}$=329 days) and aerobic/anaerobic aquatic environments ($t_{1/2}$= 2,895 days). Degradation products include 2-amino-3-(1-H-1,1,2,4-triazol-tyl) propanoic acid and CO_2. TAA, TA and triazole were not identified as environmental degradation products of cyproconazole. Cyproconazole is moderately mobile in soil (FAO Mobility Classification, http://www.fao.org/DOCREP/003 /X2570E/X2570E06.htm).

The drinking water assessment for parent cyproconazole is based on Tier I modeling. Tier I FIRST modeling indicates that PCA-corrected cyproconazole concentrations in surface source drinking water are not expected to exceed 1.14 µg/L for the annual peak concentration and 0.11 µg/L for the annual concentration. Tier I SCI-GROW modeling indicates the peak and chronic cyproconazole concentration in shallow groundwater is not expected to exceed 0.05 µg/L.

The degradation products 1,2,4-triazole and triazole conjugates (*i.e.* TA and TAA) are not addressed in this assessment. Although cyproconazole is a triazole fungicide, laboratory environmental fate studies do not show formation of 1,2,4-triazole and triazole conjugates (i.e., TA and TAA) in soil or aquatic environments. Additionally, the drinking water assessment for 1,2,4-triazole and triazole conjugates was conducted for the group of triazole fungicides (D320682).

Table 4.1.9. Summary of Estimated Surface Water and Groundwater Concentrations for Cyproconazole.

	Cyproconazole *per se*	
	Surface Water Conc., ppb[a]	**Groundwater Conc., ppb [b]**
Acute	1.14	0.05
Chronic (non-cancer)	0.11	0.05

[a] From the FIRST (Version 1.1, 12/12/05) model. Input parameters are based on 0.036 lbs a.i./acre per application with a 14 day minimum interval between applications and two applications per season (soybeans). The PCA factor was 0.83.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.036 lbs ai/A, a K_{oc} of 364 L/kg-OC, and a half-life of 228.64 days.

4.1.10 Food Residue Profile

Adequate numbers of field corn, soybean and wheat field trials were conducted in the appropriate regions at 1x the maximum use rates. Although soybean forage and hay samples were not collected in four of the soybean trials, sufficient residue data are available on forage and hay to establish tolerances on these livestock feedstuffs. The available data also support the use of low-volume applications on corn, soybeans and wheat. In addition, storage stability data for triazole-related residues are required to support the triazole, TA and TAA residue data from the field trials.

In the corn field trials conducted at the 1x rate, cyproconazole residues were <0.01-0.44 ppm in/on forage harvested at 19-22 days after treatment (DAT), and <0.01-1.50 ppm in/on stover harvested at 27-31 DAT. Residues were <0.01 ppm in/on all grain samples harvested at 27-31 DAT, including grain from applications at a 5x rate. Average free and conjugated cyproconazole residues were 0.12 ppm on forage, 0.31 ppm on stover, and <0.01 ppm on grain. The residue decline trials indicated that cyproconazole residues declined slightly in forage from 0 to 28 DAT, but remained relative steady in stover from 7 to 38 DAT.

In the soybean field trials conducted at the 1x rate, cyproconazole residues were 0.05-0.82 ppm in/on forage and 0.07-1.90 ppm in/on hay harvested at 14-15 DAT following the first application. Residues were <0.01-0.047 ppm in/on mature seeds harvested at 27-31 DAT following the second application. Average residues were 0.35 ppm on forage, 0.61 ppm on hay and 0.02 ppm on seeds. Data from the three residue decline trials showed that cyproconazole residues declined on forage and hay from 0 to 14 DAT, but remained relatively constant on seeds from 9 to 37 DAT.

In the wheat field trials conducted at the 1x rate, free and conjugated cyproconazole residues

were <0.01-0.70 ppm in/on forage and <0.01-1.32 ppm in/on hay harvested at 19-23 DAT. At maturity (28-35 DAT), cyproconazole residues were <0.01-0.77 ppm in/on straw and <0.01-0.03 ppm in/on grain. Average cyproconazole residues were 0.17 ppm on forage, 0.31 ppm on hay, 0.22 ppm on straw and 0.01 ppm on grain. In the residue decline trials, cyproconazole residues were shown to decline at longer post-treatment intervals on forage, hay and straw, but decline could not be determined for grain, as all samples had residues <LOQ.

Adequate field corn, soybean and wheat processing studies are also available depicting the potential for concentration of cyproconazole residues in processed commodities. These processing studies also provided data on triazole, TA and TAA residues in processed fractions; however, storage stability data for triazole-related residues are required to support these data.

For cyproconazole, residues in corn grain and all processed fractions were <LOQ following a 5x application to field corn; however, the study did indicate that there was the potential for at least at 5.8x concentration in aspirated grain fractions (AGF) derived from corn. For soybeans, cyproconazole residues concentrated on average by 14x in soybean AGF and 1.6x in refined oil, but did not concentrate in soybean meal (0.7x) or hulls (0.8x). For wheat grain, two processing studies are available. In the most recent wheat processing study, cyproconazole residues concentrated on average by 32x in AGF, 1.8x in bran, 2.8x in shorts, and 3.6x in germ, but did not concentrate substantially in either flour (0.8x) or middlings (1.1x). In the earlier wheat grain processing study, cyproconazole residues were also shown to concentrate in wheat grain AGF (220x) and bran (1.2x). Considering data from both wheat studies, the processing factors for wheat are 126x for AGF, 3.6x for wheat milled byproducts, and <1x for flour.

In one cattle feeding study, dairy cows were dosed orally via capsule once a day for 29-30 days with cyproconazole at levels equivalent to 2.4, 6.9 and 22.3 ppm in the diet (1.5x, 4.3x, and 14x the MDB). In an earlier cattle feeding study, dairy cows were dosed orally twice a day for 35-38 days using feed fortified with cyproconazole at 1, 3, 10, and 30 ppm (0.6x, 1.9x, 6.3x and 19x the MDB). With regards to cyproconazole residues, the results from the two feeding studies are similar. In both studies, cyproconazole residues were quantifiable (>0.01 ppm) in liver samples from all dosing levels (0.6x-19x the MDB), and the concentrations in liver were dose dependent. Cyproconazole residues were also detected at ≥0.01 ppm in kidneys and fat from dosing levels equivalent to 4.3x-19x the MDB, but were <0.01 ppm in kidney and fat from dosing levels equivalent to 0.6x-1.9x. For muscle, cyproconazole residues were <0.01 ppm in samples from all dose groups up to 19x the MDB, and quantifiable residues in milk (>0.01 ppm) were detected only in samples from the highest dose groups (14x and 19x MDB).

Using residue data from the 1.5x and 1.9x dose groups, the maximum expected cyproconazole residues in cattle commodities at 1x the MDB would be <0.01 ppm in kidney, muscle, fat and milk and 0.053-0.115 ppm in liver. Although quantifiable residues are only expected in liver at a 1x feeding level, quantifiable residues (≥0.01 ppm) were detected in milk, kidneys and fat at the 14x and 19x dose levels in both studies; therefore, tolerances will be required for these commodities at the method LOQ. However, a separate tolerance for meat is not required as cyproconazole residues were <0.01 ppm at dosing levels equivalent to 14x and 19x the MBD. The levels of Metabolites M36 and M14 at a 1x feeding level were calculated using the maximum residue values from the 3-ppm dose group (1.9x MDB). At a 1x feeding level,

residues of Metabolite M36 in milk are estimated to be 0.0132 ppm, and residues of Metabolite M14 in liver are estimated to be 0.289 ppm. Thus, the appropriate tolerance level for cyproconazole plus M14 in ruminant liver is 0.50 ppm and for cyproconazole plus M36 in milk is 0.02 ppm.

The dosing levels in the cattle feeding studies are equivalent to 16x-476x the MDB for swine. Using the residue data from the cattle feeding study, cyproconazole residues would be <0.01 ppm in all hog commodities at a feeding level equivalent to 1x the MDB, and residues would only be quantifiable in liver (0.02-0.06 ppm) at 10x the MDB. Therefore, tolerances are not required for hog fat and meat, and the tolerance for hog liver should be set at 0.01 ppm.

In the poultry feeding study, laying hens were dosed orally for 29 days with cyproconazole in the feed at actual concentrations of 0.12, 0.45 and 1.87 ppm (1.6x, 6x, and 25x the MDB for poultry). Residues of cyproconazole were <0.01 ppm in all samples of eggs and tissues from the 25x dose group. The data from the poultry feeding study indicate that quantifiable residues of cyproconazole are unlikely to occur in eggs or poultry at 10x the MDB. In addition, data from the feeding study and hen metabolism study also indicate that the other residues of concern in poultry (M14, M15, triazole, TA and TAA) will also be <LOQ at 10x the MDB. Therefore, tolerances are not required for poultry commodities [40 CFR 180.6(a)(3)]. However, if in the future, proposed new uses result in an increase in the MDB, then a new poultry feeding study which includes data for Metabolites M14 and M15 may be required.

