UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 09/06/07

MEMORANDUM

SUBJECT: *Metconazole*: Human Health Risk Assessment for Proposed New Uses on Turf and Ornamentals. PC Code: 125619, DP Barcode: D328676.

Risk Assessment Type: Single Chemical

FROM: Barry O'Keefe, Risk Assessor/Biologist
Nancy Dodd, Chemist
Jack Arthur, Environmental Scientist
Registration Action Branch 3 (RAB3)
Health Effects Division (7509C)

AND

Gregory Akerman, Ph.D., Toxicologist
Toxicology Branch
Health Effects Division (7509C)

THROUGH: Paula Deschamp, Branch Chief
Registration Action Branch 3
Health Effects Division (7509C)

TO: Mary Waller, RM Team 21
Fungicide Branch
Registration Division (RD) (7505C)

The Registration Division (RD) of OPP has requested that HED evaluate newly submitted toxicology data and conduct occupational, residential, dietary and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the proposed use of metconazole on turf grass and ornamentals.

Valent U.S.A. Corporation has requested registration of the fungicide metconazole to control plant disease organisms on ornamental plants in commercial indoor and outdoor nurseries, greenhouses and commercial and residential landscaped areas, and on turfgrass, including golf courses and residential lawns. Please refer to the previous most recent HED risk assessment completed for the active ingredient metconazole (DP Barcode 308794, B. O'Keefe, 07/06/06) for

any detailed information not pertinent to, or covered by this current risk assessment.

A summary of the findings and an assessment of human risk resulting from the proposed uses of metconazole on turf and ornamentals are provided in this document. The hazard assessment was provided by Gregory Akerman of Toxicology Branch, the dietary exposure assessment by Nancy Dodd of RAB3, the occupational and residential exposure assessment by Jack Arthur of RAB3, the drinking water assessment by Amer Al-Mudallal of the Environmental Fate and Effects Division, and the risk assessment by Barry O'Keefe.

There is currently one permanent established tolerance for metconazole at 0.1 ppm in/on banana. Additionally, there are currently no U.S. products registered for metconazole and no permanent U.S. registrations. There is a Section 18 for use of metconazole on soybeans.

Recommendations

No deficiencies were noted in the submitted request that would preclude the establishment of Section 3 uses on turf and ornamentals.

The proposed V-10116 VPP Fungicide label contains inconsistencies concerning the retreatment intervals for foliar applications to ornamental plants. The proposed label lists the interval as both 14 to 21 days and 14 to 28 days. HED recommends that the proposed label be modified to include the appropriate retreatment interval; i.e. either 14 to 21 days, or 14 to 28 days.

An inhalation toxicity study is required.

Table of Contents

1.0 Executive Summary

Metconazole (5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol) is a systemic broad-spectrum triazole that works systemically by preventing spore formation and inhibiting mycelial growth.

There is currently one permanent established tolerance for metconazole at 0.1 ppm in/on banana. Additionally, there are currently no U.S. products registered for metconazole and no permanent U.S. registrations. There is a Section 18 for use of metconazole on soybeans.

Proposed Uses

Valent U.S.A Corporation has requested registration of the fungicide metconazole to control plant disease organisms on ornamental plants in commercial indoor and outdoor nurseries, greenhouses and commercial and residential landscaped areas, and on turfgrass, including golf courses and residential lawns.

Metconazole is being proposed for use in a 50% active ingredient (ai) water dispersible granular formulation (V-10116 VPP Fungicide).

Toxicity/Hazard

The toxicological database for metconazole is complete and adequate to support the proposed use on turf and ornamentals.

The toxicology team from the Toxicology Branch of the HED evaluated the toxicology database of metconazole, selected toxicological endpoints for acute dietary and chronic dietary assessments, and reviewed the recommended acute and chronic Reference Doses (RfD). Toxicological endpoints were also chosen for occupational/residential exposure risk assessments. The toxicology risk assessment team addressed the potential enhanced sensitivity to infants and children as required by FQPA, in accordance with the 2002 OPP 10x Guidance document, and recommended reducing the 10X FQPA Safety Factor to 1X for the dietary and residential risk assessments. Metconazole is "Not Likely to be Carcinogenic to Humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range.

The acute population-adjusted dose (aPAD) for females age 13-49 years is 0.12 mg/kg/day, based on increases in skeletal variations in a developmental toxicity study in rats (NOAEL of 12 mg/kg/day; LOAEL of 30 mg/kg/day). An aPAD was not determined for the general population, including children and all infants, because an appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed.

The chronic population-adjusted dose (cPAD) for all populations is 0.04 mg/kg/day, based on increased liver weights and associated hepatocellular lipid vacuolation and centrilobular hypertrophy in males and females, plus increased spleen weights in females, in a chronic oral toxicity study in rats (NOAEL of 4.3 mg/kg/day; LOAEL of 13.1 mg/kg/day).

Dermal toxicity endpoints were not identified for the durations applicable to the proposed uses (i.e., short- and intermediate-term). Short-term inhalation and incidental oral risks are based on a toxicity endpoint NOAEL = 9.1 mg/kg/day from a 28-Day oral toxicity study in rats [LOAEL = 90.5 mg/kg/day based on decreased body weight (M), increased liver and kidney weight and hepatocellular hypertrophy and vacuolation (M/F)]. Intermediate-term inhalation and incidental oral risks are based on a toxicity endpoint NOAEL = 6.4 mg/kg/day from a 90-Day oral toxicity study in rats [LOAEL = 19.2 based on increased spleen wt (F) and hepatic vacuolation (M)].

Dietary Exposure/Risk Assessment

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support Section 3 requests for uses on turf and ornamentals.

Acute Dietary (Food and Drinking Water) Exposure Results and Characterization

An acute dietary (food and drinking water) exposure assessment was conducted for the proposed uses on turf and ornamentals, all registered food uses (imported bananas, and Section 18 on soybeans), and drinking water. The residue levels used in the assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities, and assumed 100% crop treated. Therefore, the acute dietary, food only, exposure is considered an upper bound conservative estimate.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the acute assessment. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors. The 1 in 10 year annual peak concentration of metconazole in drinking water is not expected to exceed 45.48 µg /L.

For the general U.S. population, including infants and children, an appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed. Therefore, acute dietary exposure and risk to these populations cannot be assessed. The acute dietary exposure estimate at the 95th percentile is 2% aPAD for females 13-49 years old, the only population subgroup of concern, which is below HED's level of concern.

Chronic Dietary (Food and Drinking Water) Exposure Results and Characterization

A chronic dietary (food and drinking water) exposure assessment was conducted for the proposed uses on turf and ornamentals, all established food uses (soybeans and imported bananas), and drinking water. The residue levels used in the assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities, and assumed 100% crop treated. Therefore, the chronic dietary, food only, exposure is considered an upper

bound conservative estimate.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the chronic assessment. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors. The 1 in 10 year annual average concentration of metconazole in drinking water is not expected to exceed 31.25 µg /L.

The chronic dietary (food and drinking water) exposure to metconazole is below HED's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 4% cPAD for the general U.S. population and 10% cPAD for all infants (<1 year old), the most highly exposed population subgroup.

Residential Exposure/Risk Assessment

There is potential adult short-term dermal and inhalation exposure to metconazole from its proposed use on turf and ornamentals. However, because dermal toxicity endpoints for the appropriate duration of exposure were not identified, only residential handler inhalation exposures/risks have been assessed.

An MOE ≥100 is adequate to protect residential pesticide handlers. All metconazole residential handler MOEs are estimated to be >100 for the proposed uses, and therefore, do not cause concern for HED.

Adults, adolescents and toddlers may be exposed to metconazole from its proposed residential uses. Adults and adolescents may experience short- and intermediate-term dermal exposure from golfing and other activities on treated turf, as well as from tending treated ornamentals. Toddlers may experience short- and intermediate-term dermal and incidental oral exposure from activities on treated turf. Because dermal toxicity endpoints for the appropriate durations of exposure were not identified, and because inhalation exposure is considered to be insignificant for postapplication exposures, only toddler incidental oral postapplication exposures have been assessed. Chemical-specific turf transferable residue studies were submitted for use in estimating postapplication exposures.

Postapplication risks to toddlers following the application of metconazole to home lawns were calculated for short- and intermediate-term exposures. All MOEs for the toddler lawn exposure scenarios were >100, and therefore, are not of concern to HED. In addition the total MOE for combined toddler exposures (i.e., hand-to-mouth, object-to-mouth, and incidental ingestion of soil) is >100, and therefore, does not concern HED.

Aggregate Risk Assessment

Dietary, incidental oral and inhalation routes of exposure have the same toxicity endpoints, and therefore, can be aggregated. Acute and chronic dietary routes of exposure, then acute, chronic, short-term, and intermediate-term aggregate exposure and risk assessments are required. The

acute and chronic dietary (food + drinking water) aggregate assessments are covered in the dietary section of this executive summary.

The short- and intermediate-term aggregate risk assessments take into account average (chronic) exposure estimates from dietary consumption of metconazole (food and drinking water) and non-occupational/residential use on turf (dermal for adults, and dermal plus incidental oral for children). Postapplication exposures from the use on turf are considered predominantly short-term (1-30 days). Although exposures are expected via the dermal route, quantification of dermal risk is not required, since a dermal endpoint was not identified for short-, or intermediate-term exposures. Therefore, short- and intermediate-term postaplication aggregate risk assessments were conducted only for average dietary and incidental oral exposures to toddlers.

The short-and intermediate-term aggregate MOEs from dietary exposure (food + drinking water) and non-occupational/residential handler exposure (inhalation) for adults are 3,000 and 2,900, respectively; which are not of concern to HED, since they are greater than the level of concern MOE of 100.

The short-and intermediate-term aggregate MOEs from dietary exposure (food + drinking water) and non-occupational/residential exposure (incidental oral) for children 1-2 years old are 470 and 520, respectively; which are not of concern to HED, since it is greater than the level of concern MOE of 100.

These aggregate exposure assessments are considered conservative estimates, that should not underestimate risks, because of the following inputs: 1) dietary inputs used crop specific (turf) screening level drinking water modeling data (i.e., Tier II surface water model); 2) maximum application rates and minimum application intervals were used; and 3) conservative SOPs and upper level estimates of exposure were employed.

Occupational Handler and Postapplication Exposure/Risk Assessment

HED believes short- (1 - 30 days) and intermediate-term (1 – 6 months) exposures are possible for occupational metconazole handlers. Only inhalation toxicity endpoints were identified for these anticipated exposure durations. A Margin of Exposure (MOE) ≥100 is adequate to protect occupational pesticide handlers. All metconazole occupational handler MOEs are estimated to be >100 for the proposed uses, and therefore, do not cause concern for HED.

There is the possibility for agricultural workers to have postapplication exposure to metconazole following its use on commercially grown ornamentals in nurseries and greenhouses, as well as golf course turf. However, because dermal toxicity endpoints for the appropriate durations of exposure were not identified, and because inhalation exposure is considered to be insignificant for postapplication exposures, no occupational postapplication exposure assessment was conducted.

Recommendations

No deficiencies were noted in the submitted request that would preclude the establishment of Section 3 uses on turf and ornamentals.

The proposed V-10116 VPP Fungicide label contains inconsistencies concerning the retreatment intervals for foliar applications to ornamental plants. The proposed label lists the interval as both 14 to 21 days and 14 to 28 days. HED recommends that the proposed label be modified to include the appropriate retreatment interval; i.e. either 14 to 21 days, or 14 to 28 days.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from Pesticide Handlers Exposure Database (PHED) studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies have been determined to require a review of their ethical conduct, and have received that review.

2.0 Ingredient Profile

2.1 Summary of Proposed Uses

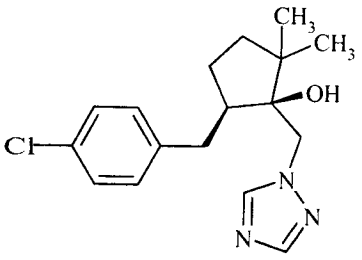
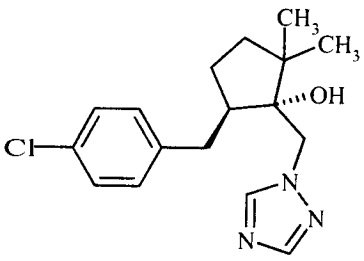
Metconazole [5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol] is a systemic triazole fungicide being proposed for use in a 50% ai water dispersible granular formulation (V-10116 VPP Fungicide). Metconazole is a broad-spectrum triazole fungicide that works systemically by preventing spore formation and inhibiting mycelial growth. A summary of the proposed metconazole uses is presented in Table 1 below.

Table 1. Use Profile for Metconazole.

Use Site	Maximum Rate for Single Application	Max. Rate per Season	Applications Intervals	Application Method and Instructions
Ornamentals (indoor and outdoor nurseries, greenhouses)	0.0025 lb ai/gallon (foliar)	3 lbs ai/acre	14 to 21 days	* Dispersed in water using low-pressure hand-wand or backpack sprayers, hydraulic or boom sprayers (high-pressure nursery sprayers) * Do not apply aerially or through irrigation equipment. * Do not apply more than 6 times per cropping cycle or six months.
	0.00125 lb ai/gallon (soil drench)		7 to 28 days	
Turf (golf courses, residential and commercial lawns, athletic fields)	0.6 lb ai/acre	3 lbs ai/acre	14 to 21 days	* Apply with standard low-pressure spray equipment. * Do not apply aerially or through irrigation equipment. * Begin applications when conditions favor disease development. * For soil-borne diseases, can be watered in after application.

2.2 Structure and Nomenclature

The formulation to be used on bananas is an 85% *cis*-isomer:15% *trans*-isomer mixture. The fungicidal activity is associated primarily with the *cis*-isomer. At a pre-registration meeting with the registrants, on 11/30/05, the registrants clearly stated their intent to produce and market only the cis/trans mixture. No known impurities of toxicological concern were identified.