Adequate storage stability data are available indicating that cyproconazole is stable under frozen storage conditions for up to 27-40 months in a variety of plant matrices, including grapes, raisins, stone fruits, peanuts (forage, hay, nutmeats and hulls, meal, oil and soapstock), and wheat forage, grain and hay. Adequate data are also available indicating that cyproconazole is stable in frozen milk and cattle tissues for 9-12 months, Metabolite M14 is stable in frozen kidney and liver for up to 20 months, and Metabolite 21a is stable in frozen milk for up to 12 months. However, Metabolite M36 was shown to decline by approximately 40% in frozen milk over 12 months of storage. For cyproconazole and Metabolites M14, M21a, and M36, these data adequately support the sample storage conditions and intervals from the submitted field trials, processing studies, and feeding studies. However, no data are available to support the stability of the triazole-related residues (triazole, TA and TAA) in plant and livestock commodities.

Adequate data are available from a limited field rotational crop study reflecting a 60-day PBI. In the two limited field trials, free and conjugated cyproconazole residues in the representative rotational crops from the 60-day PBI were <0.01 ppm in/on all samples of spinach leaves, radish roots, and wheat forage, hay, straw and grain; however, two out of four samples of radish tops had cyproconazole residues of 0.010-0.012 ppm. These data support the proposed rotational crop restrictions, which allow for the immediate replanting of corn, soybean and wheat and specify a 60-day PBI for leafy vegetables and cereal grains other than wheat, and a 365-day PBI for all other crops.

A summary of the recommended tolerances for the current petition are listed in Section 9.1. The petitioner should submit a revised Section F reflecting the recommended tolerances and commodity definitions presented in Section 9.1.

The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was utilized for determining appropriate tolerance levels for corn forage and stover, soybean forage and hay, and wheat forage, hay and straw were determined using the tolerance harmonization spreadsheet, as residue levels of cyproconazole in these commodities were generally above the method LOQ. However, the recommended tolerance levels of corn grain, soybean seed and wheat grain were based on the maximum observed residues levels, as >50% of the samples for these commodities had residues ≤LOQ.

Based on highest-average field trial (HAFT) residues of cyproconazole for corn grain (<0.01 ppm), soybean seeds (0.045 ppm) and wheat grain (0.02 ppm) from the field trials and the available processing data, separate tolerances for cyproconazole are not required for any corn grain processed fractions, soybean meal and hulls, or wheat flour. However, separate tolerances are required for soybean oil, wheat milled byproducts and AGF. Based on a 1.6x processing factor and HAFT residues at 0.045 ppm, the maximum expected residues in soybean oil would be 0.072 ppm. Based on the 3.6x processing factor for wheat germ and HAFT residues at 0.02 ppm, the maximum expected residues in wheat milled byproducts would be 0.072 ppm. These data will support separate tolerances for cyproconazole residues at 0.1 ppm in soybean oil and wheat milled byproducts.

Based on the various concentration factors for AGF from corn (5.8x), soybeans (14x) and wheat (126x), and their respective HAFT residues, the maximum expected cyproconazole residues are <0.06 ppm in corn grain AGF, 0.63 ppm in soybean AGF, and 2.52 ppm in wheat grain AGF. Therefore, the tolerance for AGF should be set at 2.5 ppm based on the wheat grain data.

4.1.11 International Residue Limits

There are no established or proposed Canadian or Codex maximum residue limits (MRLs) for cyproconazole on food or feed crops. Mexico has established tolerances for cyproconazole at 0.05 ppm in barley and wheat grain, which is equivalent to the recommended U.S. tolerance for wheat grain. Therefore, there are generally no questions about the compatibility of the proposed tolerances with international tolerances. However, HED notes that Japan has established numerous tolerances for cyproconazole, including MRLs on wheat (0.2 ppm), corn (0.1 ppm), and soybeans (0.05 ppm).

4.2 Dietary Exposure and Risk

Cyproconazole acute and chronic dietary exposure assessments were conducted using the DEEM-FCID™, Version 2.03 which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most

appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., only those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, any significant differences in user vs. per capita exposure and risk are specifically identified and noted in the risk assessment.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

As stated above, for acute and chronic assessments, HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID™ analyses estimate the dietary exposure of the U.S. population and various population subgroups. The result of the acute dietary exposure estimate is for females 13-49 years old as an endpoint of concern attributable to a single dose for general population was not identified. The results of the chronic dietary exposure estimates reported in Table 4.2 are for the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50+ years.

The acute and chronic analyses assumed tolerance-level residues, 100% CT information, and DEEM™ default processing factors. Therefore, these analyses were considered conservative and could be further refined if needed through the use of anticipated residues for all commodities, percent market share data for the proposed commodities, percent of crop treated data for registered commodities, and/or empirical processing factors.

4.2.1 Acute Dietary Risk Characterization (Females 13-49 years old)

The acute (food + water) exposure risk estimate for females 13-49 years old was 3% aPAD at the 95th percentile of the exposure distribution, and is not of concern to HED.

4.2.2 Chronic Dietary Risk Characterization

The chronic (food + water) exposure estimates were <100% cPAD for U.S. general population (4% cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 13% cPAD. Therefore, the chronic dietary exposure to cyproconazole is not of concern to HED.

Table 4.2.2. Dietary Exposure and Risk for Cyproconazole.

Population Subgroup	Acute Dietary[1] (95 Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	N/A		0.000376	3.8
All Infants (< 1 year old)			0.000480	4.8
Children 1-2 years old			0.001264	13
Children 3-5 years old			0.001015	10
Children 6-12 years old			0.000663	6.6
Youth 13-19 years old			0.000356	3.6
Adults 20-49 years old			0.000265	2.7
Adults 50+ years old			0.000229	2.3
Females 13-49 years old	0.000585	2.9	0.000261	2.6

[1] Acute toxicity endpoint was determined only for females 13-49 years old.

5.0 Residential (Non-Occupational) Risk

There are no existing or proposed residential uses for cyproconazole. All turf uses have been withdrawn. Therefore, a residential assessment was not necessary.

6.0 Aggregate Risk Assessments

Acute and chronic aggregate risks were assessed based on dietary exposure from food and drinking water sources. Since there are no residential uses, short- and intermediate-term aggregate risks were not assessed. Cancer aggregate risk was not assessed since a cancer risk assessment is not needed.

HED has also determined that 1,2,4-triazole, TA and TAA are also potential residues of concern in plants and livestock for all triazole fungicides. However, these triazole-related residues will not be regulated for specific triazole pesticides, but will be evaluated for the entire class of triazole compounds. HED has recently completed a comprehensive risk assessments considering

1,2,4-triazole and TA + TAA based on established and proposed uses of triazole fungicides. These risk assessments were last updated in October 2007 (DP#: 341803 and DP#: 344298, M. Sahafeyan, 10/30/07; note: separate memorandums). Along with other uses, these risk assessments considered the use of cyproconazole on soybeans and the use of related triazole fungicides on wheat and corn. Triazole-related residues from the application of cyproconazole to the subject crops will not be sufficiently different from those used in the in the previous risk assessment. Therefore, a separate risk assessment for these triazole-related residues will not be required for the current petition.

6.1 Acute Aggregate Risk

No acute residential exposures are expected. Since the acute dietary assessment included food and water only, the exposures in Table 4.2.2 represent aggregate exposures. The Tier 1 acute dietary analysis (food and water) resulted in an exposure estimate for females 13-49 years old of 3% aPAD (Table 4.2.2). The resulting risk estimate for females 13-49 years old is thus not of concern to HED. An acute endpoint of concern was not identified for the general population including infants and children.

6.2 Chronic Aggregate Risk

No chronic residential exposures are expected. Since the chronic dietary assessment included food and water only, the exposures in Table 5.2 represent aggregate exposures. The chronic (food + water) exposure estimates were <100% cPAD for U.S. general population (4% cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 13% cPAD. Therefore, the chronic dietary exposure to cyproconazole is not of concern to HED.

7.0 Cumulative Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for cyproconazole and any other substance, and cyproconazole does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that cyproconazole does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Risk Assessment

Reference: Memo, K. Lowe, D330711, 9/06/2007.

Based on the proposed uses in/on corn, soybean and wheat, occupational exposure is expected. The use pattern for the proposed uses is described below in Table 8.0.

Table 8.0. Proposed Use Patterns and Formulations for Cyproconazole.						
Product[a]	Formula-tion	Use Sites	Application Rates (lb ai/A)	Application Equipment	Area Treated	Timing of Application and Restrictions
Alto® 100 SL and Quadris Xtra®	Liquid	Corn (including field, popcorn and seed corn)	0.036	Aerial Groundboom Chemigation	1200 acres 200 acres 350 acres	Apply when disease first appears; Re-apply every 7-14 days; 2 applications/season; 30 days PHI; 24 hours REI
		Wheat				For early suppression: apply in spring at approx Feekes Stage 5; for control of leaf diseases: apply between Feekes Stage 8 and 10.5.1; Re-apply every 14 days; 30 days PHI; 24 hours REI
		Soybeans				For rust: application timing should be R1 (beginning flowering, approx 50 days after planting) up to R6 stage (seed development); for other diseases: begin before disease development; Re-apply every 14-28 days; 30 days PHI; 24 hours REI

a Quadris Xtra® contains 18.2% azoxystrobin (1.67 lb ai/gal) and 7.3% cyproconazole (0.67 lb ai/gal); Alto® 100 SL contains 8.9% cyproconazole (0.83 lb ai/gal).

8.1 Occupational Handler Risk Assessment

There is potential for occupational handler exposure from the proposed uses on agricultural crops. It is anticipated that the following scenarios could result in handler exposure: mixer/loaders for aerial, chemigation, or groundboom applications of liquids, applicators using aerial or groundboom equipment, and flaggers for aerial applications. Based upon the proposed use pattern, HED expects the *most highly* exposed occupational pesticide handlers are likely to be:

(1) mixing/loading liquids for aerial applications (PHED); and
(2) applying sprays via aerial equipment (PHED).

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (August, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline," that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves, as well as for "baseline" and the use of protective gloves or other PPE as might be necessary. The proposed product label involved in this assessment directs applicators and other handlers to wear a long-sleeved shirt and long pants; chemical-resistant gloves made of any waterproof material such as polyvinyl chloride, nitrile rubber or butyl rubber; and shoes plus socks.

Exposure Duration
HED believes most exposure durations will be short-term (1 - 30 days). However, the ExpoSAC maintains it is possible for commercial applicators to be exposed to intermediate-term exposure durations (1-6 months). In addition, the short- and intermediate-term toxicological endpoints are the same; therefore, the estimates of risk for short-term duration exposures are protective of

those for intermediate-term duration exposures. Long-term exposures are not expected; therefore, a long-term assessment was not conducted.

Risk Calculations
Since an oral study was selected for the short- and intermediate-term assessments, an 11% dermal-absorption factor was applied and a 100% inhalation-absorption factor was applied. A body weight of 60 kg was used since the endpoints were from a developmental toxicity study with fetal effects. The dermal and inhalation MOEs were combined for the occupational handler risk assessments because the toxicity endpoints for the dermal and inhalation routes of exposure are based on the same toxicological effects.

Daily dermal or inhalation handler exposures are estimated for each applicable handler task using the following formula:

Daily Exposure (mg ai/day) = Unit Exposure (mg ai/lb ai handled) x Application Rate (lbs ai/gallon) x Amount Handled (gal/day)

Where:

Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Unit Exposure	=	Unit exposure value (mg ai/lb ai) derived from August 1998 PHED data or from ORETF data;
Application Rate	=	Normalized application rate (lb ai/gal); and
Daily Area Treated	=	Normalized amount handled (gal/day).

The daily dermal or inhalation dose is calculated by normalizing the daily exposure by body weight and adjusting, if necessary, with an appropriate dermal or inhalation absorption factor using the following formula:

Average Daily Dose (mg/kg/day) = Daily Exposure (mg ai/day) x (Absorption Factor (%/100) / Body Weight (kg)

Where:

Average Daily Dose	=	Absorbed dose received from exposure to a pesticide in a given scenario (mg ai/kg bw/day);
Daily Exposure	=	Amount (mg ai/day) deposited on the surface of the skin that is available for dermal absorption or amount inhaled that is available for inhalation absorption;
Absorption Factor	=	A measure of the amount of chemical that crosses a biological boundary such as the skin or lungs (% of the total available absorbed); and
Body Weight	=	Body weight determined to represent the population of interest in a risk assessment (kg).

Non-cancer dermal and inhalation risks for each applicable handler scenario are calculated using a MOE, which is a ratio of the NOAEL to the daily dose. All MOE values were calculated using the formula below:

MOE= NOAEL or LOAEL (mg/kg/day) / Average Daily Dose (mg/kg/day)

A total MOE was calculated because the dermal and inhalation toxicological endpoints of concern are based on the same adverse effects. The total MOE values were calculated using the formula below:

Total MOE = NOAEL or LOAEL / (Dermal dose + Inhalation Dose)

Table 8.1 presents the exposure/risks for short and intermediate-term dermal and inhalation exposures at baseline, and with additional PPE. The combined dermal and inhalation exposure risks for mixer/loaders are not of concern (i.e., MOEs>100), **provided the mixer/loaders wear protective gloves as directed on the label.**

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); pilots are not required to wear protective gloves. With this level of protection, there are no risks of concern for applicators.

Table 8.1. Cyproconazole Occupational Noncancer Dermal and Inhalation Exposures and Risks.						
Crop or Target	App Rate (lb ai/acre)[a]	Area Treated Daily (acres)[b]	Dermal and Inhalation Unit Exposures (mg/lb ai)	Doses (mg/kg/day)[g]	MOEs[h]	Combined MOEs[i]
Mixing/Loading Liquid Concentrates for Aerial Applications						
corn, soybean, wheat	0.036	1200	Dermal Baseline[c]: 2.9 SL w/gloves[d]: 0.023	Dermal Baseline: 0.23 SL w/gloves: 0.0018	Dermal Baseline: **8.7** SL w/gloves: 1,100	Baseline Dermal and Inhalation: **8.7** PPE – SL w/gloves + Baseline Inhalation: 740
			Inhalation Baseline[e]: 0.0012	Inhalation Baseline: 0.00086	Inhalation Baseline: 2,300	
Applying Sprays via Aerial Equipment						
corn, soybean, wheat	0.036	1200	Dermal Engineering control[f]: 0.005	Dermal Engineering control: 0.0004	Dermal Engineering control: 5,100	Engineering control Dermal + Inhalation: 4,500
			Inhalation Engineering control: 0.000068	Inhalation Engineering control: 0.000049	Inhalation Engineering control: 41,000	

a Application rates are the maximum application rates determined from proposed labels for cyproconazole.
b Amount handled per day values are HED estimates of acres treated per day based on Exposure SAC SOP #9 "Standard Values for Daily Acres Treated in Agriculture," industry sources, and HED estimates.
c Baseline Dermal: Long-sleeve shirt, long pants, and no gloves.
d Dermal SL w/gloves: Single layer plus chemical-resistant gloves.
e Baseline Inhalation: no respirator.
f Engineering control: enclosed cockpit.
g Dose (mg/kg/day) = Unit exposure(mg/lb ai) x App Rate (lb ai/acre) x Area Treated (acres/day) x %Absorption (11% dermal and 100% inhalation) / Body weight (60 kg).
h MOE = NOAEL/Dose; where the short- and intermediate-term dermal and inhalation NOAEL = 2 mg/kg/day.
i Combined MOEs =NOAEL / (Dermal + Inhalation Exposure).

8.2 Occupational Post-application Exposure

Following cyproconazole application to corn, wheat and soybean, occupational exposure is possible. Post-application activities may include scouting, maneuvering irrigation equipment, hand weeding and hand harvesting.

Since no post-application data were submitted in support of this registration action, exposures during post-application activities were estimated using dermal TCs from the TC Policy Number 3.1: Agricultural TCs, August 2000, summarized in Table 8.2.1 below and the following assumptions:

Assumptions:

- Application Rate = 0.036 lb ai/A
- Exposure Duration = 8 hours per day
- Body Weight = 60 kg
- Dermal Absorption = 11%
- Fraction of a.i. retained on foliage is assumed to be 20% (0.2) on day zero (= % dislodgeable foliar residue, DFR, after initial treatment). This fraction is assumed to further dissipate at the rate of 10% (0.1) per day on following days. These are default values established by HED's ExpoSAC.

Table 8.2.1. Post-application Activities and Dermal TCs.

Proposed Crops	Policy Crop Group Category	TCs (cm^2/hr)	Activities
Soybeans and Wheat	Field / row crop, low / medium	100	Hand weeding, scouting
		1500	Scouting, irrigation
Corn	Field / row crop, tall	400	Scouting
		1000	Irrigation, scouting
		17,000	Hand harvesting

The information in this table is based on proprietary and non-proprietary data.

Daily dermal exposures were calculated on each post-application day after application using the following equation:

$$DE_{(t)}\ (mg/day) = (TR_{(t)}\ (\mu g/cm^2) \times TC\ (cm^2/hr) \times Hr/Day)/1000\ (\mu g/mg)$$

Where:

DE(t) = Daily exposure or amount deposited on the surface of the skin at time (t) attributable for activity in a previously treated area, also referred to as potential dose (mg ai/day);

TR(t) = Transferable residues that can be dislodgeable foliar residue at time "t"

($\mu g/cm^2$);
TC = Transfer Coefficient (cm^2/hour); and
Hr/day = Exposure duration meant to represent a typical workday (hours).

Note that the ($TR_{(t)}$) input may represent levels on the day of application in the case of short-term risk calculations. Once daily exposures are calculated, the calculation of daily absorbed dose and the resulting MOEs use the same algorithms that are described above for the handler exposures. These calculations are completed for each day or appropriate block of time after application.

Risks are not of concern (i.e., MOE>100) on day 0 (REI = 12 hours) for all post-application activities. Table 8.2.2 presents a summary of occupational post-application risks associated with use of cyproconazole.

Table 8.2.2. Summary of Occupational Post-application Risks for Cyproconazole.

Crop Grouping	Application rate (lb ai/acre)	Transfer Coefficient ($\mu g/cm^2$)	Day after Application	MOE at Day 0 (Level of Concern = 300)
Soybean, Wheat	0.036	100 (Hand weeding, scouting)	0 (12 hours)	17,000
		1500 (Scouting, irrigation)		1,100
Corn		400 (Scouting)		4,200
		1000 (Irrigation, scouting)		1,700
		17,000 (Hand harvesting, Detasseling)		99
			1 day	110

8.3 REI

Cyproconazole is classified in Toxicity Category III for acute dermal, acute oral, and acute inhalation. It is classified in Toxicity Category IV for primary eye irritation and primary skin irritation and it is not a dermal sensitizer. Therefore, the Worker Protection Standard (WPS) interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to cyproconazole from soybeans, wheat and corn.