Table 2. Metconazole Nomenclature		
Chemical Structure	 *Cis*-isomer	 *Trans*-isomer
Molecular Formula	$C_{17}H_{22}ClN_3O$	
Common name	metconazole	
Company experimental names	AC 900768 or CL 900768 (isomer mixture of approximately 85% *cis*-isomer and 15% *trans*-isomer) CL 354801 (*cis*-isomer) CL 345802 (*trans*-isomer)	
IUPAC name	(1*RS*, 5*RS*; 1*RS*, 5*SR*)-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl) cyclopentanol	
CAS name	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol	
CAS Registry Number	125116-23-6	
End-use products/EP	Metconazole 90 SL; Caramba™ Fungicide (no US Registration)	
Chemical Class	triazole fungicide	
Known Impurities of Concern	None	

2.3 Physical and Chemical Properties

Table 3. Physicochemical Properties of the Technical Grade Metconazole		
Parameter	Value	Reference [1]
Molecular Weight	319.837	44721503
Melting point/range	100.0-108.4°C (using Electrothermal Digital Melting Point Apparatus) (AC900,768 technical grade)	44721505
pH	No data were submitted.	
Relative density (20°C)	1.14 (relative density to water at 4 deg C, using capillary-stoppered, density-specific gravity bottle) (Lot No. AC 8879-140B)	44721505
Water solubility (20°C)	Using shake flask method: 18.7±1.0 mg/L (*cis*-isomer, WL148271, KNF-S-474m) 13.6±1.7 mg/L (*trans*-isomer, WL148271, KNF-S-474m)	44721505
Solvent solubility (g/L) at 20°C	hexane: 1.40 toluene: 103 2-propanol: 132 ethyl acetate: 260 dichloromethane:481 methanol: 403 acetone: 363	44721505
Vapor pressure (20°C)	Using gas-saturation method at 20°C: $< 1.23 \times 10^{-5}$ Pa or 9.23×10^{-8} mm Hg (AC 900,768) $< 1.04 \times 10^{-5}$ Pa or 7.80×10^{-8} mm Hg (*cis*-isomer, CL 354,801) $< 1.96 \times 10^{-6}$ Pa or 1.47×10^{-8} mm Hg (*trans*-isomer, CL 354,802)	44721505
Dissociation constant (pK_a)	11.38±0.03 and 1.06±0.03 (in water using spectrophotometric method) (Lot No. AC 8879-140B)	44721505
Octanol/water partition coefficient Log (K_{ow})	K_{ow} (log K_{ow}) = 7090±989 (3.85) (using flask shaking method) (Lot No. AC 8879-140B) (TGAI) K_{ow} (log K_{ow}) = 7150±803 (3.85) (using flask shaking method) (*cis*-isomer, CL 354,801) K_{ow} (log K_{ow}) = 6800±1700 (3.8) (using flask shaking method) (*trans*-isomer, CL 354,802)	44721505
UV/visible absorption spectrum	Not required for TGAI; required for pure active ingredient	

[1] DP Barcode Number 256877, Shyam Mathur, 9/12/00.

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Studies available and considered (animal, human, general literature)

In a previous human health risk assessment for proposed tolerance on imported bananas (Memo Date: 7/06/06), a data gap existed from the lack of a reproduction and fertility effects study with the cis/trans metconazole (the isomer mixture is the formulation for the proposed use). The data gap was bridged using a two-generation reproduction study with cis-only metconazole (MRID 44721608). Subsequently, a new two-generation reproduction study (MRID 46808447) using cis/trans metconazole was submitted and reviewed by HED. With this new submission, there is no longer a need to bridge the data gap with the previously submitted cis-only toxicity studies and the data gap is satisfied.

The following data are available:
Acute- Oral rat, dermal rat, inhalation rat, eye irritation rabbit, dermal irritation rabbit, and skin sensitization guinea pig.
Subchronic- Oral 28-day rat; oral 90-day rat, oral 90-day mouse, oral 90-day dog;
Chronic- Oral rat and dog;
Reproductive/developmental- Oral developmental rabbit and rat; 2-generation reproductive rat
Other- Oral rat and mouse cancer studies, dermal toxicity and dermal penetration studies, subchronic neurotoxicity, mutagenicity screens and mechanistic studies.

3.1.2 Mode of action, metabolism, toxicokinetic data

Metconazole is a member of the triazole class of systemic fungicides and acts primarily as an inhibitor of ergosterol biosynthesis. Like other triazoles, the primary target organ in mammalian toxicity studies is the liver. Other toxicological effects seen are effects on the blood, spleen, and body weight. Developmental studies in rats and rabbits show some evidence of developmental effects (skeletal variations, post-implantation loss, reduction in fetal body weight), but only at dose levels that are maternally toxic.

Metabolism studies in rats indicated that metconazole is excreted primarily in the feces with greater than 90% of the administered dose excreted by three days post-dosing. Biliary excretion is the major route of elimination. Plasma kinetic studies show a low potential for bioaccumulation following single or multiple dosing regimens and the plasma half-life of low- and high-dose rats was slightly shorter in males than females. In an experiment in which the triazole ring was labeled, a single high (200 mg/kg) dose of metconazole showed approximately 5% of the parent compound was excreted as free triazole.

3.1.3 Sufficiency of studies/data

The toxicity database for metconazole is complete (see Appendix A-2 for Toxicity Profile table). The data are sufficient for selection of appropriate toxicity end points of concern for risk

assessment scenarios and for FQPA evaluation.

3.1.4 Toxicological Effects

The liver is the primary target organ in the mouse, rat and dog following oral exposure to metconazole via subchronic or chronic exposure durations. While liver effects have been reported consistently across multiple durations and species, these effects were considered slight and minimal in some studies and appearing to be "adaptive" responses, but based on the weight of evidence from the consistency of these reported effects and evidence that these effects increase in severity with duration, and leading to liver tumors in the chronic mouse study, they were considered "adverse" and formed the basis of the study LOAELs. Metconazole is considered nongenotoxic and the liver tumors appear to have been formed via a mitogenic mode of action and therefore, metconazole is classified as "not likely to be carcinogenic to humans" at levels that do not cause mitogenesis.

Other major critical effects observed in oral studies were decreased body weight, decreased body weight gains, and blood effects (reductions in erythrocyte and/or platelet parameters) in the mouse, rat, dog and/or rabbit. Splenic effects including increased spleen weight and hyperplasia were observed in the mouse, rat and dog at dose levels where liver effects were also observed. In dogs, lenticular degeneration (cataracts) was observed at the highest dose tested. Furthermore, at high dietary levels, there is evidence that metconazole is a gastrointestinal irritant in the dog.

The proposed mode of action for metconazole is via inhibition of sterol (ergosterol) biosynthesis in fungi which is consistent with altered cholesterol levels observed in mice and rats. The critical effects are considered relevant to humans because they were observed in at least three species. There was no greater susceptibility to the fetuses of rats or rabbits following *in utero* exposure to metconazole. In the developmental toxicity study in rats, skeletal variations (predominantly lumbar ribs) occurred in the presence of maternal toxicity (decreased body weight gains). In the prenatal developmental toxicity study in rabbits, developmental effects (increased post-implantation loss and reduced fetal body weights) were observed at the same dose that caused maternal toxicity (decreased body weight gains, reduced food consumption and alterations in hematology parameters). In the two-generation reproduction study in rats, offspring toxicity (reduced fetal body weights F2 offspring and decreased viability in F1 and F2 offspring) was observed only at the highest tested dose, a dose which also resulted in parental toxicity as evidenced by reduced parental body weight and body weight gains, increased incidence of fatty hepatocyte changes in male parental animals and increased incidence of spleen congestion in F1 parental females. Metconazole did not demonstrate the potential for neurotoxicity in the four species (mouse, rat, dog and rabbit) tested.

The chemical is non-genotoxic and is classified as not likely to be carcinogenic below a defined dose that doesn't cause mitogenesis based on bioassays in the rat and the mouse, combined with a lack of *in vitro* or *in vivo* mutagenicity.

3.1.5 Dose-response

The liver is the primary target organ of toxicity following exposure to metconazole. Other toxicological effects were seen on the blood, spleen, and body weight. Developmental studies in rats and rabbits show some evidence of developmental effects (skeletal variations, post-implantation loss, reduction in fetal body weight), but only at dose levels that are maternally toxic. The only study in which an effect of concern could be observed following a single dose was the developmental study in rats. This study showed an increase in skeletal variations beginning at a dose of 30 mg/kg/day (LOAEL) which increased in incidence and severity at the highest dose tested (75 mg/kg/day). Available subchronic and chronic data (all oral studies – 28-day [rat]; 90-day [rat, mouse, dog]; two-generation study [rat]; chronic [rat, dog]; and carcinogenicity studies [rat, mouse]) all show the liver, spleen, kidney, and blood as target organs. These effects were observed in all species and at approximately the same dose in all species. The 28-day LOAEL of 90.5 mg/kg/day showed that liver and kidney damage occurs within a short time frame. Although the liver weight increase and associated histopathology (hypertrophy and vacuolation) and changes in serum enzymes associated with liver changes may be indicative of an adaptive response, the sustained exposures in the 90-day, chronic, and cancer studies show that these effects persist with increasing exposure: LOAELs of 19.2 mg/kg/day [rat] and 50.5 mg/kg/day [mouse] in the 90-day studies; 13.1 mg/kg/day [rat] and 37 mg/kg/day [dog] in the chronic studies; and 13.8 mg/kg/day [rat] and 58.1 mg/kg/day [mouse] in the cancer studies. Importantly, other effects are also seen at these LOAELs: effects on the spleen (rats and mice) and the kidney (rats).

Overall, metconazole appears to affect the liver, kidney, spleen, and certain blood parameters in all the species tested. Dose levels at which these effects occur are similar across species with the rat and dog being slightly more sensitive than the mouse.

3.1.6 FQPA

There are adequate data in the metconazole database to characterize the potential for pre-natal or post-natal risks to infants and children: a two-generation reproduction study in rats; developmental studies in rats; and developmental studies with rabbits. The effects seen in these studies do not suggest that pups are more susceptible: pup effects were only seen in the presence of maternal toxicity and, in general, were of comparable or less severity to the effects observed in adults.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

The absorption, distribution, metabolism and excretion (ADME) of metconazole was investigated in rats following single oral doses of cis and or cis/trans metconazole radiolabeled at the cyclopentyl or triazole ring (cis only). Initial studies showed less than 2% of the cyclopentyl-labeled dose was expired in the air. Following a single oral administration of low dose (2 mg/kg) ^{14}C-cyclopentyl (cis/trans metconazole), greater than 80% of the administered dose was excreted in 24 hours with total excretion exceeding 90% in three days. Excretion was primarily via feces (80% male, 67% female) with biliary excretion being the prominent route of elimination. At 72 hours, 15% and 26% of the radioactivity was excreted via urine in males and females, respectively. A delay in excretion was observed following the administration of high dose (164

mg/kg) ^{14}C-cyclopentyl (cis/trans metconazole); however by 72 hours, 80% or more of the radioactivity was excreted. Males excreted lower amounts of radioactivity in the urine and greater amounts of radioactivity in the feces than females at low and high dose. Plasma pharmacokinetic studies showed a low potential for bioaccumulation following single or multiple dosing regimen. The time to maximum plasma concentration for male and female rats treated with either 2 mg/kg or 200 mg/kg was at the earliest sampling intervals of 0.25 hours and 4 hours, respectively. The plasma half-life of low- and high-dose rats was slightly shorter in males than females, ~20-25 hours and ~34 hours, respectively.

Radioactivity measurements of tissues showed higher concentrations in the gastrointestinal tract, adrenals and liver. The pattern of metabolites was similar at the low and high dose. Analysis of fecal and urine samples showed little or no parent compound with ten key metabolites representing over 50% of the administered dose. Metconazole metabolites consist primarily of mono- and poly-hydroxylated derivatives of the parent molecule. Hydroxylation occurs mainly on the alkyl constituents of the phenyl and cyclopentyl rings. Sulfate conjugation to the cyclopentyl ring hydroxyl groups was also identified. Monohydroxy metabolites were found in the feces and di- and tri- hydroxy compounds were found more often in the urine. Administration of 200 mg/kg radiolabeled cis metconazole (^{14}C-triazole ring) showed approximately 5% of the administered dose excreted as free triazole.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Data Base

The database for metconazole is adequate for FQPA consideration. Acceptable developmental toxicity studies are available in the rat and rabbit as well as a two-generation reproductive toxicity study in the rat.

3.3.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity observed in the toxicology database. There is not a concern for neurotoxicity resulting from exposure to metconazole since there was no evidence of neurotoxicity in short-term studies in rats, mice and dogs, and long-term toxicity studies in rats and dogs. A subchronic neurotoxicity study showed no evidence of neurotoxicity in rats administered metconazole in diet at doses of 0, 50, 170 or 500 ppm (corresponding to 0, 4.84, 15.69 or 47.08 mg/kg/day in males and 0, 5.10, 17.62 or 49.82 mg/kg/day in females) for 28 days. The neurotoxicity NOAEL was >47.1/49.9 mg/kg/day in males and females, respectively. No neurotoxicity was observed at doses (47.1/49.9 mg/kg/day in males/females) that caused systemic toxicity including significant decreases in bodyweight, bodyweight gain and food consumption. Functional observational battery (FOB) and motor activity testing revealed no treatment-related effects at any dose. Brain weights, anatomical measurements and microscopic neuropathology examinations were unaffected by treatment.

3.3.3 Developmental Toxicity Studies

Developmental Toxicity in Rats

In a developmental toxicity study (MRID 44721522), Metconazole (95.3% a.i., batch 89-01 Ref. ST89/088, *cis:trans* 83.7:16.3) was administered to 25 (Crl:CD^R (SD) BR VAF/Plus strain) female rats/dose by gavage at dose levels of 0, 12, 30 or 75 mg/kg bw/day from days 6 through 15 of gestation.