9.0 Data Needs and Label Recommendations

9.1 Regulatory Recommendations and Residue Chemistry Deficiencies

Provided the petitioner submits revised Sections B and F and ILVs of the HPLC/MS method for Metabolite M14 in liver and the HPLC/UV method for M36 in milk, HED concludes that the residue chemistry database is sufficient for conditional registration and establishment of permanent tolerances for free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] in or on the following commodities:

Aspirated Grain Fractions 2.5
Corn, field, forage 0.60
Corn, field, grain 0.01

Corn, field, stover	1.2
Soybean, seed	0.05
Soybean, forage	1.0
Soybean hay	3.0
Soybean, oil	0.10
Wheat, forage	0.80
Wheat, hay	1.3
Wheat, straw	0.90
Wheat, grain	0.05
Wheat, grain, milled byproducts	0.10
Fat of cattle, goat, horse and sheep	0.01
Meat byproducts (except liver) of cattle, goat, horse and sheep	0.01

Additionally, HED has determined that a tolerance is required for the combined free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] and its metabolite M36 [δ-(4-chlorophenyl)-β,δ-dihydroxy-γ-methyl-1*H*-1,2,4-triazole-1-hexenoic acid] in or on the following commodity:

Milk	0.02

and that tolerances are required for the combined free and conjugated residues of cyproconazole [α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol] and its metabolite M14 [2-(4-chlorophenyl)-3-cyclopropyl-1-[1,2,4]triazol-1-yl-butane-2,3-diol] in or on the following commodities:

Liver of cattle, goat, horse, and sheep	0.50
Hog liver	0.01

Residue Chemistry Deficiencies

860.1200 Directions for Use

- The field trial data support only a single application to soybeans prior to harvest of forage or hay. The use directions for soybean should be amended to allow for only one application at up to 0.036 lb ai/A, prior to the harvest or grazing of forage or hay.

860.1300 Nature of the Residue - Plants

- To upgrade the existing wheat metabolism study to adequate, data are required supporting the stability of ^{14}C-residues during the analytical phase of the study.

860.1300 Nature of the Residue - Livestock

- To upgrade the goat metabolism study to adequate, the deficiencies previously cited in the goat metabolism study must be resolved (see D217295, G. Kramer, 6/14/96).

860.1340 Residue Analytical Methods

- Method AM-0842-0790-0 for determining cyproconazole in plant commodities is an improved version of the current enforcement, which allows for use of either NPD or MSD. As this method is superior to the current enforcement method, it will be forward to FDA to either replace or supplement the existing tolerance enforcement method for plant commodities.

- The LC-MS/MS method (Syngenta Method RAM 499/01) for determining cyproconazole in livestock commodities has undergone a successful ILV trial and radiovalidation trial. Therefore, a copy of the method will be forwarded to ACB for evaluation as an enforcement method.

- As M14 in liver and M36 in milk need to be included in the tolerance expression, enforcement methods will be required for these residues. HED thus requests that the petitioner submits ILVs of the HPLC/MS method for Metabolite M14 in liver and the HPLC/UV method for M36 in milk. Radiovalidation data should also be submitted. Once the ILVs and radiovalidation data are submitted, the methods will be forwarded to ACB for evaluation as enforcement methods.

860.1380 Storage Stability

- Storage stability data for triazole, TA, TAA in plant raw agricultural commodity (RAC) and processed fractions and in livestock commodities are required in order to support the available data on triazole-related residues in the submitted field trials, processing studies and feeding studies. However, storage stability data for these compounds has been requested as part of the Human-Health Aggregate Risk Assessment for 1,2,4-T, TA and TAA (M. Doherty, *et al.,* 2/7/06). Submission of the data requested in the 2/7/06 document will satisfy storage stability data requirement for the subject petitions.

860.1850 Confined Accumulation in Rotational Crops

- Although the submitted confined rotational crop study was considered acceptable for purposes of this petition, the study contained numerous deficiencies and can not be upgraded. Therefore, a new confined study may be required for any future uses of cyproconazole resulting in seasonal use rates above 0.072 lb ai/A in rotated crops.

860.1900 Field Accumulation in Rotational Crops

- Although the interim 60-day data from the limited field rotational crop trials are adequate and support the proposed label restrictions for rotated crop, the final results from the limited field trials should be submitted once they are available.

860.1550 Proposed Tolerances

The petitioner is requested to submit a revised Section F specifying the following:

- The revised tolerances and commodity definitions summarized above.

Note to RD: The preferred chemical name for cyproconazole is "α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol." 40 CFR §180.485(a) should be revised to use this terminology. Also, the time-limited tolerance established for soybean seed under 40 CFR §180.485(b) should be deleted once a tolerance is established in section (a).

Appendix A

Table A.1. Acute Toxicity of Cyproconazole.			
Guideline No.	Study Type	Results	Toxicity Category
870.1100 (81-1)	Acute Oral (rat)	M: 1020 mg/kg F: 1330 mg/kg	III
870.1100 (81-1)	M-36 metabolite, Acute Oral (rat)	MRID-43674701, >2000 mg/kg	III
870.1100 (81-1)	M-36 metabolite, Acute Oral (mouse)	MRID-43674732 >2000 mg/kg	III
870.1200 (81-2)	Acute Dermal (rabbit)	LD50 > 2000 mg/kg	III
870.1300 (81-3)	Acute Inhalation (rat)	LC50 > 5.6 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

Table A.2. Subchronic, Chronic, and Other Toxicity Profile of Cyproconazole.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3050	28-Day oral - rat	40624305 (1986) Acceptable/non-guideline 0, 10, 30,100, 300 and 1000 ppm 0, 0.5, 1.5, 5.0, 15, 50 mg/kg/d	NOAEL= 5 mg/kg/day LOAEL = 15 mg/kg/day, based on elevated LDH, increased liver weight (relative and absolute) and liver vacuolation.
870.3100	90-Day oral toxicity (rat)	40607718 (1986) Acceptable/guideline 0, 20. 80 or 320 ppm 0, 1, 4 and 16 mg/kg/d	NOAEL = 20 ppm (1 mg/kg/day) LOAEL = 80 ppm (4 mg/kg/day) based on 1) lack of a dose response relationship, 2) lack of correlation with histopathological or organ weight changes, 3) because similar changes were not seen in male and female rats fed the same level (20 ppm) of SAN619F in a chronic/carcinogenicity study (MRID No. 41164701), and 4) because the creatinine, sodium, and calcium values observed in the 90-day study were within the range of baseline values for these parameters in several strains of rats of this age.
870.3100	90-Day oral toxicity (rat)	43078601 (1993) Acceptable/supplementary 0, 20, 350, 700, or 1400 ppm M/F: 0/0, 1.4/1.6, 24.7/29.6, 52.8/57.3, and 106.8/118.1 mg/kg/d	NOAEL = 20 ppm (1.5/2.0 mg/kg/day in males/females) LOAEL = 350 ppm (27.3/35.4 mg/kg/day in males/females), based on decreased body weight gain in males and increased liver weights in females.
870.3100	90-Day oral toxicity (mouse)	46950013 (1987) Acceptable/non-guideline 0, 5, 15, 300, or 600 ppm M: 0, 0.7, 2.2, 43.8, or 88.7 mg/kg bw/d F: 0, 1.0, 3.2, 70.2, or 128.2 mg/kg bw/d	NOAEL = 15 ppm (2.2 and 3.2 mg/kg bw/day in males and females) LOAEL = 300 ppm (43.8 and 70.2 mg/kg bw/day in males and females), based on decreased body weight gain in both sexes and evidence of liver effects (increased liver weight in both sexes, periacinar hepatocytic eosinophilia in males, and single cell hepatocyte necrosis in both sexes).
870.3150	90-Day oral toxicity (dog)	40607719 (1986) Acceptable/guideline 0, 20, 100, 500 0, 0.8. 4.0 and 20.0 mg/kg	NOAEL = 0.8 mg/kg/day LOAEL = 4.0 mg/kg/day, based on increased absolute liver weight & hepatocytomegaly.
870.3200	21/28-Day dermal toxicity (rat)	40624306 (1988) Acceptable/guideline 0, 50, 250, 1250 mg/kg/d	NOAEL = 250 mg/kg/day LOAEL 1250 mg/kg/day, based on decreased body weight gain and food consumption (M), increased AST (males), creatinine (females), cholesterol (both sexes).