There were no mortalities observed during the duration of the study. Post-dosing salivation was observed in some dams at 75 mg/kg/day, which was first evident during the second week of treatment. No other clinical signs of toxicity were observed. A slight reduction in food consumption (10%) was observed on GD 6-7 in the 30 and 75 mg/kg/day group. This correlated with poor body weight gain during the initial two days of treatment and resulted in an overall decrease in body weight gain during the treatment period at 30 and 75 mg/kg/day (912% and 918%, respectively). There was no increase in pre-implantation loss at any dose and the numbers of corpora lutea and implantation sites at all doses were similar to the control group. **The maternal LOAEL is 30 mg/kg bw/day, based on decreased body weight gains during the treatment period. The maternal NOAEL is 12 mg/kg bw/day.**

Post-implantation loss was significantly higher at 75 mg/kg/day compared to the control group. There were 79 resorptions (36 early, 43 late) at 75 mg/kg/day versus 18 resorptions (15 early, 3 late) in the control group. No difference in post-implantation loss was observed at 30 mg/kg/day and below. Hydrocephaly was observed at 75 mg/kg/day (2 fetuses, separate litters) where maternal toxicity was evident. No malformations were observed at 30 mg/kg/day and lower. A statistically significant increase in visceral anomalies compared to the control was observed at 75 mg/kg/day which included cranial hemorrhage, dilated renal pelvis, dilated ureter and displaced testis. No increase in the incidence of visceral anomalies was observed at the lower dose levels. A dose-related increase in the incidence of extra lumbar ribs was observed at 12, 30 and 75 mg/kg/day compared to the control group. The incidence of lumbar ribs was statistically significant at 30 and 75 mg/kg/day (relative to control). At 12 mg/kg/day, the fetal and litter incidences for skeletal anomalies were similar to the controls and were not statistically significant. The fetal incidence of extra lumbar ribs fell within the historical control range; however, the litter incidence of lumbar ribs at 12 mg/kg/day fell slightly outside the range for historical controls. Additional skeletal anomalies were observed at 30 and 75 mg/kg/day, including increased incidence of cervical ribs and extra pre-sacral vertebra. At 75 mg/kg/day, a reduction in mean fetal weights relative to the control group was observed. **The developmental LOAEL is 30 mg/kg/day, based on a statistically significant increase in the overall incidence of skeletal anomalies, including extra lumbar ribs, cervical ribs and extra pre-sacral vertebra. The developmental NOAEL is 12 mg/kg bw/day.**

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

Developmental Toxicity in Rabbits

In a developmental toxicity study (MRID 44721602), AC900768 (cis/trans Metconazole, 98.3% a.i., lot # AC 10575-61; cis/trans ratio 80:15) was administered to 25 female New Zealand White [HRa:(NZW)SPF] rabbits/dose in diet by gavage at dose levels of 0, 5, 10, 20 or 40 mg/kg bw/day from days 6 through 28 of gestation.

No relevant maternal clinical signs or treatment-related effects on survival were reported. Isolated incidences of localized alopecia were observed, but were not clearly attributed to treatment. Does at 40 mg/kg/day lost weight from gestation day (GD) 24-29 which resulted in an overall decrease (-15%) in bodyweight gain for this group. Food consumption was reduced 16% at 40 mg/kg/day on gestation days 24-29 and was slightly less than the control group throughout the treatment period, but at no time reached statistical significance. Gravid uterine weight was also reduced at 40 mg/kg/day. This decrease was associated with a statistically significant ($p<0.01$) increase in post-implantation loss and reduced fetal body weight compared to the control group. Other maternal findings at 40 mg/kg/day include increased liver weight, reduced hemoglobin, hematocrit, and mean corpuscular volume. Reduced platelet counts and alkaline phosphatase levels were also observed at 40 mg/kg/day. **The maternal LOAEL is 40 mg/kg bw/day, based on a decrease in bodyweight gain, decreased food consumption, increased liver weight, statistically significant decreases in RBC parameters and elevated alkaline phosphatase levels. The maternal NOAEL is 20 mg/kg bw/day.**

Post-implantation loss observed at 40 mg/kg/day was associated with an observed increase in the number of does with any (early and late) resorptions. Reduced, but not statistically significant, live litter size and fetal body weights were observed at 40 mg/kg/day compared to the control group. No treatment-related gross external, soft tissue or skeletal malformations or anomalies were observed at any dose. **The developmental LOAEL is 40 mg/kg bw/day, based on increase in early and late resorptions and a slight decrease in fetal body weight. The developmental NOAEL is 20 mg/kg bw/day.**

The developmental toxicity study in the rabbit is classified acceptable, guideline, and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit.

3.3.4 Reproductive Toxicity Study

An acceptable new two-generation reproduction study (MRID 46808447) using cis/trans metconazole was submitted and reviewed by HED. This study replaces the two–generation reproduction study with cis-only metconazole (MRID 44721608) that was used in the human health risk assessment for proposed tolerance on imported bananas (Memo Date: 7/06/06). Since the cis/trans isomer mixture is the formulation for the proposed use, the new reproduction study is being used in this assessment to characterize reproductive toxicity. With this new submission, there is no longer a need to bridge the data gap with the previously submitted cis-only toxicity studies.

In a two-generation reproduction study (MRID 46808447) cis/trans Metconazole (KNF-474m, lot number 9Z521) was administered to [(24Crj:CD(SD)[IGS]rats/sex/dose in the diet at target

dose levels of 0, 30, 150, or 750 ppm (0, 1.97, 9.79 and 49.4 mg/kg bw/day and 0, 2.14, 10.78 and 53.2 mg/kg bw/day for males and females, respectively in the F_0 generation; 0. 2.13, 10.63 and 53.0 mg/kg bw/day and 0, 2.20, 11.21, and 55.5 mg/kg bw/day for males and females, respectively, in the F_1 generation). F_0 and F_1 male and female parental animals were administered test or control diet for at least 70 days prior to mating, throughout mating, gestation, lactation, and until necropsy. One litter was produced by each generation.

Parental systemic toxicity was evident at 750 ppm. During the pre-mating period of the F_0 generation, body weight and body weight gain were slightly, but significantly decreased compared to the control group during treatment weeks 1 and 2 in F_0 males (decrease of 5%) and during treatment weeks 6-10 in F_0 females (decrease of 4-5%). Reduced body weight gains were noted for two weeks after initiation of treatment in F_0 males (decrease of 11%) and throughout the pre-mating growth period and on gestation day 20 in F_0 females. In F_1 parental animals, body weight was significantly decreased for both sexes (decrease of 6-12% in F_1 males, decrease of 5-11% in F_1 females) compared to the control group throughout the pre-mating period and into the breeding period. This was partly due to significantly lower body weight at selection. Body weight gain of males at treatment weeks 1-4 (decrease of 10% weight gain, decrease of 10-15% food consumption during this time) and of females at treatment week 10 (decrease of 8%) was significantly reduced. Higher incidences of centrilobular fatty change of hepatocytes were observed in high-dose F_0 and F_1 males [19/24 (79%) and 20/24 (83%), respectively] compared to 0/24 controls of both generations. A higher incidence [16/20 (80%)] of spleen congestion was observed in F_1 females compared to 0/24 control females. **The parental systemic LOAEL for KNF-474m in CD rats is 750 ppm (49.4 and 53.2 mg/kg/day for males and females, respectively) based on decreased body weight and decreased weight gain in male and female parental animals, increased incidence of fatty hepatocyte change in male parental animals, and increased incidence of spleen congestion in F_1 parental females. The parental systemic NOAEL is 150 ppm (9.79 and 10.78 mg/kg/day for males and females, respectively).**

Offspring toxicity was evident at 750 ppm as decreased viability index on lactation day 0 and reduced body weight in F_2 offspring. There was an increase in stillborn pups on lactation day 0 (16 high-dose group vs. 4 control) of the F_2 generation leading to the decreased viability index. Significantly reduced body weight was observed on lactation days 0, 14, and 21 in the F_2 offspring (decreases of 13%, 8%, 10% in males and 11%, 10%, 12% in females, respectively). **The offspring LOAEL for KNF-474m in CD rats is 750 ppm (49.4 and 53.2 mg/kg/day for males and females, respectively) based on decreased viability on lactation day 0 and decreased body weight in F_2 offspring. The offspring NOAEL is 150 ppm (9.79 and 10.78 mg/kg/day for males and females, respectively).**

Reproductive toxicity was evident at 750 ppm as prolonged duration of gestation and decreased gestation index driven by dystocia (maternal deaths during delivery). Prolonged duration of gestation and maternal deaths during delivery, were noted in both F_0 and F_1 females. Gestation length was significantly increased in F_0 females by treatment (23.0 days vs. 22.2 days in control) and corresponded with dystocia in five F_0 females and four F_1 females; all died during delivery, some with fetuses in the uterus. The deaths, along with two females of each generation that

failed to produce live pups caused the gestation index to be decreased in both F_0 and F_1 females. Other reproductive parameters were not different from control. There were no effects of treatment on male reproductive parameters. **For female CD rats, the reproductive LOAEL for KNF-474m is 750 ppm (53.2 mg/kg/day) based on increased gestation length and decreased gestation index driven by dystocia. The NOAEL is 150 ppm (10.78 mg/kg/day). For male CD rats, the reproductive NOAEL is greater than or equal to 750 ppm (49.4 mg/kg/day), and the LOAEL is not identified.**

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800; OECD 416) in rats.

3.3.5 Additional Information from Literature Sources

No additional studies from the open literature were found.

3.3.6 Pre-and/or Postnatal Toxicity

Available evidence (two developmental toxicity studies and one two-generation reproductive toxicity study) suggest there is no concern for pre- and/or post-natal toxicity resulting from exposure to metconazole, because the pre and postnatal effects observed in rats and rabbits occurred only at maternally toxic dose levels.

3.3.6.1 Determination of Susceptibility

Both the rat and rabbit developmental toxicity studies show that when pup effects are observed, they are seen only in the presence of maternal toxicity and are of comparable severity. In the first rat study, an increase in skeletal variations (predominantly an increase in lumbar ribs) is seen at 30 mg/kg/day; the dose at which the dams show a significant decrease in body weight gain. In a second rat developmental study (MRID 4808443), again fetal effects including increased early and late resorptions, decreased fetal weight and increased fetal anomalies were observed only at 64 mg/kg/day, a dose that also showed adverse effects in the dams (decreased body weight, decreased food consumption, increased placental weight and increased incidence of swollen placentae). In the rabbit developmental study, post-implantation loss and a slight reduction in fetal body weight is observed in the pups at 40 mg/kg/day. At that same dose, does experienced blood (reduction in hematocrit, hemoglobin and other parameters) effects and a decrease in body weight gain.

In the two-generation study, pup effects (decreased viability at lactation day 0, decreased pup weight) were seen only at dose levels (49.4/ 53.2 mg/kg/day) that parental effects (decreased body weight, decreased body weight gain, increased incidence of fatty hepatocyte changes and increased incidence of spleen congestion) were observed. These data do not suggest that the pups are more susceptible than adults to metconazole exposure.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Post-natal Susceptibility

The available evidence suggests there is no qualitative or quantitative evidence of pup susceptibility following exposure to metconazole in developmental and reproductive toxicity studies with metconazole. Therefore, there is no residual uncertainty for pre- and/or post-natal toxicity.

3.3.7 Recommendation for a Developmental Neurotoxicity Study

None

Metconazole did not cause clear clinical or other signs of neurotoxicity in at least four species tested (mouse, rat, rabbit and dog). The only clinical sign that could potentially be interpreted as neurological was the post-dosing salivation in the pregnant rat in the developmental toxicity study (MRID 44721522). The salivation was observed following gavage in some dams at the highest test dose (75 mg/kg/day). This effect was not observed in any other study and is considered unlikely to indicate neurotoxicity. In addition, no evidence of neurotoxicity was observed in neurobehavioral assessments including in-hand observations, functional observational battery and motor activity testing in a 28-day neurotoxicity study in the rat (MRID 4680884).

3.4 FQPA Safety Factor for Infants and Children

The metconazole risk assessment team evaluated the quality of the toxicity and exposure data and, based on these data, recommended that the FQPA Safety Factor be reduced to 1x. The recommendation is based on the following:

- There is no evidence of susceptibility following *in utero* exposure in the rat and rabbit developmental toxicity studies and following both *in utero* and post-natal exposure in the two-generation rat reproduction study.

- There is no evidence of increased susceptibility in the offspring based on the result of the two-generation reproduction study.

- The residue levels used in the dietary assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities, and assumed 100% crop treated. Therefore, the acute and chronic dietary, food only, exposure is considered an upper bound conservative estimate. The contribution from drinking water is minimal. HED concludes that the acute and chronic exposure estimates in this analysis are unlikely to underestimate actual exposure.

- The drinking water component of the dietary assessment utilizes water concentration values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations which will not likely be exceeded.

- While there is potential for postapplication residential exposure, the best data and approaches currently available were used in the metconazole residential assessment. The Agency used the current conservative approaches for residential assessment, many of which include recent upgrades to the SOPs. The Agency believes that the calculated risks represent conservative estimates of exposure because maximum application rates are used to define residue levels upon which the calculations are based. Exposures are unlikely to be under estimated because the assessment was a screening level assessment.

3.5 Hazard Identification and Toxicity Endpoint Selection

Hazard identification and toxicity endpoint selection were made for two different population subgroups: (1) Females 13-49 years of age, and (2) General Population including infants and children. Doses and endpoints were also selected for exposure routes (i.e., oral, dermal and inhalation) depending upon the appropriateness of the endpoint and the relevancy of the endpoints to the population of concern. Developmental (*in utero* exposure) endpoints were selected to assess dietary risks for Females 13-49 years of age, whereas non-developmental (systemic toxicity) endpoints were selected to assess dietary and non-occupational (residential) risks to the general population, including children and infants.

3.5.1 Acute Reference Dose (aRfD/aPAD) - Females age 13-49

Study Selected: Developmental Toxicity in Rats OPPTS 870.3700a §83-3a

MRID No. 44721522

Executive Summary: See Executive Summary in Section 3.3.3.

Dose and Endpoint for Establishing aRfD: Developmental toxicity NOAEL = 12 mg/kg/day, based on the increased incidence of skeletal anomalies including extra lumbar ribs, cervical ribs and extra pre-sacral vertebra at the LOAEL of 30 mg/kg/day.

Uncertainty Factor (UF): 100 (10X for interspecies extrapolation and 10X for intraspecies variations)

$$\textbf{Acute RfD/aPAD} \text{ (Females 13-49 years)} = \frac{12 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.12 mg/kg}$$

3.5.2 Acute Reference Dose (aRfD) - General Population

Study Selected: None

Comments about Study/Endpoint/Uncertainty Factor: There was no appropriate single-dose endpoint identified for acute oral exposure of the general population to metconazole.

3.5.3 Chronic Reference Dose (cRfD/cPAD)

Study Selected: Chronic Oral Toxicity in Rats OPPTS 870.4100a §83-1a

MRID No.: 44721609

Executive Summary: In a chronic toxicity study (MRID 44721609) metconazole (WL148271, 95.3% pure, 79.8% cis: 15.5% trans, batch # 89-01) was administered to 20 Fischer 344 rats/sex/dose in the diet at dose levels of 10, 100, 300 or 1000 ppm (equivalent to 0.4, 4.3, 13.1 and 43.9 mg/kg bw/day in males and 0.5, 5.3, 16.0 and 53.8 mg/kg bw/day in females) for two years. A group of 40 Fischer 344 rats/sex were fed untreated diet and served as controls. A second group of 10 rats/sex/dose were fed the test material at the same four concentrations named above and 20 rats/sex were fed the control diet for one year for an interim sacrifice.