Table A.2. Subchronic, Chronic, and Other Toxicity Profile of Cyproconazole.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in (rat)	40607721 (1985) Acceptable/guideline 0, 6. 12, 24, 48 mg/kg/d	Maternal NOAEL = 6 mg/kg/day Maternal LOAEL = 12 mg/kg/day, based on decreased BWG during dosing Developmental NOAEL = 6 mg/kg/day Developmental LOAEL = 12 mg/kg/day, based on increased incidence of supernumerary ribs, malformations [hydrocephaly] at 24 & 48 mg/kg/day and cleft palate at 48 mg/kg/day.
870.3700b	Prenatal developmental in (rabbit)	42175401 (1991), Acceptable/guideline 0, 2, 10, 50 mg/kg/d	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 50 mg/kg/day, based on decreased body weight gain. Developmental NOAEL. = 2 mg/kg/day Developmental LOAEL = 10 mg/kg/day, based on increased incidence of malformed fetuses & litters with malformed fetuses.
870.3700b	Prenatal developmental in (rabbit)	40607720 (1986) Acceptable/guideline 0, 2, 10, 50 mg/kg/d	Maternal NOAEL = 10 mg/kg/day Maternal LOAEL = 50 mg/kg/day, based on inhibited BWG during treatment. Developmental NOAEL < 2 mg/kg/day Developmental LOAEL = 2 mg/kg/day, based on incidence of hydrocephalus internus.
870.3800	Reproduction and fertility effects (rat)	4067723 (1987) Acceptable/guideline 0, 4, 20, 120 ppm 0, 0.4, 1.7 or 10.6 mg/kg/d	Parental NOAEL = 20 ppm (1.7 mg/kg/day) Parental LOAEL = 120 ppm (10.6mg/kg/day), based on liver effects. Reproductive toxicity NOAEL = 120 ppm (10.6 mg/kg/day), although gestation length was slightly increased and litter size were decreased, the changes are not considered treatment-related. Reproductive LOAEL was not determined.
870.4100b	Chronic toxicity (dog)	41212901 (1988) Acceptable/guideline 0, 30, 100, and 350 ppm M/F: 0/0, 1.0/1.0, 3.2/3.2, and 12. 1/12.6 mg/kg/d)	NOAEL = 30 ppm (1.0 mg/kg/day) LOAEL = 100 ppm (3.2 mg/kg/day), based on liver effects (P450 induction in females and histopathology, laminar eosinophilic intrahepatocytic bodies in males).
870.4200b .	Carcinogenicity (mouse)	41147201(1989) Acceptable/guideline 0, 5, 15, 100,200 ppm M/F: 0/0.69/1.03, 1.84/2.56, 13.17/17.65, or 27.85/36.30 mg/kg/d	NOAEL = M/F: 1.8/2.6 mg/kg/day LOAEL = M/F: 13.2/17.7 mg/kg/day, based on increased incidence of hepatocytic single-cell necrosis; increased incidence of hepatocellular adenomas and carcinomas

Table A.2. Subchronic, Chronic, and Other Toxicity Profile of Cyproconazole.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300	Combined Chronic Toxicity/Carcinogenicity (rat)	41164701 (1988) Acceptable/guideline 0, 20, 50 or 350 ppm M/F: 0/0, 1.0/1.2, 2.2/2/7 and 15.6/21.8 mg/kg/d	NOAEL = 50 ppm (2.2 mg/kg/day) LOAEL = 350 ppm (15.6 mg/kg/day), based on decreased body weight and increased incidence of fatty infiltration in liver (M). Dosing was inadequate in females.
870.5100	Bacterial Reverse Mutation Test	40607725 (1986) Acceptable/guideline 0, 1,5, 10, 100, 500, 1000 ug/plate w/wt rat S9 mix	Negative.
870.5100	Bacterial Reverse Mutation Test	40624307 (1985) Unacceptable/guideline 0, 10, 100, 250, 400, 500 or 550 ug/plate w/wt rat S9 mix	Negative.
870.5300	*In Vitro* Gene Mutation assay in Chinese Hamster Ovary cells	40607726 (1985) Acceptable/guideline 0, 20, 50, 100 or 200 ug/mL w/wt S9.	Negative.
870.5375	*In Vitro* Mammalian Chromosomal Aberration	41757801 (1990) Unacceptable/guideline 60.1, 100.0, 150.0 or 200 ug/mL wt S9; 45.0, 59.9, 99.9 or 150.0 w S9.	Can not be interpreted.
870.5375	*In Vitro* Mammalian Chromosomal Aberration	46950019 (1995) Acceptable/guideline 0, 50, 100, 200 or 400 µg/mL without S9 0, 25, 50, 100 or 200 µg/mL with metabolic 0, 50, 100, 200 or 400 µg/mL without S9 0, 100, 200, 400 or 800 µg/mL with metabolic activation	Negative.
870.5375	*In Vitro* Mammalian Chromosomal Aberration	41757701 (1988) Unacceptable/guideline 100, 150 or 200 ug/mL wt S9; 100, 150, 200 or 250 w S9.	Positive w/wt S9.

Table A.2. Subchronic, Chronic, and Other Toxicity Profile of Cyproconazole.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5395	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice	40607728 (1984) Acceptable/guideline 0, 16.7, 55.7, 167 mg/kg	Negative.
	Cell Transformation	40607724 (1985) Acceptable 0, 20, 50, 100 or 200 ug//mL w/wt S9 (assumed)	Negative.
870.5450	Rodent Dominant Lethal	41961401 (1991) Acceptable/guideline 20, 40 or 80 mg/kg/d	Negative.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	40607729 (1988) Unacceptable/guideline 0.15,0.5, 1.5, 5, 15, 50, 100, 150 ug//mL	Can't be evaluated.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	40607727 (1985) Unacceptable/guideline 0.15,0.5, 1.5, 5, 15, 50, 100, 150 ug//mL	Can't be evaluated.
870.7485	Metabolism and pharmacokinetics (rat)	41701901 (1987) Acceptable/guideline oral - 10mg/kg , 910 mg/kg x 14 days; iv - 10 and 130 mg/kg	Absorption, distribution, excretion and blood kinetics were examined. Almost completely absorbed in males (84%) and females (106%), extensively metabolized; diastereomers A & B of parent + 13 metabolites identified & isolated; 35 metabolites detected; metabolic profiles for urine, feces, bile similar; major metabolic reactions include oxidative elimination of triazole ring; hydroxylation of C bearing CH3 group; oxidation of CH3 group to carbinol & further to oxidation carboxylic acid; rapid excretion with majority appearing in feces [biliary excretion]; residual '4C found within renal fat, adrenals, liver; potential liver accumulation in long-term studies.

Table A.2. Subchronic, Chronic, and Other Toxicity Profile of Cyproconazole.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	46152903 (2003) 0.5 mg/kg. Animals were dosed with the radioactive test substance daily for up to 14 days	The majority of the total administered dose (96.5%) was recovered in the feces (56.3%) and urine (40.2%). The highest blood levels were found ten days after the start of dosing (0.08 ppm SAN 619F equivalents). Three days after the final dosing, radioactivity was almost completely excreted. The calculated half-life for the depletion of radioactivity (assuming mono-phasic first-order kinetics) from the tissues ranged from one to three days. The greater persistence and longer half-life of radioactivity in blood compared to plasma indicated some partitioning of radioactivity into the red blood cells. The highest concentrations of radioactivity were observed in the liver (1.37 ppm SAN 619F equivalents), adrenals (0.93 ppm), lungs (0.56 ppm), fat (0.49 ppm), kidneys (0.25 ppm), pancreas, (0.22 ppm), and ovaries (0.16 ppm) seven days after the start of dosing. Urine was found to contain at least 21 metabolite fractions by two-dimensional TLC. Individual fractions were detected in similar proportions on Days 0-1, 6-7, and 13-14. The combined urinary metabolite fractions accounted for 20.8-41.0% of the daily administered doses.
870.7600	Dermal penetration (rat)	43 173701 (1993), Acceptable/guideline 0, 2.5 15 and 120 ug/cm2 for 0.5, 1,2,4 10,24 hr	At dose levels of 2.5, 15, and 120 .ig/cm2 cyproconazole, the percent absorbed [0.87-7.69, 0.59-11.88, and 0.92-0.89, respectively] increased with duration of exposure and decreased with dose. The quantity absorbed increased with dose and duration of exposure. At the 10-hour exposure time point, 10.8 1% of the low dose was absorbed. % absorbed = 11% for 10 hours

Cyproconazole Toxicology Executive Summaries

Reference: Memo, P. Terse, TXR No. 0053768, 11/17/2005.

1) Developmental Toxicity Study in New Zealand Rabbits MRID 42175401

In a developmental toxicity study (MRID 42175401), cyproconazole (95% a.i. Batch # 8507)) was administered to pregnant New Zealand White rabbits (18/dose) in 1% aqueous methyl cellulose by gavage at dose levels of 0, 2, 10, or 50 mg/kg bw/day from days 6 through 18 of gestation.

Maternal toxicity as indicated by decreased body-weight gain and food consumption was observed at the high-dose level. The pregnancy rate was 88.9% in the control, low-, and mid-dose groups and 77.8% in the high-dose group. The number of litters with viable young was 16, 11, 14, and 10 for the control, low-, mid-, and high-dose groups, respectively. There was no effect noted on the numbers of implants or live fetuses per doe, on the number of resorptions or fetal deaths, and overall mean fetal weight and mean fetal weight/sex were comparable among the groups. Pre- and post-implantation losses were comparable among the groups.

There was an increased incidence of total external/visceral or skeletal malformations at the high-dose level, which was statistically significant when compared to the concurrent control group. The incidence in external/visceral and skeletal variations was increased in a dose-related manner in some instances. It is concluded that the highest dose level resulted in a slight increase in the incidence of several malformations and variations. This is based on the facts that (1) several of the malformations were not observed in either the concurrent control or historical control data; (2) each of these malformations occurred in more than one fetus and in more than one litter; (3) the malformation, malrotated hindlimbs, was also observed at the mid-dose but at a lower incidence than in the high-dose group (dose-related); (4) of the twenty-three skeletal malformations observed in the study, all but 4 were observed only at the high-dose level [one control fetus had one malformation, one mid-dose fetus displayed 3 malformations, and one additional mid-dose fetus displayed 1 malformation (2 different litters)]; and (5) the mid- and high-dose fetuses displayed more malformations/variations per fetus than the low-dose, concurrent, and historical control groups. Also to be considered are the facts that (1) the high-dose had the highest number of non-pregnant does and, were these does to have been pregnant, the number of fetal findings might have been greater for this group; and (2) both the mid- and high-dose groups had fewer fetuses/litter than the low-dose and control groups [5.O and 5.5 vs 6.9 and 6.4, respectively).