There were no compound related effects on the incidence or cause of mortality among the treatment groups and no relevant clinical signs were observed. Food consumption was reduced in the high dose group (1000 ppm) in both sexes (10% male, 5% female) during the first 13 weeks of treatment. In the high-dose animals, a statistically significant reduction in mean body weight gain was observed throughout the study with an overall reduction of 7% in males and 6% in females.

A slight, but statistically significant decrease (2-4%, $p<0.01$) in mean hemoglobin concentration was observed in males at 1000 ppm on weeks 51, 77 and 104. In addition, a decrease in mean corpuscular volume (3-5%, $p<0.01$) in high-dose males was observed on weeks 77 and 104. A mild reduction in total hemoglobin in high-dose females was observed (1-2%, $p<0.05$) on weeks 13, 26, 51 and a non-significant decrease of the same magnitude on week 77. These parameters indicate mild microcytic anemia and are considered treatment-related. No abnormal leukocyte cell types were observed in the blood films at any dose.

Statistically significant decreases in total cholesterol, triglycerides, bilirubin, albumin (females only), alkaline phosphatase (males only) and alanine aminotransferase (both sexes at 1000 ppm and females at 300 ppm) were observed during bleeding periods throughout the study in the high dose groups, but not at termination. Decreased total cholesterol (11%, $p<0.05$) in females at 300 ppm was observed on week 26 and decreased albumin (3%) was observed in this group on weeks 26 ($p<0.01$) and 51 ($p<0.05$). Urine osmolarity was higher (25-32%, $p<0.01$) in males at 1000 ppm and urine volume was decreased (18-39%, $p<0.01$) in this group.

At termination, absolute and relative spleen weights were increased in males at 300 ppm (39%) and in both sexes (56% male and 21% female) at the high dose. Relative spleen weights were also elevated in females at 52 week (9%, $p<0.05$) at 1000 ppm. Increased relative liver weight was observed at week 52 in males at 300 ppm (5%, $p<0.01$) and 1000 ppm (20%, $p<0.01$). Relative liver weight were increased 12% ($p<0.05$) at week 104 in high-dose females. At week 52 sacrifice, livers with enlarged and/or mottled appearance were reported in males at 300 and 1000 ppm. Hepatocellular hypertrophy and hepatocellular lipid vacuolation were observed at

week 52 in males at 300 and in both sexes at 1000 ppm. At termination sacrifice, hepatocellular hypertrophy and vacuolation were restricted to the high dose animals. Males in the high dose group also exhibited an increased incidence of eosinophilic and clear-cell hepatocellular foci at termination. An increased incidence of splenic histiocytic foci was observed in both sexes at the high dose. **The LOAEL is 300 ppm (13.1 mg/kg/day), based on increased spleen (non-statistically significant) and liver weights and increased hepatocellular vacuolation and hypertrophy. The NOAEL is 100 ppm (4.3 mg/kg/day).**

This chronic study in the rat is acceptable/guideline and satisfies the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452] in the rat.

Dose and Endpoint for Establishing cRfD: NOAEL = 4.3 mg/kg/day, based on increased liver weights and increased hepatocellular vacuolation and centrilobular hypertrophy at the LOAEL of 13.1 mg/kg/day. At the same dose, non-statistically significant increases in spleen weights were observed in males and females, and histopathology changes in the spleen in a concurrent carcinogenicity study at this dose (MRID 44721611).

Uncertainty Factor (UF): 100 (10X for interspecies extrapolation and 10X for intraspecies variations)

Chronic RfD/cPAD (general population including infants & children) = $\frac{\text{4.3 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ = **0.04 mg/kg/day**

3.5.4.1 Incidental Oral Short-Term Exposure

Study Selected: 28-Day Oral Toxicity in Rats OPPTS 870.3100 §82-1a

MRID No.: 44721515

Executive Summary: In a 28-day oral toxicity study (MRID 44721515), seven Fisher F344 rats/sex/dose were fed a diet of metconazole (94.5% a.i.; 85% cis:15% trans; nominal 80:20, batch 88-10) at dose levels of 0, 30,100, 1000 or 3000 ppm (equivalent to (m/f): 0, 2.7/3.1, 9.1/10.1, 90.2/97.0, and 261.2/287.4 mg/kg bw/day). Hematology and blood chemistry parameters were measured at 28 days. Urine samples were analyzed after a water loading in week 4. Gross examinations were performed on all animals and nine tissues were examined microscopically in the control and high dose groups. Only the livers and adrenals were examined in all dose groups.

Administration of metconazole had no effect on survival during the 28-day study period. Overall body weight gain was decreased in males at 1000 ppm (-27%) and in both sexes at 3000 ppm (males -71%, females -58%). At week 4, bodyweight in males at 1000 and 3000 ppm were

statistically significantly reduced compared to the controls (-14% and -34%, respectively) and in females at 3000 ppm, the mean body weight was 19% lower than the control group. Food consumption was reduced 10-30% in these groups.

At 3000 ppm, a slight reduction in mean cell hemoglobin concentration and erythrocyte mean diameter was observed. Platelet counts at 3000 ppm were reduced 20%. Marked increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (γ-GT) were observed at the high dose. Glucose levels were reduced 15-30% in both sexes at the high dose. Cholesterol decreased 25% in both sexes at 3000 ppm and a 23% reduction in cholesterol was observed in males at 1000 ppm. Urinalysis revealed no treatment-related changes.

Dose-related changes in absolute liver weights were observed at 1000 ppm and 3000 ppm in males (4% and 8%, respectively) and in females (21% and 67%, respectively). Relative spleen and kidney weights were statistically significantly higher at 3000 ppm. Macroscopic examination showed enlarged and pale livers in both sexes at 1000 ppm and 3000 ppm. Enlarged livers were also observed in 3/7 males at 100 ppm. Junctional ridge thickening and/or ulceration of the forestomach was observed in 4/7 males at 3000 ppm. The primary target organ was the liver as revealed by increased incidences of fatty vacuolation and hepatocellular hypertrophy in both sexes at 1000 and 3000 ppm. No microscopic abnormalities were observed in the liver at 100 ppm. Increased incidence of hyperkeratosis was observed in the forestomach of males at 3000 ppm which correlated with the macroscopic findings. Most animals at 3000 ppm showed adrenal cortical vacuolation. **The LOAEL is 1000 ppm (90.5 mg/kg/day), based on decreased body weight, increased liver and kidney weights, hepatocellular vacuolation and hypertrophy. The NOAEL is 100 ppm (9.1 mg/kg/day).**

This 28-day oral toxicity study in the rat is classified as acceptable/guideline and satisfies the guideline requirement for a 28-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

Dose and Endpoint for Risk Assessment: NOAEL = 9.1 mg/kg/day, based on decreased body weight, increased liver and kidney weight, hepatocellular hypertrophy and vacuolation at the LOAEL of 90.5 mg/kg/day.

Uncertainty Factor (UF): 100 (10X for interspecies extrapolation and 10X for intraspecies variations).

Comments about Study/Endpoint: This study was selected because (1) endpoints identified were observed following short-term (28 days) exposure and (2) the route of exposure (oral) and endpoints are appropriate for the population (infants and children) and duration (1-30 days) of concern.

3.5.4.2 Incidental Oral Intermediate-Term Exposure

Study Selected: 90-Day Oral Toxicity in Rats OPPTS 870.3100 §82-1a

Executive Summary: In a 90-day oral toxicity study (MRID 44721517), WL148271 (94.5% pure with a cis/trans ratio of 81:19, batch # 88-10) was administered in diet to 10 F344 rats/sex/dose at dose levels of 0, 30, 100, 300, 1000 or 3000 ppm (equivalent to 0, 1.9, 6.4, 19.2, 64.3 and 192.7 mg/kg/day in males and 0, 2.1, 7.2, 22.1, 71.4, and 208.0 mg/kg bw/day in females). Two satellite groups (10/sex/group) were fed 0 or 3000 ppm for 13 weeks, followed by a 7 week recovery period.

There were no treatment-related effects on mortality. Food consumption was reduced in both sexes at 1000 ppm (males 12%, females 9%, both $p<0.01$) and 3000 ppm (males 33%, females 22%, both $p<0.01$). Overall body weight was reduced in males at 1000 ppm (9%,$p<.0.01$) and in both sexes at 3000 ppm (males 35%, females 19%, both $p<0.01$). Discharges from the eyes and alopecia were observed in most high dose (3000 ppm) animals in both sexes, but not in the control animals. The eyes of lower dose animals were not examined.

Hematological findings revealed changes in parameters consistent with mild hypochromic microcytic anemia at the high dose in both sexes. Decreased hemoglobin (4%, $p<0.01$), mean corpuscular hemoglobin (2.7%, $p<0.01$) and mean corpuscular hemoglobin concentration (2%, $p<0.01$) were also observed in females at 1000 ppm. Elevated white blood cell counts were observed in females at 300 ppm and above. Some recovery was observed in the satellite high dose group; however mean corpuscular volume, platelet count and plateletcrit remained low in males. Clinical chemistry revealed statistically significant ($p<0.01$) increases in plasma alkaline phosphatase (m 35%, f 42%), gamma-glutamyl transpeptidase, aspartate aminotransferase (m 77%, f 70%) and alanine aminotransferase (m136%, f 94%) in both sexes at 3000 ppm. Alanine aminotransferase was also elevated in males (13.6%, $p<0.01$) at 1000 ppm. Cholesterol was decreased in males at 1000 ppm (36%, $p<0.01$) and 3000 ppm (48%, $p<0.01$) and triglyceride levels were down 69% ($p<0.01$) in males at 1000 ppm and in both sexes (m 96% and f 70%) at 3000 ppm. The decreased cholesterol and triglycerides is indicative of perturbations in hepatic lipid metabolism.

Increased adjusted liver weight ($p<0.01$) was observed in the male and female at 1000 ppm (31% and 20%, respectively) and at 3000 ppm (11% and 53%, respectively). Increased spleen weights were reported in females at 300 and above and in both sexes at 3000 ppm. Decreased relative adrenal weights were also observed in males at 3000 ppm (11%, $p<0.05$). Histopathological changes in the liver were observed in all males at 1000 and in both sexes 3000 ppm including centrilobular hepatocyte hypertrophy and fatty vacuolation. An increased incidence of fatty vacuolation (4/10, $p<0.05$) was observed in males at 300 ppm and a single incidence of centrilobular hypertrophy was in this group. In the satellite group, a reduction in the incidence of fatty vacuolation was observed in high-dose males (4/10, $p<0.01$), but remained statistically significant in females, 6/10 ($p<0.05$). Increased incidences of pigmented Kupffer cells was also observed in the high dose group (9/10 males, 10/10 females). In the spleen, decreased hematopoiesis was observed in all high dose animals. Pigment deposit was observed in 9/10 males and all females at 3000 ppm and white pulp was reduced in the high-dose males (3/10, $p<0.001$)) and females (9/10, $p<0.001$). Forestomach focal hyperplasia was observed in the

forestomach of 6 males and 2 females at the high dose. Moderate or slight adrenal cortical vacuolation was observed in all males and 6 females at 3000 ppm. **The NOAEL for this study is 100 ppm (6.4 mg/kg/day) and the LOAEL is 300 ppm (19.2 mg/kg/day) based on increased hepatocellular fatty vacuolation and increased spleen weight in females.**

This 90-day oral toxicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

Dose and Endpoint for Risk Assessment: NOAEL = 6.4 mg/kg/day, based on increased hepatocellular fatty vacuolation and increased spleen weight at the LOAEL of 19.2 mg/kg/day.

Uncertainty Factor (UF): 100 (10X for interspecies extrapolation and 10X for intraspecies variations).

Comments about Study/Endpoint: This study was selected because (1) endpoints identified were observed after sub-chronic exposure (90 days) and (2) the route of exposure (oral) and endpoints are appropriate for the population (infants and children) and duration (1-6 months) of concern.

3.5.5 Dermal Absorption

Dermal Absorption Factor: 16%

In a dermal absorption study in rats (MRID 46808450), metconazole was applied at a single concentration of 354 $\mu g/cm^2$ (2.5 mg/animal). Mean penetration of radioactivity reached a maximum of 16% at 72 hours following an 8-hour exposure.

3.5.6 Dermal Exposure (Short, Intermediate and Long Term)

In a previous human health risk assessment for proposed tolerance on imported bananas (Memo Date: 7/06/07), quantification of dermal risk (all durations) was calculated using a NOAEL from an oral toxicity study and applying a dermal absorption factor since a dermal toxicity study was not available. An acceptable guideline 21-day dermal toxicity study in the rat was subsequently submitted and reviewed and showed no dermal or systemic toxicity at the Limit Dose. No evidence of dermal or systemic toxicity was observed following repeated dermal applications of metconazole at 1000 mg/kg/day, 6 hours/day for 21 consecutive days. The target organ (liver) was not affected via dermal exposure. In addition, there are no neurotoxicity or developmental toxicity concerns. Based on the proposed use pattern, no long-term dermal exposure is expected.

3.5.7 Inhalation Exposure (Short, Intermediate and Long Term)

3.5.7.1. Inhalation Exposure Short Term:

Study Selected: 28-Day Oral Toxicity in Rats OPPTS 870.3100 §82-1a

MRID No.: 44721515

Executive Summary: See Executive Summary for rat 28-Day oral toxicity study above, under Section 3.5.4.1 [Incidental Oral Exposure - Short Term].

Dose and Endpoint for Risk Assessment: NOAEL = 9.1 mg/kg/day, based on decreased body weight, increased liver and kidney weight, hepatocellular hypertrophy and vacuolation at the LOAEL of 90.5 mg/kg/day.

Comments about Study/Endpoint: In the absence of repeated exposure inhalation toxicity studies, an oral study for this population subgroup was selected. Absorption via the inhalation route is presumed to be equivalent to oral absorption.

3.5.7.2. Inhalation Exposure Intermediate Term:

Study Selected: 90-Day Oral Toxicity in Rats OPPTS 870.3100 §82-1a

MRID No.: 44721517

Executive Summary: See Executive Summary for rat 90-Day oral toxicity study above, under Section 3.5.4.2 [Incidental Oral Exposure - Intermediate Term].

Dose and Endpoint for Risk Assessment: NOAEL = 6.4 mg/kg/day, based on based on increased hepatocellular fatty vacuolation and increased spleen weight at the LOAEL of 19.2 mg/kg/day.

Comments about Study/Endpoint: In the absence of repeated exposure inhalation toxicity studies, an oral study for this population subgroup was selected. Absorption via the inhalation route is presumed to be equivalent to oral absorption.

3.5.7.3. Inhalation Exposure Long Term:

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: Based on the proposed use pattern, no long-term dermal exposure expected.

3.5.8 Level of Concern for Margin of Exposure

A summary of the level of concern margins of exposure (MOEs) for risk assessment

purposes are presented below:

Table 4 Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1 - 30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	N/A	N/A	N/A
Inhalation	100	100	N/A
Residential Exposure			
Dermal	N/A	N/A	N/A
Inhalation	100	100	N/A
Incidental Oral	100	100	N/A

Occupational exposure: Based on the conventional uncertainty factor of 100 X (10X for interspecies extrapolation and 10X for intraspecies variation).

Residential exposure: Based on the conventional uncertainty factor of 100 X (10X for interspecies extrapolation and 10X for intraspecies variation).

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. For short- and intermediate-term risk assessments, the oral and inhalation routes can be combined due to the common endpoint (liver toxicity) via the oral and inhalation (oral equivalent) routes. Quantification of dermal risk is not required. There are no potential long-term dermal or inhalation exposures to metconazole.

3.5.10 Classification of Carcinogenic Potential

3.5.10.1 Carcinogenicity Study in Rats

MRID No. 44721611

Executive Summary: In a carcinogenicity study (MRID 44721611) metconazole (95.3% a.i., 79.8% cis, 15.5% trans; Lot 89-01) was administered to 50 Fischer 344 rats/sex/dose in diet at dose levels of 0, 100, 300 or 1000 ppm (equivalent to 0, 4.6, 13.8, 46.5 mg/kg bw/day in males and 0, 5.5, 16.6, 56.2 mg/kg bw/day in females) for two years.

There were no treatment-related effects on mortality or cause of death. Food consumption was reduced in high-dose males during the first 8 weeks of treatment and in high-dose females during the initial 11 weeks of treatment. Reductions in food consumption contributed to decreased bodyweights in males during the initial 13 weeks of treatment at 1000 ppm. Bodyweights were reduced in females at 1000 ppm throughout the treatment period, compared to the control animals. During the treatment period, mean bodyweight gains were reduced 6% in males and 9% in females at the high dose.

Hematological evaluations revealed statistically significant decreases in erythrocyte mean diameter in high-dose males at 12, 18 and 24 months and females at 1000 ppm at 12 months. Erythrocyte morphological changes were observed in high-dose males at 24 months, indicative of mild hemolytic anemia.

Statistically significant ($p<0.01$) increases in relative liver weight at 1000 ppm were observed in males and females (12% and 13%, respectively). Increased relative spleen weight at the high dose were observed in males (16%) and females (21%, $p<0.05$). Relative adrenal weight was also increased (11%) in males at 1000 ppm. Histopathological findings revealed increased incidences of hepatocellular vacuolation in males at 1000 ppm and centrilobular hypertrophy and pigment deposition were observed in males at 300 ppm and above. An increased incidence in eosinophilic foci (females, high dose) and clear-cell foci (both sexes at high dose) in the liver were also observed. In the spleen, an increase in the incidence of histiocytic foci was reported in the high dose animals. Adrenal cortical vacuolation was observed in males at 300 and 1000 ppm. An increase in the incidence of forestomach lesions was also observed in the treated animals. Neoplastic findings included pituitary adenoma at 300 ppm, islet cell adenoma at 100 ppm and mononuclear cell leukemia at 100 and 300 ppm in both sexes and in females at 1000 ppm. The increased incidences of pituitary and islet cell tumor were within historical control range and are not considered to be treatment-related. The incidence of mononuclear cell leukemia for high-dose females (30%) fell outside the in-house historical control range (7 studies, 5-28%), but within the NTP historical control frequency of 6-31% for Fisher 344 females. **The LOAEL for systemic toxicity is 300 ppm (13.8 mg/kg/day), based on increased adrenal cortical vacuolation, increased incidence of hepatocellular hypertrophy and hepatocellular vacuolation. The NOAEL for systemic toxicity is 100 ppm (4.6 mg/kg/day).**

At the doses tested, there was not a treatment related increase in tumor incidence mononuclear cell leukemia when compared to controls. The incidence of mononuclear cell leukemia fell outside the in-house control range, but within the reported NTP range for non-treated Fischer 344 rats. Dosing was considered adequate based on increased liver and spleen weights and the marked hepatic effects of hepatocellular hypertrophy and vacuolation at the high dose.

This carcinogenicity study in the rats is acceptable (guideline) and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in rats.

3.5.10.2 Carcinogenicity Study in Mice

MRID No.: 44721612

Executive Summary: In a carcinogenicity study (MRID 44721612) WL148271(cis/trans ratio 84:16 metconazole, 95.3% a.i., batch/lot 42/89-579) was administered to 51 mice (Crl:CD-1(ICR)BR strain)/sex/dose in diet at dose levels of 0, 30, 300 or 1000 ppm (equivalent to 0, 4.4, 43.6 or 144.9 mg/kg bw/day for males and 0, 5.2, 53.0 or 179.2 mg/kg bw/day for females) for 91 weeks. In addition, 12 mice/sex/dose were administered the technical for an interim sacrifice at week 52.

Treatment had no adverse effect on survival. An increased incidence of swollen abdomens was observed in the high dose groups beginning at approximately week 50. Food consumption was significantly reduced during the first week of treatment in high-dose males (14%) and females (10%) relative to the control animals and continued, to a lesser degree, throughout the treatment period. Decreased terminal body weights were observed in males in the high dose group (7%) and in females at 300 and 1000 ppm (8% and 13%, respectively). During the first week of treatment, high-dose animals lost weight which resulted in an overall reduction in body weight gain for this group. Subsequent to week 1, the body weight gains for the high-dose animals were similar to the control group.

Hematology revealed elevated leukocytes in males at 300 ppm (+35%) and above and in females at 1000 ppm (+228%). Increased levels on neutrophils and lymphocytes were also observed in the high dose animals. Clinical chemistry findings included decreased cholesterol (-33% males, -47% females) and triglycerides (-17% males, -22% females). Aspartate- and alanine aminotransferase levels were significantly increased in females (21% and 15%, respectively) at 300 ppm and in both sexes at the high dose.

All high-dose animals showed increased liver weights and reduced spleen weights relative to the controls at the interim and terminal sacrifice. Relevant gross pathology findings in the liver included enlargement, thickening, multiple masses and pale areas/foci in high dose animals. Small, pale spleens were observed in high dose males (5/12) and in females at 300 ppm (1/12) and 1000 ppm (6/12). Histopathological findings revealed liver toxicity including hepatocyte vacuolation and hypertrophy at 300 and 1000 ppm at week 52 and 91. The incidence of liver vacuolation at 300 ppm was 20/51 in males and 36/51 in females compared to 11/50 for both male and female control animals at week 91. The incidence of liver hypertrophy at 300 ppm was 13/51 and 8/51 in male and female mice respectively at week 91. There were no incidences of liver hypertrophy in the control animals. These findings were accompanied by single cell necrosis, pigment deposit, oval cell and multifocal hyperplasia, and biliary proliferation at week 91 in high-dose animals. Spleen atrophy with prominent trabeculae and stroma were observed at 300 ppm (9/49 males, 15/50 females) and above. Adrenal corticomedullary pigmentation was observed in high dose males and in females at 300 ppm (49/51) and above. **The LOAEL is 43.6 mg/kg/day, based on decreased cholesterol and triglycerides, increased liver weight, elevated aminotransferases (AST/ALT), liver vacuolation and hepatocellular hypertrophy and necrosis, spleen atrophy and adrenal pigmentation. The NOAEL is 4.4 mg/kg/day.**

Neoplastic findings were noted in the liver where an increase in the incidence of hepatocellular adenomas was seen in females at 300 and 1000 ppm and in males at 1000 ppm. At the interim

sacrifice, a single incidence of liver adenoma was observed at each dose in the male mice and 73% (8/11) of the high dose females showed liver adenomas. Overall, the incidences of liver adenomas in males were 11/62, 17/63, 16/63 and 35/62 at 0, 30, 300 and 1000 ppm, respectively. In females, the overall incidences of liver adenomas were 0/62, 1/63, 4/63 and 50/63 for 0, 30, 300 and 1000 ppm, respectively. Hepatocellular carcinoma was observed in one high dose female (1/11) at the interim sacrifice. The total (interim plus terminal sacrifice) incidences of liver carcinoma were 4/62, 4/63, 7/63 and 7/62 for males at 0, 30, 300 and 1000 ppm, respectively. The incidences of liver carcinoma in females were 0/62, 1/63, 0/63 and 20/63 at 0, 30, 300 and 1000 ppm, respectively. Statistical analysis showed a significant increase in the number of tumor bearing male animals at 1000 ppm (38/63, $p<0.001$) and in females at 300 ppm (4/63, $p<0.05$) and 1000 ppm (52/63, $p<0.001$). At the doses tested, there were treatment-related increases in tumor incidences hepatocellular adenoma and carcinomas when compared to controls. The CD-1 mouse in-house historical control values for liver adenomas are 10-33% (males) and 0-2% (females) and 2-8% (males) and 2-18% females for liver carcinomas. Dosing was considered adequate based on increased liver weight, elevated aminotransferase enzyme levels, liver vacuolation, hypertrophy and necrosis.

This carcinogenicity study in the mouse is acceptable and satisfies guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

3.5.10.3 Mutagenicity

There is no mutagenicity concern for metconazole. When the genotoxic potential of metconazole was tested in several *in vitro* and *in vivo* mutagenicity assays, all tests were negative with the exception of the chromosomal aberration assay (in the presence of S-9 mix (metabolic activation)). Overall, metconazole is considered to be non-genotoxic. These assays satisfy the Subdivision F Guideline requirements for mutagenicity testing. See Appendix A.3.6 for study summaries.

3.5.10.4 Classification of Carcinogenic Potential

Carcinogenicity studies showed an increased incidence of mononuclear cell leukemia in female rats and increased incidence of liver tumors (hepatocellular adenomas in male mice and hepatocellular carcinomas in female mice) in the mouse. The CARC concluded that the increased incidence of mononuclear cell leukemia in female rats was not treatment-related. The leukemia incidences in the cancer study, when considered collectively with a concurrent rat chronic toxicity study, were within the historical control range for the strain. The committee also reviewed the mouse liver tumor data, mechanistic study data and the registrant's position paper to support a non-linear non-genotoxic mode of action (MOA) for induction of mouse liver tumors. The registrant showed a probable sequence of key precursor events leading to increased incidence of mouse liver tumors occurring at threshold dose levels including the induction of drug metabolizing enzymes, enhanced cell proliferation (mitogenic activity), hepatocellular hypertrophy, hepatocellular degeneration, clinical chemistry alterations, single cell necrosis/pigment deposition, hyperplasia and hepatocellular tumor formation. The committee concluded that the increased incidence of liver tumors was treatment-related, the dosing was

adequate and not excessive, there was no concern for mutagenicity, and the committee determined a plausible MOA for non-genotoxic liver tumors in mice.

Cancer Assessment Review Committee (CARC) Classification: "Not Likely to be Carcinogenic to Humans" based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects were not likely below a defined dose that doesn't cause mitogenesis (memo, J. Kidwell, TXR# 0054211, 4/14/06). A non-genotoxic mode of action for mouse liver tumors was established. No quantification required.

3.5.11 Summary of Toxicological Doses and Endpoints for Metconazole for Use in Human Risk Assessments

Table 5. Summary of Toxicological Doses and Endpoints for Metconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	An appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed.			
Acute Dietary (Females 13-49 years of age)	NOAEL= 12 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.12 mg/kg/day aPAD= 0.12 mg/kg/day	**Developmental toxicity in rats:** LOAEL= 30 mg/kg/day based on increases in skeletal variations.
Chronic Dietary (All Populations)	NOAEL= 4.3 mg/kg/day	UF_A=10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.04 mg/kg/day cPAD = 0.04 mg/kg/day	**Chronic oral toxicity study in rats:** LOAEL = 13.1 mg/kg/day based on increased liver (M) weights and associated hepatocellular lipid vacuolation (M) and centrilobular hypertrophy(M). Same effects seen in F at 54 mg/kg/day, plus increased spleen wt.
Incidental Oral Short-Term (1-30 days)	NOAEL= 9.1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**28-Day oral toxicity study in rats:** LOAEL = 90.5 mg/kg/day based on decreased body weight (M), increased liver and kidney weight and hepatocellular hypertrophy and vacuolation (M/F).
Incidental Oral Intermediate-Term (1-6 months)	NOAEL= 6.4 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**90-Day oral toxicity study in rats:** LOAEL = 19.2 based on increased spleen wt (F) and hepatic vacuolation (M).
Dermal Short-Term (1-30 days) Dermal Intermediate-Term (1-6 months)	Quantification of dermal risk is not required due to lack of systemic or dermal toxicity at the Limit Dose in a 21-day dermal toxicity study in the rat and the lack of target organ toxicity, neurotoxicity, developmental or reproductive toxicity.			
Inhalation Short-	NOAEL= 9.1	UF_A= 10x	Residential LOC	**28-Day oral toxicity study in rats:**

Table 5. Summary of Toxicological Doses and Endpoints for Metconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Term (1-30 days)	mg/kg/day	UF_H=10x FQPA SF= 1x	for MOE = 100	LOAEL = 90.5 mg/kg/day based on decreased body weight (M), increased liver and kidney weight and hepatocellular hypertrophy and vacuolation (M/F).
Inhalation Intermediate-Term (1-6 months)	NOAEL= 6.4 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	**90-Day oral toxicity study in rats:** LOAEL = 19.2 mg/kg/day based on increased spleen wt (F) and hepatic vacuolation (M).
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 6. Summary of Toxicological Doses and Endpoints for Metconazole for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days)	Quantification of dermal risk is not required due to lack of systemic or dermal toxicity at the Limit Dose in a 21-day dermal toxicity study in the rat and the lack of target organ toxicity, neurotoxicity, developmental or reproductive toxicity.			
Dermal Intermediate-Term (1-6 months)				
Inhalation Short-Term (1-30 days)	NOAEL=9.1 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**28-Day oral toxicity study in rats:** LOAEL = 90.5 mg/kg/day based on decreased body weight (M), increased liver and kidney weight and hepatocellular hypertrophy and vacuolation (M/F).
Inhalation Intermediate-term (1-6 months)	NOAEL=6.4 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	**90-Day oral toxicity study in rats:** LOAEL = 19.2 mg/kg/day based on increased spleen wt (F) and hepatic vacuolation (M).
Cancer (oral, dermal, inhalation)	Classification: "Not Likely to be Carcinogenic to Humans"			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to

extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.6 Endocrine disruption

EPA is required under the 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 (EDSP).