The maternal NOAEL was 10 mg/kg/day, the LOAEL was 50 mg/kg/day, based on decreased body-weight gains and food consumption.

The developmental toxicity NOAEL was 2 mg/kg/day, the LOAEL was 10 mg/kg/day, based on the increased incidence of malformed fetuses and litters with malformed fetuses.

This developmental toxicity study is classified **acceptable/Guideline** and satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit.

This study provided the basis for the dose and endpoint selected for acute dietary and short- and intermediate-term dermal and inhalation assessment.

2) Chronic Toxicity Study in Beagle Dogs MRID 41212901

In a chronic toxicity study (MRID 41212901), cyproconazole (95% a.i.) was administered through diet to 4 beagle dogs/sex/dose at concentrations of 0, 30, 100 or 350 ppm [equivalent to 0, 1.0, 3.2, or 12.1 9 (males); 12.6 (females) mg/kg/day, respectively] for 52 weeks.

The results indicated liver as a target organ of toxicity. Absolute and relative liver weights were increased in the high dose animals of both sexes compared to controls but statistical significance was attained only in the males. Elevated alkaline phosphatase and ALT levels (males), decreased total protein, albumin and cholesterol levels were observed in high dose animals. Relative kidney weight was increased significantly in both the low and high dose females but there was no dose dependence. Statistically significant increases were observed in cytochrome P450 in both sexes of the high dose and in the mid dose females. Glutathione S-transferase (GST) values in the mid and high dose females were significantly and dose dependently decreased. Laminar eosinophilic intrahepatocytic bodies were observed in all high dose males, one mid dose male and two high dose females.

Under the conditions of this study, the LOAEL for cyproconazole in beagle dogs is 3.2 mg/kg/day (100ppm), based on liver effects [P450 induction and GST inhibition in females and histopathology (laminar eosinophilic intrahepatocytic bodies in male)]. The NOAEL is 1.0 mg/kg/day (30 ppm).

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in dog.

This study provided the basis for the dose and endpoint selected for chronic dietary, long-term dermal and inhalation assessment.

3) Subchronic Oral Toxicity Study in Rats MRID 46152901

In a subchronic oral toxicity study (MRID 46152901), SAN 619 A (Cyproconazole, 95.5% a.i., Batch # Charge 8507) was administered to 15 Wistar rats/sex/dose in the diet at dose levels of 0, 20, 350, 700, or 1400 ppm (equivalent to 0/0, 1.4/1.6, 24.7/29.6, 52.8/57.3, and 106.8/118.1 mg/kg/day in males/females) for 13 weeks. Five rats/sex/dose were subjected to neuropathological examination, and also evaluated in the functional observational battery, and for the assessment of motor activity.

No treatment-related effect was observed on survival, clinical signs, the functional observational battery, food consumption ratios, water consumption, the eyes, gross pathology or neuropathology.

At ≥350 ppm, absolute and relative to body liver weights were increased (p≤0.05) by 13-55% in the both sexes. Increased incidences of liver fatty change in males and liver hypertrophy in both sexes were observed. Increased incidences of thyroid gland follicular hypertrophy were noted in both sexes. Pituitary gland distal lobe hypertrophy was observed in the males. Additionally, relative to body spleen weights were decreased (p≤0.05) in the females by 14-25%, compared to controls.

Systemically, body weights and cumulative body weight gains were decreased (p≤0.01) throughout treatment in the ≥700 ppm males and 1400 ppm females. Food consumption was reduced (p≤0.01) in the 1400 ppm males during Weeks 1-7 and 11-13, and overall mean food consumption (calculated by reviewers) was also decreased. Motor activity was decreased (p≤0.05) in the 1400 ppm males at Week 13 in total distance, number of movements, and movement times.

Additional effects were observed on the liver. Increased (p≤0.001) gamma-glutamyl transpeptidase was observed in the 1400 ppm males and the ≥700 ppm females. Additional differences (p≤0.01) noted at 1400 ppm included increased alanine aminotransferase and aspartate aminotransferase in the males, decreased triglycerides in the males, and increased cholesterol and globulin in the females.

Increased (p≤0.05) leukocytes were observed in the ≥700 ppm groups. Several types of leukocytes were increased in number (g/l) in the 700 and/or 1400 ppm groups, including neutrophils, lymphocytes, monocytes, and large unstained cells. Urinary leukocyte levels were increased (p≤0.05) in the 1400 ppm males.

In addition to the increase in relative to body spleen weight, spleen congestion was also observed in the ≥700 ppm females. Additionally, a decreased incidence of extramedullary hematopoiesis in the spleen was noted in the 1400 ppm group.

Increased incidences of the following microscopic lesions were also observed: (i) fatty change in the adrenal cortex in ≥700 ppm males; (ii) single cell necrosis in the adrenal gland cortex in ≥700 ppm females; (iii) ceroid deposition in the adrenal gland cortex in ≥700 ppm females; and (iv) renal hemosiderosis in the 1400 ppm males and ≥700 ppm females.

The LOAEL is 350 ppm (equivalent to 24.7/29.6 mg/kg/day in males/females), based on increased liver weight and increased incidence of liver hypertrophy in both sexes and increased incidence of liver fatty change in males. The NOAEL is 20 ppm (equivalent to 1.4/1.6 mg/kg/day in males/females).

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3100a; OECD 408) for a subchronic oral toxicity study in the rat.

This study provided the basis for the dose and endpoint selected for short- and intermediate-term incidental oral risk assessment.

4) 21-Day Dermal Toxicity Study in New Zealand White Rabbits MRID 43968317

In a 21-day dermal toxicity study (MRID 43968317), SAN 619 F 320 SC 412 DP Formulation (29.4% a.i.; Batch #: 6616-01) was applied as supplied to the shaved intact skin of 5 New Zealand White rabbits/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day (limit dose), 6 hours/day for at least 21 consecutive days. Dermal irritation was evaluated daily using the Draize method.

No compound-related effects on mortality, clinical signs, body weight, body weight gain, food consumption, organ weights, or gross pathology were observed.

At 1000 mg/kg/day, dermal irritation characterized by slight to well defined erythema and edema with sloughing was observed in both sexes. Histopathological effects observed in the treated skin in both sexes included: (i) trace to minimal diffuse acanthosis; (ii) trace to minimal diffuse inflammatory cells in the superficial dermis; and (iii) minimal diffuse hyperkeratosis. The dermal effects were transient in the males (occurring between Days 5-15) and only slight erythema was observed in 3/5 females from Day 15 to the end of the study.

The systemic LOAEL was not observed. The systemic NOAEL is 1000 mg/kg/day (limit dose).

The dermal LOAEL was established at 1000 mg/kg/day (limit dose) based on erythema, edema, sloughing and histopathological effects (acanthosis, inflammatory cells infiltration, and hyperkeratosis) in both sexes. The dermal NOAEL is 300 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.3200; OECD 410) for a 21-day dermal toxicity study in rabbits.

5) Dermal Penetration Study in Human and Rat Skin MRID 44883301

In a non-guideline study (MRID 44883301), the penetration rate of [^{14}C]-cyproconazole through human and rat skin was assessed *in vitro*. [^{14}C]-Cyproconazole (>98% radiochemical purity, batch # 900919) was mixed with SAN 1414 F 360 SL 001 BS (6.41% w/w cyproconazole, 300 g/L didecyldimethylammonium chloride) to a final nominal radioactive concentration of 1 µCi/18 mg, at nominal doses of 0.641, 0.01, or 0.0012 mg a.i./cm^2. The doses approximated exposure to the undiluted commercial formulation and to the dilute aqueous spray used in the field. The formulated test substance was applied to excised rat skin or human skin (1.77 cm^2/sample) mounted in an *in vitro* dermal penetration cell to compare the rates of dermal penetration. Ten samples of each type of tissue were treated and results from the first five were reported. The integrity of the skin was first tested using tritiated water, and then penetration of the test formulations was measured at 0, 1, 2, 4, 6, 10, and 24 h following application to the skin samples.

The rate of penetration of [^{14}C]-cyproconazole following dermal application of SAN 1414 F 360 SL 001 BS was greater through rat skin than through human skin. The rate of penetration of the undiluted formulation through rat skin was 12.30 µg/cm^2/h, compared to 0.501 µg/cm^2/h for

human skin. As the dilution factor increased, the rate of penetration decreased, and the permeability coefficients increased.

Recovery of radioactivity from the isolated rat and human skin samples was >90% of the applied dose for all formulations. The amount of radioactivity found in the receptor fluid was greater for rat skin (32.39-72.40% of the applied dose) than for human skin (1.32-49.22% of the applied dose), reflecting the greater permeability of rat skin compared to human skin. This percentage increased with increasing dilution for both species.