4.0 Dietary Exposure/Risk Characterization

4.1 Drinking Water Residue Profile

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Revised Drinking Water Exposure Assessment for Metconazole Based on The Proposed Labels of BAS 556 01F, Caramba™, V-10116 VPP, Metconazole 50 WDG, and Metconazole Technical" (J. Lin, DP Number 340378, 6/20/07) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

No monitoring data of metconazole were available to EFED. Surface water concentrations were estimated using the Tier II model PRZM (version 3.12) and EXAMS (version 2.98). Ground water concentrations were estimated using the Tier I SCI-GROW model. Metconazole may be applied by aerial or ground as per the labels for this product except for turf use (ground application only). This memo only addresses the estimations of parent metconazole.

Based on modeling results, the estimated surface water drinking water concentrations for metconazole are as follows:

45.48 ug /L for the 1 in 10 year annual peak concentration (acute);
31.25 ug /L for the 1 in 10 year annual mean concentration (non-cancer chronic); and
22.80 ug /L for the 30 year annual mean concentration (cancer chronic).

The 1 in 10 year annual peak (acute), 1 in 10 year annual mean (non-cancer chronic), and the 30-year annual mean concentration (cancer chronic) were all derived from metconazole use on Pennsylvania turf. These values were highest among all modeling scenarios examined. The turf use is 5 applications of 0.6 lb ai/acre per application and application intervals of 14 days.

The SCI-GROW estimated drinking water concentrations from ground water for metconazole are not expected to exceed 0.384 µg/L, which was based on 5 applications of a 0.60 lb ai/acre per application.

4.2 Dietary Exposure and Risk

Reference: *Metconazole. Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Section 3 Registration on Turf and Ornamentals. DP Number: 340068, N. Dodd, 06/27/07.*

For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to point of departure (POD, NOAEL, LOAEL, e.g.) divided by the required uncertainty or safety factors.

For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD. HED is generally concerned when estimated cancer risk exceeds one in one million. References which discuss the acute and chronic risk assessments in more detail are available on the EPA/pesticides web site: "Available Information on Assessing Exposure from Pesticides, A User's Guide," 21-JUN-2000, web link: http://www.epa.gov/fedrgstr/EPA-PEST/2000/July/Day-12/6061.pdf; or see SOP 99.6 (20-AUG-1999).

Residue Data used for Acute and Chronic Assessments:

The residue levels used in the acute and chronic assessments were the established tolerance levels for banana, soybean commodities, and livestock commodities. The assessments are conservative assessments using 100% crop treated.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the chronic assessment. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors.

Conservative acute and chronic dietary exposure assessments were conducted. The residue levels used in the assessments were the established tolerance levels for banana, soybean commodities, and livestock commodities. The assessments assumed that 100% of the crop was treated. Although not needed at this time, HED could refine the exposure and risk estimates with the following information: 1) a soybean processing study; 2) projected market share/percent crop

treated data; and 3) anticipated residue data.

DEEM-FCID™ Program and Consumption Information

Metconazole acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database 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 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.

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.

Results and Discussion

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 results reported in Table 7 below 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.

Results of Acute Dietary (Food and Drinking Water) Exposure Analysis

The results of the acute dietary (food and drinking water) exposure analysis are reported in Table 7 below. An acute dietary exposure assessment was conducted for the proposed uses on turf and ornamentals, all established food uses (soybeans and imported bananas), and drinking water. Except for water, a conservative (Tier 1) assessment was conducted. The residue levels used in the assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities. The assessment assumed that 100% of the crop was treated.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the acute assessment. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors.

For the general U.S. population, including infants and children, an appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed. Therefore, acute dietary exposure and risk to these populations cannot be assessed. The acute dietary exposure estimate at the 95th percentile is 2% aPAD for females 13-49 years old, the only population subgroup of concern, which is below HED's level of concern.

Results of Chronic Dietary (Food and Drinking Water) Exposure Analysis

The results of the chronic dietary (food and drinking water) exposure analysis are reported in Table 7 below. A chronic dietary exposure assessment was conducted for the proposed uses on turf and ornamentals, all established food uses (soybeans and imported bananas), and drinking water. Except for water, a conservative (Tier 1) assessment was conducted. The residue levels used in the assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities. The assessment assumed that 100% of the crop was treated.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the chronic assessment. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors.

The chronic dietary (food and drinking water) exposure to metconazole is below HED's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 4% cPAD for the general U.S. population and 10% cPAD for all infants (<1 year old), the most highly exposed population subgroup.

Table 7. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Metconazole				
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	not applicable*		0.001404	4
All Infants (< 1 year old)			**0.003886**	**10**
Children 1-2 years old			0.003107	8
Children 3-5 years old			0.002717	7
Children 6-12 years old			0.001843	5
Youth 13-19 years old			0.001197	3
Adults 20-49 years old			0.001173	3
Adults 50+ years old			0.001121	3
Females 13-49 years old	**0.002967**	**2**	0.001148	3

* For the general U.S. population, an appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed.

Characterization of Inputs

The residue levels used in the assessment were the established tolerance levels for banana, soybean commodities, and livestock commodities, and assumed 100% crop treated. Therefore, the acute and chronic dietary, food only, exposure is considered an upper bound conservative estimate. Although not needed at this time, HED could refine the exposure and risk estimates with the following information: 1) a soybean processing study; 2) projected market share/percent crop treated data; and 3) anticipated residue data.

Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the acute and chronic dietary assessments. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors.

Conclusions

Acute and chronic dietary exposure assessments were conducted for the proposed uses on turf

and ornamentals, all established food uses (soybeans and imported bananas), and drinking water. Except for water, conservative (Tier 1) assessments were conducted. Estimated concentrations of metconazole in drinking water from the proposed uses on turf and ornamentals were provided by EFED and incorporated directly into the acute and chronic assessments. A Tier II drinking water assessment for the proposed uses on turf and ornamentals was performed using PRZM/EXAMS modeling with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors.

The acute dietary (food and drinking water) exposure to metconazole is below HED's level of concern for the general U.S. population and all population subgroups. For the general U.S. population, an appropriate dose/endpoint attributable to a single dose was not observed in the available oral toxicity studies reviewed. The acute dietary exposure estimate at the 95th percentile is 2% aPAD for females 13-49 years old, the only population subgroup of concern.

The chronic dietary (food and drinking water) exposure to metconazole is below HED's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 4% cPAD for the general U.S. population and 10% cPAD for all infants (<1 year old), the most highly exposed population subgroup.

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

Reference: *Metconazole: Occupational and Residential Exposure/Risk Assessment for Use on Ornamentals and Turf. (PC#: 125619; DP#:341832); J. Arthur; 08/03/07.*

5.1 Residential Handler Exposure and Risk Characterization

There is potential adult short-term dermal and inhalation exposure to metconazole from its proposed use on turf and ornamentals. However, because dermal toxicity endpoints for the appropriate duration of exposure were not identified, only residential handler inhalation exposures/risks have been assessed.

An MOE ≥100 is adequate to protect residential pesticide handlers. All metconazole residential handler MOEs are estimated to be >100 for the proposed uses, and therefore, do not cause concern for HED.

A summary of these exposures and risks is presented in Table 8.

Table 8 Residential Handler Short-term Inhalation Exposures and Risks

Scenario	Exposure Route	Max. Rate Application	Unit Exposure	Amount Treated/Day	Daily Dose (mg/kg/day)[1]	Inhalation MOE[2]
1) mixer/loader/applicator w/ hose-end sprayer (ornamentals)	Inhalation	0.0025 lb ai/ Gal.	0.017 mg/lb ai	100 Gal.	0.000061	150,000
2) mixer/loader/applicator w/ low-pressure hand-wand sprayer (ornamentals)	Inhalation	0.0025 lb ai/ Gal.	0.03 mg/lb ai	5 Gal.	0.0000054	1,700,000
3) mixer/loader/applicator w/ hose-end sprayer (turf)	Inhalation	0.6 lb ai/ Acre	0.017 mg/lb ai	0.023 Acre = 1000 ft^2	0.0000034	2,700,000
4) mixer/loader/applicator w/ low-pressure hand-wand sprayer (turf)	Inhalation	0.6 lb ai/ Acre	0.03 mg/lb ai	0.5 Acre	0.00013	71,000

1. Daily Dose = Application Rate * Unit Exposure * Amount Treated * Absorption factor (100% for inhalation)/Body Weight (70 kg).
2. Inhalation MOE = Inhalation short-term NOAEL (9.1 mg/kg/day) ÷ Daily Dose

5.2 Residential Postapplication Exposure and Risk Characterization

Adults, adolescents and toddlers may be exposed to metconazole from its proposed residential uses. Adults and adolescents may experience short- and intermediate-term dermal exposure from golfing and other activities on treated turf, as well as from tending treated ornamentals. Toddlers may experience short- and intermediate-term dermal and incidental oral exposure from activities on treated turf. However, because dermal toxicity endpoints for the appropriate durations of exposure were not identified, and because inhalation exposure is considered to be insignificant for postapplication exposures, only toddler incidental oral postapplication exposures have been assessed.

HED relies on a standardized approach for completing residential risk assessments that is based on the proposed metconazole label and guidance contained in the following five documents:

- Series 875, Residential and Residential Exposure Test Guidelines: Group B - Postapplication Exposure Monitoring Test Guidelines (V 5.4, Feb. 1998): This document provides general risk assessment guidance and criteria for analysis of residue dissipation data.

- Standard Operating Procedures for Residential Exposure Assessment (Dec. 1997): This document provides the overarching guidance for developing residential risk assessments including scenario development, algorithms, and values for inputs.

- Science Advisory Council for Exposure Policy 12 (Feb. 2001): Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessment: This document provides additional, revised guidance for completing residential exposure assessments.

- Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment (August 1999 Presentation To The FIFRA SAP): This document provides rationale for Agency changes in SOPs.

The SOPs for Residential Exposure Assessment define several scenarios that apply to uses specified in the proposed label. These scenarios served as the basis for the residential postapplication assessment of metconazole, and include:

- Exposure from hand-to-mouth activity on treated turf: Postapplication dose calculations for toddlers from incidental non-dietary ingestion of pesticide residues on treated turf from hand-to-mouth transfer;

- Exposure from object-to-mouth activity on treated turf: Postapplication dose calculations for toddlers from incidental non-dietary ingestion of pesticide residues on treated turf from object-to-mouth transfer; and

- Exposure from soil ingestion activity on treated turf: Postapplication dose calculations for toddlers from incidental non-dietary ingestion of pesticide residues from ingesting soil in a treated turf area.

The registrant has submitted two turf transferable residue (TTR) studies in support of the registration of metconazole. The following are brief summaries of these studies.

1) Valent U.S.A. Corporation, "*Transferable Turf Residue of Metconazole on Turfgrass.*" (December 15, 2005, Project No., V-27246; MRID 46805108)

This study was designed to determine transferable residues of metconazole from turf treated with V-101161.81 FL fungicide at a target application rate of 1.2 lb formulated product/acre (0.6 lb ai/A). V-101161.81 FL fungicide, formulated as a water dispersible granule containing 20.9% active ingredient (ai) metconazole, was applied twice, 15 days apart, using a tractor mounted platform boom sprayer. V-101161.81 FL is a mixture of two isomers of metconazole (85% *cis*- and 15% *trans*-metconazole). The field trial was conducted at one location in Grand Rapids, Ottawa County, Michigan (EPA Region V). Transferable residues were measured using the modified California roller method for turf transferable residues (TTR). Triplicate TTR samples were collected at -1 (pre-treat), 0 and 13 days after last application (DALA) for the first treatment interval, and at 0, 1, 2, 3, 5, 7, 10, 14, 21, and 28 DALA after the second (final) treatment interval.

Residue analyses for metconazole were conducted on samples through the 10 DALA sampling interval. The samples collected after this sampling interval were not analyzed since the residues had declined to or less than the limit of detection (LOD) (i.e., 0.001 $\mu g/cm^2$) by the 5 DALA sampling interval. The maximum average total metconazole TTR occurred at 1 DALA and was 0.079 $\mu g/cm^2$ and declined rapidly to less than the LOD by 5 DALA. The *cis*-metconazole residues dropped below LOD by 5 DALA and the *trans*-metconazole residues dropped below the LOD by 2 DALA. These levels are potentially underestimated due to the lack of field fortification recovery sampling. Field fortification samples reflect potential loss of analyte that occurs during sample collection, shipment, storage, and analysis. The TTR value on day 1, when the TTR peaked, represents 1.2 percent of the original application rate.

First-order dissipation kinetics were assumed to generate dissipation curves for total metconazole, *cis*-metconazole and *trans*-metconazole. The estimated half-life values were 0.785 days (R^2=0.617) for total metconazole residues, 0.699 days (R^2=0.620) for *cis*-metconazole residues and 0.558 days (R^2=0.546) for *trans*-metconazole residues.

2) Valent U.S.A. Corporation, "*Transferable Turf Residue of Metconazole on Turfgrass.*" (December 15, 2005, Project No., V-25718; MRID 46805107)

This study was designed to determine transferable residues of metconazole from turf treated with V-101161.81 FL fungicide at a target application rate of 1.2 lb formulated product/acre (0.6 lb ai/A). V-101161.81 FL fungicide, formulated as a water dispersible granule containing 21.3%

active ingredient (ai) metconazole, was applied twice, 14 days apart, using a tractor mounted, compressed air driven boom sprayer. V-101161.81 FL is a mixture of two isomers of metconazole (85% *cis*- and 15% *trans*-metconazole). The field trial was conducted at one location in Athens, Clarke County, Georgia (EPA Region II). Transferable residues were measured using the modified California roller method for turf transferable residues (TTR). Triplicate TTR samples were collected at -1 (pre-treat), 0 and 13 days after the first application, and at 0, 1, 2, 3, 5, 7, 10, 14, 21, 28, and 35 days after the second (final) application (DALA).

Residue analyses for metconazole were conducted on samples collected through the 7 DALA sampling interval. The samples collected after this sampling interval were not analyzed since the residues had declined to or less than the limit of detection (LOD) (i.e., 0.001 $\mu g/cm^2$) by the 3 DALA sampling interval. The maximum average total metconazole residue occurred immediately following the first application (0.026 $\mu g/cm^2$). Residues declined to less than the LOD by 5 DALA. The *cis*-metconazole residues dropped below LOD by 5 DALA and the *trans*-metconazole residues dropped below the LOD by 2 DALA. The TTR value on day 0 represents 0.38 percent of the original application rate.

First-order dissipation kinetics were assumed to generate dissipation curves for total metconazole, *cis*-metconazole and *trans*-metconazole. The estimated half-life values were 1.03 days (R^2=0.864) for total metconazole residues, 0.869 days (R^2=0.879) for *cis*-metconazole residues and 0.750 days (R^2=0.740) for *trans*-metconazole residues.

The TTR results from the above studies are not used here in the assessment of residential postapplication exposure from metconazole-treated lawns. TTR study results are only applicable to dermal assessments and dermal assessments, as previously mentioned, are not conducted for metconazole.

Residential Postapplication Exposure on Treated Lawns

Postapplication risks to toddlers following the application of metconazole to home lawns were calculated for short- and intermediate-term incidental oral exposures. A summary of the estimated exposures and risks, along with the algorithms used for each toddler exposure scenario are presented below in Tables 9 - 11. All MOEs for toddler lawn exposure scenarios were >100 and therefore, are not of concern to HED. In addition, the total MOEs for combined toddler exposures (i.e., short-term and intermediate-term hand-to-mouth, object-to-mouth, and incidental ingestion of soil) are >100 (see Table 12), and therefore, do not concern HED.

Table 9. Oral Hand-to-mouth Short- (ST) and Intermediate-term (IT) Exposures and Risks for Children from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Turf Transferrable Residue at Day "0" (ug/cm^2)[1]	Exposure Time (hrs/day)	Extraction by saliva	Hand Surface Area (cm^2/event)	Frequency (events/ hr)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	MOE[3]
0.6	0.05	0.34	2	0.5	20	20 (ST)	15	0.009 (ST)	1000 (ST)
						9.5 (IT)		0.0042 (IT)	1500 (IT)

[1] Turf Transferrable Residue (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2
[2] Daily Dose = (Turf Transferrable Residue x Extraction by Saliva x Hand Surface Area x Frequency x 1E-3 mg/ ug x Exposure Time) / (Body Weight)
[3] MOE = Short-term Oral NOAEL (9.1 mg/kg/day) or Intermediate-Term Oral NOAEL (6.4 mg/kg/day) /Daily Dose.

Table 10. Oral Object-to-mouth (Turfgrass) Short- (ST) and Intermediate-term (IT) Exposures and Risks for Children from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Grass Residue at Day "0" (ug/cm^2)[1]	Surface Area Mouthed (cm^2/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	MOE[3]
0.6	0.20	1.3	25	15	0.0022	4100 (ST)
						2900 (IT)

[1] Grass Residue (ug/cm^2) = = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2
[2] Daily Dose = [Grass residue (ug/cm2) x Surface Area Mouthed (cm2/day) x 1E-3 mg/ug] / [Body Weight (kg)]
[3] MOE = Short-term Oral NOAEL (9.1 mg/kg/day) or Intermediate-Term Oral NOAEL (6.4 mg/kg/day) /Daily Dose

Table 11. Short- (ST) and Intermediate-term (IT) Exposure and Risk for Children from Ingestion of Soil from Treated Lawns

Application Rate (lb ai/A)	Fraction of ai Available	Soil Residue at Day "0" (ug/g)[1]	Ingestion Rate (mg/day)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	MOE[3]
0.6	1	4.51	100	15	0.00003	300,000 (ST)
						210,000 (IT)

[1] Soil residue (ug/g) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm^2 x 0.67 cm^3/g soil]
[2] Daily Dose = [Soil residue (ug/g) x Ingestion rate (mg/day) x 1E-6 g/ug] / [Body Weight (kg)]
[3] MOE = Short-term Oral NOAEL (9.1 mg/kg/day) or Intermediate-Term Oral NOAEL (6.4 mg/kg/day) /Daily Dose

Table 12. Children's Residential Combined Short- and Intermediate-term Risk from Treated Turf				
Route	Daily Dose (mg/kg/day)	MOE	Total ST MOE[1]	Total IT MOE[2]
Hand-to-Mouth	0.009 (ST)	1000 (ST)	810	1000
	0.0042 (IT)	1500 (IT)		
Object-to-Mouth	0.0022	4100 (ST)		
		2900 (IT)		
Soil Ingestion	0.00003	310,000 (ST)		
		220,000 (IT)		

1. Total ST MOE = 1 ÷ [(1/ST Hand-to-Mouth MOE) + (1/ST Object-to-Mouth MOE) + (1/ST Soil Ingestion MOE)]
2. Total IT MOE = 1 ÷ [(1/IT Hand-to-Mouth MOE) + (1/IT Object-to-Mouth MOE) + (1/IT Soil Ingestion MOE)]

6.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Based on the proposed uses on turfgrass, and that fact that common toxicity endpoints exist for the incidental oral, and acute and chronic dietary routes of exposure, then acute, chronic, and short-term aggregate exposure and risk assessments are required.

6.1 Acute & Chronic Aggregate Risk

Acute and chronic aggregate exposures include food plus drinking water exposures. The use on imported bananas does not contribute to residues in drinking water in the US. The dietary component also includes exposure from soybeans, because a Section 18 use on soybeans was approved last year. Refer to section 4.2 for these risk estimates.

6.2 Short- and Intermediate-Term Aggregate Risk

The short- and intermediate-term aggregate risk assessments take into account average (chronic) exposure estimates from dietary consumption of metconazole (food and drinking water) and non-occupational/residential use on turf (dermal and inhalation exposures for adults, and dermal plus incidental oral exposures for children).

For adults applying metconazole to turf, short- and intermediate-term exposures were aggregated. The exposure scenario with the highest daily dose and lowest MOE was used; i.e., mixer/loader/applicator with a low pressure handwand sprayer.

The short-and intermediate-term aggregate MOEs from dietary exposure (food + drinking water) and non-occupational/residential handler exposure (inhalation) for adults are 3,000 and 2,900, respectively; which are not of concern to HED (see Table 13 below), since they are greater than the level of concern MOE of 100.

Table 13. Short- and Intermediate-Term Aggregate Risk Calculations for Adult Handlers

Population/ Exposure Duration	Inhalation Exposure			Dietary Exposure			Short- or Intermediate-Term Aggregate MOE[2]
	NOAEL (mg/kg/day)	Exposure (mg/kg/day)	MOE[1]	NOAEL (mg/kg/day)	Exposure (mg/kg/day)	MOE[1]	
Adult ST	9.1	0.00013	70,000	4.3	0.001404	3,100	3,000
Adult IT	6.4	0.00013	49,000	4.3	0.001404	3,100	2,900

[1] MOE = NOAEL / Exposure; The Level of Concern MOE is 100.

[2] Aggregate MOE = $1/ [(1/MOE_{Incidental\ Oral}) + (1/MOE_{Food + Drinking\ Water})]$

Postapplication exposures from the use on turf are considered predominantly short-term (1-30 days). Although exposures are expected via the dermal route, quantification of dermal risk is not required, since a dermal endpoint was not identified for short-, or intermediate-term exposures. Therefore, short- and intermediate-term postapplication aggregate risk assessments were conducted only for average dietary and incidental oral exposures to toddlers. The short-and intermediate-term aggregate MOEs from dietary exposure (food + drinking water) and non-occupational/residential exposure (incidental oral) for children 1-2 years old are 470 and 520, respectively; which are not of concern to HED (see Table 14 below), since it is greater than the level of concern MOE of 100.

Table 14. Short-and Intermediate-Term Aggregate Risk Calculations for Postapplication Exposures

Population/ Exposure Duration	Incidental Oral Exposure			Dietary Exposure			Short-or Intermediate-Term Aggregate MOE[2]
	NOAEL (mg/kg/day)	Exposure (mg/kg/day)	MOE[1]	NOAEL (mg/kg/day)	Exposure (mg/kg/day)	MOE[1]	
Kids 1-2 yrs/ST	9.1	0.01123	810	4.3	0.003886	1,100	470 ST
Kids 1-2 yrs/IT	6.4	0.00643	1000	4.3	0.003886	1,100	520 IT

[1] MOE = NOAEL / Exposure; The Level of Concern MOE is 100.

[2] Aggregate MOE = $1/ [(1/MOE_{Incidental\ Oral}) + (1/MOE_{Food + Drinking\ Water})]$

These aggregate exposure assessments are considered conservative estimates, that should not underestimate risks, because of the following inputs: 1) dietary inputs used crop specific (turf) screening level drinking water modeling data (i.e., Tier II surface water model); 2) maximum application rates and minimum application intervals were used; and 3) conservative SOPs and upper level estimates of exposure were employed.

7.0 Cumulative Risk Characterization/Assessment

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 as to metconazole and any other substances. For the purposes of this action, therefore, EPA has not assumed that metconazole has 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 Exposure/Risk Pathway

Reference: *Metconazole: Occupational and Residential Exposure/Risk Assessment for Use on Ornamentals and Turf. (PC#: 125619; DP#:341832); J. Arthur; 08/03/07.*

8.1 Occupational Handler Exposure and Risk

Based upon the proposed use pattern, HED believes the most highly exposed occupational pesticide handlers are most likely to be 1) mixer/loader/applicator using a backpack sprayer, 2) mixer/loader/applicator using low-pressure hand-wand sprayer, 3) a mixer/loader loading open pour water dispersible granules to support groundboom application, 4) applicator using groundboom, 5) mixer/loader/applicator using hand-gun sprayer, 6) mixer/loader/applicator using high-pressure hand-wand, 7) mixer/loader liquid for airblast, and 8) applicator using airblast sprayer. HED believes short- (1 - 30 days) and intermediate-term (1 – 6 months) exposures are possible for occupational metconazole handlers. Only inhalation toxicity endpoints were identified for these anticipated exposure durations.

No chemical specific data were available with which to assess potential exposure to occupational pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). The proposed label directs applicators and other handlers to wear long-sleeved shirt, long pants, and shoes plus socks.

An MOE ≥100 is adequate to protect occupational pesticide handlers. All metconazole occupational handler MOEs are estimated to be >100 for the proposed uses, and therefore, do not cause concern for HED.

Table 10 below presents a summary of short- and intermediate-term occupational handler exposures and risks.

Table 10. Occupational Handler Short- and Intermediate-term Inhalation Exposures and Risks

Scenario	Exposure Route	Max. Rate Application	Unit Exposure	Amount Treated/Day	Daily Dose (mg/kg/day)[1]	Short-term MOE[2]	Intermediate-term MOE[2]
1) mixer/loader/applicator w/ backpack sprayer (ornamentals, turf)	Inhalation	0.0025 lb ai per Gallon	0.03 mg/lb ai	40 Gal.	0.000043	210,000	150,000
2) mixer/loader/applicator w/ low-pressure hand-wand sprayer (ornamentals, turf	Inhalation	0.0025 lb ai per Gallon	0.03 mg/lb ai	40 Gal.	0.000043	210,000	150,000
3) mixer/loader, open pour water dispersible granules to support groundboom (ornamentals, turf)	Inhalation	0.6 lb ai per Acre	0.00077 mg/lb ai	40 Acres	0.00026	34,000	24,000
4) applicator, groundboom (ornamentals, turf)	Inhalation	0.6 lb ai per Acre	0.00074 mg/lb ai	40 Acres	0.00025	36,000	25,000
5) mixer/loader/applicator, LCO hand-gun sprayer (turf)	Inhalation	0.6 lb ai per Acre	0.022 mg/lb ai	5 Acres	0.00094	9700	6800
6) mixer/loader/applicator, liquid with high-pressure hand-wand (ornamentals)	Inhalation	0.0025 lb ai per Gallon	0.12 mg/lb ai	1000 Gal.	0.0043	2100	1500
7) mixer/loader liquid for airblast (ornamentals)	Inhalation	0.6 lb ai per Acre	0.00077 mg/lb ai	20 Acres	0.00013	69,000	48,000
8) applicator using airblast (ornamentals)	Inhalation	0.6 lb ai per Acre	0.0045 mg/lb ai	20 Acres	0.00077	12,000	8300

1. Daily Dose = Application Rate * Unit Exposure * Amount Treated * Absorption factor (100% for inhalation)/Body Weight (70 kg).
2. Inhalation MOE = inhalation short-term NOAEL (9.1 mg/kg/day) or intermediate-term NOAEL (6.4 mg/kg/day) ÷ Daily Dose

8.2 Occupational Postapplication Exposure and Risk

There is the possibility for agricultural workers to have postapplication exposure to metconazole following its use on commercially grown ornamentals in nurseries and greenhouses, as well as golf course turf. However, because dermal toxicity endpoints for the appropriate durations of exposure were not identified, and because inhalation exposure is considered to be insignificant for postapplication exposures, no occupational postapplication exposure assessment is required.

Restricted Entry Interval (REI)

Metconazole is classified in Acute Toxicity Category III for acute dermal, primary eye irritation and primary skin irritation. It is not a dermal sensitizer. The label correctly indicates an interim restricted entry interval of 12 hours under the requirements of the Worker Protection Standard (WPS). The WPS requirement applies only to the proposed ornamental uses in this assessment (i.e., not to the golf course use).

9.0 Data Needs and Label Recommendations

The proposed V-10116 VPP Fungicide label contains inconsistencies concerning the retreatment intervals for foliar applications to ornamental plants. The proposed label lists the interval as both 14 to 21 days and 14 to 28 days. HED recommends that the proposed label be modified to include the appropriate retreatment interval; i.e. either 14 to 21 days, or 14 to 28 days.

An inhalation toxicity study is required.

10.0 References:

1. Metconazole. Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Section 3 Registration on Turf and Ornamentals. DP Barcode: D340068, N. Dodd, 06/27/07.

2. Revised Drinking Water Exposure Assessment for Metconazole Based on The Proposed Labels of BAS 556 01F, Caramba™, V-10116 VPP, Metconazole 50 WDG, and Metconazole Technical" (J. Lin, DP Number 340378, 6/20/07).

3. Metconazole: Occupational and Residential Exposure/Risk Assessment for Use on Ornamentals and Turf. (PC#: 125619; DP#:341832); J. Arthur; 08/03/07.

4. Metconazole: Human Health Risk Assessment for Proposed Tolerance on Imported Bananas. PC Code: 125619, Petition No.: 9E5052, DP Barcode: D308794; B. O'Keefe; 07/06/06.