For rat skin, the percentage of radioactivity recovered in the surface wash (8.88-16.47% of the applied dose) was less than that recovered in the skin sample (17.45-50.78% of the applied dose). Conversely, for human skin, the percentage of radioactivity recovered in the surface wash (35.52-66.42% of the applied dose) was greater than that recovered in the skin sample (22.54-27.44% of the applied dose).

This study is classified as **acceptable/non-guideline**.

6) *In Vivo* Bone Marrow Chromosome Aberration Assay MRID 46152902

In an *in vivo* bone marrow chromosome aberration assay (MRID 46152902), 5 CD1 mice/sex/dose/sampling time were treated once via oral gavage (10 mL/kg) with SAN 619 A (Cyproconazole; 95.5% a.i., Batch #: CHARGE 8507) in Arachis oil at doses of 0, 50, 100, or 200 mg/kg. Bone marrow cells were harvested at 16, 24, or 48 hours after treatment in the 0 and 200 mg/kg groups, and after 24 hours in the 50 and 100 mg/kg treatment groups and the positive controls (cyclophosphamide; 64 mg/kg).

No mortalities were observed. Signs of toxicity (hyperactivity, ataxia, piloerection, hunched posture, and decreased body weight) were observed at 200 mg/kg, and to a lesser degree at 100 mg/kg. Although there was no indication of bone marrow toxicity (decreased mitotic index), the animals received the maximum tolerated dose (MTD). No treatment-related increases in the percent of aberrant cells (including or excluding gaps) were observed at any dose or sampling time compared to concurrent controls. The positive control induced the appropriate response. **There was no evidence of chromosome aberration induced over background.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirement (OPPTS 870.5385; OECD 475) for *in vivo* cytogenetic mutagenicity data.

In a rat metabolism study (MRID 46152903, 46622801), [Phenyl-U-^{14}C]-SAN 619F (cyproconazole; Batch # ILA-117.1; 95.9% radiochemical purity) in 2/2/1 polyethylene glycol/ethanol/water (v/v) was administered to female HanBrl: WIST (SPF) rats by gavage at a nominal dose level of 0.5 mg/kg. Animals were dosed with the radioactive test substance daily for up to 14 days, and groups of four rats were killed 1, 7, 14, or 20 days after the first administration. The distribution of radioactivity between tissues was determined in all subgroups. Radioactivity in the urine, feces, and blood was measured, and identification of metabolites in the urine and feces was determined in the subgroup of rats killed 20 days after the first administration.

Recovery of [Phenyl-U-^{14}C]-SAN 619F was 97.1% of the total administered dose seven days after administration of the last dose. The majority of the total administered dose (96.5%) was recovered in the feces (56.3%) and urine (40.2%). The cage wash accounted for 0.19%, while the carcass/tissues retained ≤0.42% of the total administered dose.

Blood kinetics showed increasing residue values with ongoing administrations, peaking at approximately 0.075 ppm SAN 619F equivalents within eight days after the start of dosing. The highest blood levels were found ten days after the start of dosing (0.08 ppm SAN 619F equivalents). After administration of the final dose, blood residues declined rapidly, with a depletion half-life of approximately 40 h.

During the dosing period, a steady state in terms of excretion was reached approximately four days after the first administration. Thereafter, the amount of daily excretion remained nearly constant until the end of dosing, accounting for approximately 40% of the daily dose for urine and 55% of the daily dose for feces. Three days after the final dosing, radioactivity was almost completely excreted.

The levels of radioactivity reached plateau levels by seven days after the start of dosing, and decreased rapidly once dosing ceased. The calculated half-life for the depletion of radioactivity (assuming mono-phasic first-order kinetics) from the tissues ranged from one to three days. The greater persistence and longer half-life of radioactivity in blood compared to plasma indicated some partitioning of radioactivity into the red blood cells. The highest concentrations of radioactivity were observed in the liver (1.37 ppm SAN 619F equivalents), adrenals (0.93 ppm), lungs (0.56 ppm), fat (0.49 ppm), kidneys (0.25 ppm), pancreas, (0.22 ppm), and ovaries (0.16 ppm) seven days after the start of dosing. All other tissues had concentrations of radioactivity that were comparable to or below the concentrations in blood throughout the time course.

Urine was found to contain at least 21 metabolite fractions by two-dimensional TLC. Individual fractions were detected in similar proportions on Days 0-1, 6-7, and 13-14. The combined urinary metabolite fractions accounted for 20.8-41.0% of the daily administered doses.

More than 92.5% of the radioactivity was extractable from feces, accounting for 25.6-56.3% of the administered daily dose. Feces were found to contain at least 13 metabolite fractions by two-dimensional TLC. The combined fecal metabolite fractions accounted for 23.7-52.5% of the administered daily dose, while non-extractable radioactivity accounted for 1.9-3.8% of the daily dose. Two of the fractions (Fractions 9 and 10) were identified as unmetabolized parent, and Fraction 6 was identified as NOA 421153 (a diol metabolite of SAN 619F).

This metabolism study in the rat is classified **acceptable/guideline** and does satisfy the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OPP 85-1] in rats.
In a non-guideline study (MRID 46152909.), 5 CD-1 (Crl:CD®-1 (ICR) BR) mice/sex/dose were exposed to SAN 619 A (Cyproconazole; 97.4% a.i.; Lot #: MU 809073) daily in the diet at concentrations of 0, 50, 100 or 200 ppm (equivalent to 0/0, 9.0/12.7, 16.7/21.5, and 24.8/29.5 mg/kg/day [M/F], respectively) for 14 days. An additional group of 5 mice/sex was treated with phenobarbitone, a known potent hepatic enzyme inducer. On Day 15, all animals were killed

and the livers of all animals were either processed or frozen. The hepatic 100x*g* supernatant, microsomal fraction, and cytosolic fraction were obtained by standard differential centrifugation, and protein contents, microsomal cytochrome P450 content, enzyme activities, and immunoblot analysis for isozyme-specific cytochrome P450 expression were determined. The purpose of this study was to examine whether repeated administration of SAN 619 A caused induction of enzymes in the liver and to compare induction to phenobarbitone.

No effects of treatment were observed on mortality, clinical observations, body weights, food consumption, gross pathology, or carcass weight. Relative (to body) liver weights were increased ($p \leq 0.05$) in both sexes at $\geq$100 ppm. Absolute liver weights were increased ($p \leq 0.001$) in the 200 ppm males and the $\geq$100 ppm females. At $\geq$50 ppm, an increased incidence of centrilobular and midzonal hepatocellular hypertrophy in both sexes was observed with a dose-dependent increase in severity. In both sexes, hypertrophy was frequently associated with centrilobular cytoplasmic vacuolation and hepatocellular necrosis. At 200 ppm, an increase in the incidence of mitotic activity was observed. These liver weight and histopathological changes were similar to those observed in phenobarbitone-treated animals.

Hepatic microsomal protein content in females and cytochrome P450 content in both sexes were increased at $\geq$50 ppm. Except for an additional increase in the protein content in the 100x*g* supernatant in phenobarbitone-treated females, similar effects on protein content were observed between mice treated with SAN 619 A and phenobarbitone. At $\geq$50 ppm, hepatic 7-pentoxyresorufin O-dependentylation (PROD), 7-benzyloxyresorufin O-debenzylation (BROD), coumarin 7-hydroxylation (COH) activities were increased ($p \leq 0.05$) in both sexes. Microsomal epoxide hydrolase (EH) and glutathione S-transferases (GST) activities were increased ($p \leq 0.05$) in males at 200 ppm and $\geq$50 ppm, respectively. In females, EH and GST activities were both increased ($p \leq 0.01$) at $\geq$100 ppm. Additionally in females, 7-Methoxyresorufin O-demethylation (MROD) and 7-ethoxyresorufin O-deethylation (EROD) were increased ($p \leq 0.001$) at ≥50 ppm. Slight increases ($p \leq 0.05$) in lauric acid 11- and 12-hydroxylation activities were also observed in females at $\geq$50 ppm. The determination of regio- and stereoselective hydroxylation of testosterone demonstrated an increase in total oxidation rates of testosterone for both sexes of SAN 619 A-treated mice. Oxidation at all positions, except the 1α position in males, contributed to this increase. The expression of CYP 1A2, CYP 3A, and two protein bands for CYP 2B, as determined by immunoblot analysis, was increased in both sexes of SAN 619 A-treated mice at $\geq$50 ppm. In females, expression of one of two protein bands for CYP 4A was slightly decreased at ≥100 ppm.

The induction of enzyme activities and cytochrome P450 enzyme expression were similar to those observed for phenobarbitone. In phenobarbitone-treated mice, increases ($p \leq 0.01$) were also observed in activities for UDP-glucuronosyltransferase in both sexes and MROD, EROD, and lauric acid 11-hydroxylation in males, but increased lauric acid 12-hydroxylation activity was not observed in phenobarbitone-treated females. Additionally, peroxisomal fatty acid oxidation was slightly decreased ($p \leq 0.01$) in phenobarbitone-treated males. The profile of testosterone metabolism in phenobarbitone-treated mice was similar to that observed for mice treated with 200 ppm SAN 619 A. However, oxidation at the 16α position in females and the 6α position in both sexes was more potent, and conversion to androstenedione in both sexes was less potent when compared to SAN 619 A-treated mice. The expression of CYP 1A2 in

phenobarbitone-treated females, was considerably higher in than that observed at 200 ppm in SAN 619 A-treated mice. Additionally, decreased expression of both protein bands identified by the antibody for CYP 4A were observed in both sexes of phenobarbitone-treated mice, but not SAN 619 A-treated mice.

In summary, these results demonstrate an increase in isozyme-specific cytochrome P450 activities (CYP 2B, CYP 2D, and CYP 3A families, CYP 2A4/5, and CYP 2A12 in both sexes and CYP 1A1/2, 2E1, and 4A in females) and expression (CYP 1A2, CYP 3A, and CYP 2B), and increased phase II enzyme activities (EH and GST in both sexes and lauric acid 11- and 12-hydroxylation in females).

The submitted study is classified as **acceptable/non-guideline**.

7) 13-Week feeding Study in Beagle Dogs MRID 40607719

In a 13 Week feeding study (MRID 40607719), cyproconazole (95.6% a.i.) was administered through diet to 4 beagle dogs/sex/dose at concentrations of 0, 20, 100 or 500 ppm (approximately 0, 0.8, 4.0, or 20 mg/kg/day) for 13 weeks.

Changes associated with treatment observed in both sexes administered the highest dietary level, included "slack muscle tone", inhibited body weight gain, increased platelet counts, decreased: bilirubin, total cholesterol, HDL-cholesterol, triglycerides, total protein and albumin and increased alkaline phosphatase and gamma glutamyl transferase. Decreased food consumption was seen in high dose males. Increased absolute and relative liver weights and increased relative kidney weights were noted for high dose males and females; relative brain weights were increased in high dose females. Histopathologic evidence of liver toxicity in high dose males and females included hepatocytomegaly, degeneration of single hepatocytes and cytoplasmic inclusions. Evidence of liver effects in mid dose dogs was increased absolute liver weights in males and hepatocytomegaly in males and females. However, these effects were considered adaptive changes.

Under the conditions of this study, the LOAEL for cyproconazole in beagle dogs is 20.0 mg/kg/day (500 ppm), based on "slack muscle tone", inhibited body weight gain, liver effects (increased alkaline phosphatase and gamma glutamyl transferase) and histopathologic evidences (hepatocytomegaly, degeneration of single hepatocytes and cytoplasmic inclusions). The NOAEL is 4.0 mg/kg/day (100 ppm).

This subchronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in non-rodent.

8) Developmental Toxicity Study in Chinchilla Rabbits MRID 40607720

In a developmental toxicity study (MRID 40607720), SAN 619F (95.6 % a.i. Lot # 8507)) was administered to pregnant Chinchilla rabbits (16/group) in 4% aqueous methyl cellulose by gavage at dose levels of 0, 2, 10, or 50 mg/kg bw/day from days 6 through 18 of gestation.

Evidence of maternal toxicity included reduced body weight gain (-26%) during treatment and decreased food consumption during the initial phase of treatment, both at 50 mg/kg. However, corrected body weight changes between groups were comparable indicating maternal changes in body weight gain could be due to increased resorptions.

Developmental toxicity, observed at 50 mg/kg, was evident from the decreased number of live fetuses/dam and an increased incidence of non-ossification in certain forelimb and hindlimb digits. Evidence of Developmental toxicity at dosages of 10 and 50 mg/kg was indicated by an increased incidence of embryonic and fetal resorptions.

Evidence of developmental toxicity included hydrocephalus internus, observed in 1 fetus at each dosage level, and agenesia of the left kidney and ureter in 1 high-dose fetus. The incidence of hydrocephalus internus was 0.85, 0.83 and 0.93 for the low-, mid- and high-dose fetuses and 0.08 for the historical control incidence. Hydrocephaly was also seen at 2 dosage levels in a developmental toxicity study in rats with this test material, however, this anomaly did not occur in the concurrent controls of either study. In the another developmental toxicity study in New Zealand White rabbits, Hydrocephaly was not seen.

The maternal NOAEL was 10 mg/kg, the LOAEL was 50 mg/kg, based on decreased body-weight gains and food consumption.

Developmental toxicity NOAEL was not attained; Developmental LOAEL was 2 mg/kg, based on incidence of hydrocephalus internus.

This developmental toxicity study is classified **Unacceptable/Guideline** and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rabbit because: 1) a NOAEL for developmental toxicity apparently was not attained and 2) the concentrations of test material were not within the acceptable range (± 15% of nominal concentration) for the mid- and high dose suspensions immediately after preparation.

In a developmental toxicity study (MRID 40607721), SAN 619F (95% a.i. Lot # 8507)) was administered to pregnant Wistar/Han rats (25/dose) in 4% aqueous methyl cellulose by gavage at dose levels of 0, 6, 12, 24 or 48 mg/kg bw/day from days 6 through 15 of gestation.

Evidence of maternal toxicity included inhibited body weight gain (11.4%) during treatment at dosage levels of 12 mg/kg and above and decreased body weight and food consumption among females in the 24 and 48 mg/kg dosage groups. These differences in maternal body weights could have been influenced by treatment-related intrauterine effects (e.g., increased number of resorptions, decreased fetal weight). Evidence of fetal toxicity was apparent from observed dose-related increases in the number of litters with supernumerary ribs at dosages 12 mg/kg and above. Developmental toxicity was apparent at 24 and 48 mg/kg from the following observations: decreased total number of fetuses/dam, decreased number of live fetuses/dam, increased percentage and number of fetal resorptions, decreased body weight and incomplete ossification in phalangeal nuclei and the absence of ossification in calcanea. There was evidence of developmental toxicity in the 24 and 48 mg/kg groups. Hydrocephaly was observed in 1 fetus in the 24 mg/kg and 2 fetuses in the 48 mg/kg groups. Cleft palate was observed in 2 fetuses in

the 48 mg/kg group.

The maternal NOAEL was 6 mg/kg, the LOAEL at 12 mg/kg based on decreased body weight gain during treatment. The developmental toxicity NOAEL was 6 mg/kg, the LOAEL at 12 mg/kg based on increased incidence of supernumerary ribs.

This developmental toxicity study is classified **acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

9) Two-Generation Reproductive Toxicity Study in Rats MRID 40607723

In a 2-generation reproduction study (MRID 40607723) cyproconazole (purity, 95.6% a.i.; lot # 8507) was administered to groups of 26/sex KFM-Wistar albino rats/dose, in the diet, at concentrations of 0, 4, 20, or 120 ppm (F0, M/F: 0, 0.28/0.33, 1.39/1.67, 8.29/9.88 mg/kg/day, respectively) during the pre-mating (10 wks and 12 wks, for the F0 and F1 generation, respectively), mating, pregnancy and lactation periods.

Two of the reproductive parameters investigated in parental animals were affected by treatment in F0 animals only: the duration of gestation at the mid- and high doses was increased and a lower number of implantation sites was seen in high-dose females, both in comparison to respective concurrent control values. However, the HED/Peer Review committee (TXR # 0053466, Nov 15, 1993) concluded that the effects noted (increased gestation length and litter size) were not treatment related. Evidence of liver toxicity was seen in high dose F0 males (increased lipid storage and relative weight) and females (increased relative weight).

Parameters examined among the offspring which showed treatment-related effects included decreased litter sizes in both the F1 and F2 high-dose groups and the F1 mid-dose group during the early phase of lactation (litters were standardized at day 4 post partum), decreased live birth index in the high-dose F1 offspring and decreased viability index in the high-dose F1 and F2 offspring. However, the HED/Peer Review committee (TXR # 0053466, Nov 15, 1993) concluded that the effects noted (litter size) were not treatment related.

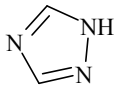
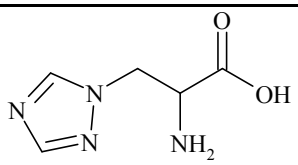
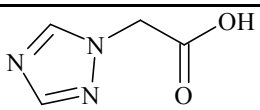
The parental LOAEL for the systemic toxicity is 120 ppm (8.29 mg/kg/day), based on liver effects ((increased lipid storage and relative weight). The parental NOAEL for systemic toxicity is 20 ppm (1.39 mg/kg/day).

The offspring toxicity NOAEL is > 120 ppm (8.29 mg/kg/day), LOAEL is not established.

The reproductive toxicity NOAEL is > 120 ppm (8.29 mg/kg/day), LOAEL is not established.

This study is classified **Acceptable/Guideline** and satisfies the guideline requirement (It was noted that although dose levels were not adequate, study need not be repeated since similar effects (increased resorptions, decreased litter size) were observed in the rat developmental study at dose levels of 24 and 48 mg/kg and a NOAEL for these effects was established in that study.

Appendix B

Nomenclature of Triazole-related Metabolites.	
Compound	
Common name (Abbr)	1,2,4-Triazole (Triazole)
Chemical Name	1*H*-1,2,4-Triazole
CAS registry number	288-88-0
Compound	
Common name (Abbr)	Triazole alanine (TA)
Chemical Name	α-amino-1*H*-1,2,4-triazole-1-proanoic acid
CAS registry number	114419-45-3
Compound	
Common name (Abbr)	Triazole Acetic Acid (TAA)
Chemical Name	1*H*-1,2,4-Triazole-1-Acetic acid
CAS registry number	28711-29-7

Proposed Metabolic Profile of Cyproconazole in Laying Hens.