11.0 Tolerance Summary

No tolerances are proposed in connection with the proposed uses on turf and ornamentals.

12.0 Appendix: Toxicity Profile

12.1 Appendix 1.: Metconazole Toxicology Data Requirements

Table A.1. Metconazole Toxicology Data Requirements

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	90-Day Inhalation	yes	yes
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	no
870.6100b	90-Day Neurotoxicity (hen)	no	no
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90-Day Neuro. Screening Battery (rat)	no	yes
870.6300	Develop. Neuro	no	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes
Special Studies for Ocular Effects			
	Acute Oral (rat)	no	no
	Subchronic Oral (rat)	no	no
	Six-month Oral (dog)	no	no

12.2 Appendix 2.: Acute Toxicity Data on Metconazole Technical

Table A.2 Acute Toxicity Profile – Metconazole Technical				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [mouse]	44721512	LD_{50} = >566 mg/kg	III
870.1100	Acute oral [rat]	44721512	LD_{50} = >566 mg/kg	III
870.1100	Acute oral [rat]	44721513	LD_{50} = >1459 mg/kg	III
870.1100	Acute oral [rat]	44721514	LD_{50} = >5000 mg/kg	IV
870.1200	Acute dermal [rat]	44721512	Dermal LD_{50} > 2000	III
870.1200	Acute dermal [rabbit]	44721512	Dermal LD_{50} > 2000	III
870.1200	Acute inhalation [rat]	44721512	LD_{50} = >5.6 mg/L	IV
870.2400	Acute eye irritation [rat]	44721513	moderate irritant	III
870.2500	Acute dermal irritation [rabbit]	44721513	mild irritant	IV
870.2600	Skin sensitization [guinea pig]	44721513	neg.	-

12.3 Appendix 3. Subchronic, Chronic and Other Toxicity Profile

Table A.3 Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	28-Day oral toxicity rodents (rat)	44721515 (1990) M/F: 0, 30, 100, 1000, 3000 ppm M: 0, 2.7, 9.1, 90.5, 261.1 mg/kg/day F: 0, 3.1, 10.1, 97, 287.4 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 9.1/10.1 mg/kg/day LOAEL (M/F) = 90.5/97 mg/kg/day based on depression of body weight in M, liver and kidney weight increases with associated histopathological effects (hypertrophy and fatty vacuolation) in liver only.
870.3100	90-Day oral toxicity rodents (rat)	44721517 (1991) M/F: 0, 30, 100, 300, 1000, 3000 ppm M: 0, 1.94, 6.4, 19.2, 64.3, 192.7 mg/kg/day F: 0, 2.1, 7.2, 22.1, 71.4, 208.0 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 6.4/7.2 mg/kg/day LOAEL (M/F) = 19.2/22.1 mg/kg/day based on increased spleen weight in females and hepatic vacuolation in males.
870.3100	90-Day oral toxicity rodents (mouse)	44721519 (1991) M/F: 0, 30, 300, 3000 (wk 1)/2000(wk 2-13) ppm M: 0, 9.58, 50.5, 341.1 mg/kg/day F: 0, 6.94, 60.7, 438.5 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 9.58/6.94 mg/kg/day LOAEL (M/F) = 50.5/60.7 mg/kg/day based on increase in absolute and relative liver weights, hepatocellular hypertrophy and vacuolation, and increase in relative spleen weight (F), elevated AST and ALT activity.
870.3150	28-Day oral toxicity non-rodents (dog)	44721520 (1991) M/F: 0, 100, 1000, and 7000-10000 ppm in diet Unacceptable/non-guideline (some preliminary test data provided)	NOAEL (M/F) = 100 ppm in diet LOAEL (M/F) = 1000 ppm in diet (increase in relative and absolute thyroid wt. in one/two females) Deficiencies: low n (2M/2F per dose); decrease in food consumption means low exposure to test compound; actual dose received per dose group not provided.
870.3150	90-Day oral toxicity non-rodents (dog)	44721521 (1991) M/F: 0, 60, 600, 6000 ppm in diet M: 0, 2.5, 24.4, 225.2 mg/kg/day F: 0, 2.6, 24.3, 206.6 mg/kg/day Acceptable/guideline	NOAEL (M/F) = 2.5/2.6 mg/kg/day LOAEL (M/F) = 24.4/24.3 mg/kg/day based on decreased food consumption and body weight gain in females and elevated platelets and reticulocytes in males.
870.3200	21-day Dermal Toxicity	46808439 (2006) 0, 250, 500, 1000	**NOAEL**: 1000 mg/kg

Table A.3 Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		mg/kg/day Acceptable/guideline	**LOAEL**: > 1000 mg/kg No evidence of dermal toxicity
870.6200	Subchronic (13-week) Oral Neurotoxicity- rat	46808440 (2002) 0, 50, 170, 500 ppm M: 0, 4.84, 15.69, 47.08 mg/kg/day F: 0, 5.10, 17.62, 49.82 mg/kg/day Acceptable/Non-guideline	**Systemic** NOAEL (M/F) = 4.84/5.10 mg/kg/ **Systemic** LOAEL (M/F) = 15.69/ 17.62 mg/kg/ based on decreases in body weight and food consumption. **Neurotoxicity** NOAEL (M/F) ≥ 47.08/49.82 mg/kg/day
870.3700	Prenatal development in rodents (rat)	44721522 (1991) 0, 12, 30, 75 mg/kg/day Gavage Acceptable/Guideline	**Maternal** NOAEL = 12 mg/kg/day LOAEL = 30 mg/kg/day based on decrease in body weight gain. **Developmental** NOAEL = 12 mg/kg/day LOAEL = 30 mg/kg/day based on increased incidence of skeletal variations (predominantly lumbar ribs).
870.3700	Prenatal development in rodents (rat)	46808443 (2002) 0, 1, 4, 16, 64 mg/kg/day Gavage Acceptable/Guideline	**Maternal** NOAEL= 16 mg/kg/day LOAEL= 64 mg/kg/day based on decreased body weight and food consumption, increased placental weight and increased incidence of swollen placentae **Developmental** NOAEL= 16 mg/kg/day LOAEL= 64 mg/kg/day based on based on an increase in early and late resorptions, decreased fetal body weight and increased incidence of incomplete ossification of sternebrae.
870.3700	Prenatal developmental in non-rodents (rabbit) Definitive Study	44721602 (1997) 0, 5, 10, 20, 40 mg/kg/day gavage Acceptable/Guideline	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on reductions in body weight gain, food consumption, and changes in various hematology parameters (reductions in hematocrit, hemoglobin, mean corpuscular volume and increases in platelet counts and alkaline phosphatase activity). **Developmental** NOAEL = 20 mg/kg/day LOAEL = 40 mg/kg/day based on increases in post-implantation losses.
870.3700	Prenatal developmental in non-rodents (rabbit)	44721603 (1991) 0, 4, 10, 25, 62.5 mg/kg/day (Exp. #1)	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 62.5 mg/kg/day based on body weight changes and slight clinical signs

Table A.3	Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]		
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		0, 2, 4, 10 mg/kg/day (Exp. #2) Acceptable/Guideline	(anorexia/reduced or altered fecal output, cold ears). **Developmental** NOAEL = 4 mg/kg/day LOAEL = 10 mg/kg/day based on examining data from the two experiments. Effects at 62.5 mg/kg/day show total litter loss, decreased live fetuses, increased early and late resorptions. Effects at 25 mg/kg/day show some malformations: hydrocephaly (4 fetuses from 4 different litters, but NOT seen at 62.5 mg/kg/day) and limb effects (2 fetuses from 2 different litters, with one fetus with same effect at 62.5 mg/kg/d). Hydrocephaly and limb effects were observed at 10 mg/kg/day in Experiment #2, but not at that same dose in Experiment #1.
870.3800	Reproduction and fertility effects 2-generation- rat	46808447 (2002) 0, 30, 150 and 750 ppm M/F: 0/0, 2/2, 10.8/10.6, 53.2/53.0 mg/kg/day Acceptable/Guideline	**Parental/Systemic** NOAEL (M/F) = 9.8/10.8 mg/kg/day LOAEL (M/F) = 49.4/53.2 mg/kg/day based on: decreased body weight and decreased weight gain in male and female parental animals, increased incidence of fatty hepatocyte change in male parental animals, and increased incidence of spleen congestion in F1 parental females. **Reproductive** NOAEL (M/F) = ≥49.4/ 10.8 mg/kg/day LOAEL (M/F) = 53.2 mg/kg/day based on increased gestation length and decreased gestation index driven by dystocia (difficult labor). **Offspring** NOAEL (M/F) = 9.8/10.8 mg/kg/day LOAEL (M/F) = 49.4/53.2 mg/kg/day based decreased viability on lactation day 0 and decreased body weight in F2 offspring.
870.4100a	Chronic toxicity rodents (rat)	44721609 (1992) 0, 10, 100, 300, 1000 ppm M: 0, 0.44, 4.3, 13.1, 43.9 mg/kg/day F: 0, 0.52, 5.3, 16.0, 53.8 mg/kg/day Acceptable/Guideline	NOAEL = (M/F) = 4.3/16.0 mg/kg/day LOAEL = (M/F) = 13.1/ 53.8 mg/kg/day based on an increase in mean adjusted liver weights at 12 months (M) and 24 months (F), increase in spleen weights at 24 months (F), and increased hepatocellular lipid vacuolation (M/F) and centrilobular hypertrophy (M/F).
870.4100b	Chronic toxicity- dog	44721610 0, 30, 300, 1000, 3000 ppm in diet M: 0, 1.1, 12.0, 38.5, 110.0	NOAEL (M/F) = 12.0/10.3 mg/kg/day LOAEL (M/F) = 38.5/36.8 mg/kg/day based on decreased body weight gain weeks 1-13 (males), increased alkaline phosphatase

Table A.3 Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		mg/kg/day F: 0, 1.1, 10.3, 36.8, 113.7 mg/kg/day Acceptable/Guideline	activity (both sexes) and increased incidence of Kupffer cell pigmentation (females).
870.4200	Carcinogenicity - rat	44721611 (1992) 0, 100, 300, 1000 ppm M: 0, 4.6, 13.8, 46.5 mg/kg/day F: 0, 5.5, 16.6, 56.2 mg/kg/day Acceptable/Guideline	Non-neoplastic findings at (M/F) 13.8/56.2 mg/kg/day: increased incidence of hepatocellular lipid vacuolation (M/F), centrilobular hypertrophy (M/F), liver pigment deposition (M), histiocytic foci in the spleen (M/F),and increase in severity of chronic renal nephropathy (M). Evidence of mononuclear cell leukemia (F).
870.4300	Carcinogenicity-mouse	44721612 (1992) 0, 30, 300, 1000 ppm M: 0, 4.5, 39.5, 166.9 mg/kg/day F: 0, 5.9, 58.1, 195.5 mg/kg/day Acceptable/Guideline	Non-neoplastic findings at (M/F) 166.9/58.1 mg/kg/day: increase in vacuolation, hypertrophy, splenic atrophy and adrenal corticomedullary pigmentation, sinusoidal hypercellularity/single cell necrosis. Neoplastic findings: increase in liver cell tumors at high dose (M/F): Increased incidence of hepatocellular adenomas in males and hepatocellular carcinomas in females.
870.5500	*Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay	44721613 (1990) Up to limit dose of 5000 µg/ plate (*S. typhimurium*) and (*E. coli*) in the presence and absence of metabolic activation (± S9) Acceptable/Guideline	Test material was not cytotoxic with or without S9 activation in five *S. typhimurium* strains and one strain of *E. coli*, and did not induce a genotoxic response in any strain.
870.5300	*In vitro* Mouse Lymphoma Mutagenesis Assay WL136184* **cis* only isomer	44721615 (1991) Six doses up to 125 µg/ml (toxicity was observed above that dose) in the presence and absence of metabolic activation (± S9) Acceptable/Guideline	There was no evidence of biologically significant induction of mutant colonies.
870.5375	*In vitro* Cytogenetics Test	44721616 (1991) From 6.25 to 400 µg/ml, with and without metabolic activation (± S9) Acceptable/Guideline	Weakly positive (induced chromosome aberrations in Chinese hamster ovary cells) in the presence of S9 activation, negative without S9 activation.
870.5395	*In vivo* Mammalian Erythrocyte	44721618 (1995) Up to the limit dose of 2000	There was no statistically significant increase in the frequency of micronucleated

Table A.3	Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]		
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Micronucleus Test: Mouse	mg/kg Acceptable/Guideline	polychromatic erythrocytes in mouse bone marrow at any dose or collection time.
870.5550	*In vivo/in vitro* Mammalian UDS test Rat	44721620 (1995) Up to the limit dose of 2000 mg/kg Acceptable/Guideline	Negative for unscheduled DNA synthesis.
870.7485	Metabolism and pharmacokinetics: rat	44721622 (1992) single high dose: 164 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after five days: feces (males - 81.3%, females - 65.5%) and urine (males - 13.6%, females - 28.4%)
870.7485	Metabolism and pharmacokinetics: rat	44721622 (1992) single high dose: 164 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after five days: feces (males - 81.3%, females - 65.5%) and urine (males - 13.6%, females - 28.4%)
870.7485	Metabolism and pharmacokinetics: rat	44721623 (1991) single low dose: 2 mg/kg Radiolabel: (cyclopentyl-^{14}C) Acceptable/Guideline	Approximately 94% of radioactivity in excreta after 72 hrs: feces (males - 80%, females - 67%) and urine (males - 14.8%, females - 26%). Metabolite information presented.
870.7485	Metabolism and pharmacokinetics: rat WL136184* **cis* only isomer	44721624 (1991) single high dose: 200 mg/kg (males only) Radiolabel: (Triazole - ^{14}C) Acceptable/Guideline	Approximately 96% of radioactivity in excreta after seven days: feces (76%) and urine (20%). Metabolite information presented.
870.7485	Metabolism and pharmacokinetics: rat WL136184* **cis* only isomer	44721625 (1991) single low dose: 2 mg/kg Radiolabel: (Cyclopentyl - ^{14}C) Acceptable/Guideline	Excretion/retention in bile-duct cannulated rats. Approximately 80% of radioactivity was excreted in the bile after 48 hrs: males (78.7%) and females (83.3%).
870.7485	Metabolism and pharmacokinetics: rat	46808449 (2002) male/female rat single low dose: 2 mg/kg single high dose: 200 mg/kg repeated dose: 2 mg/kg Acceptable/Non-guideline	Low potential for bioaccumulation following single or multiple dosing regimen. The time to maximum plasma concentration for male and female rats treated with either 2 mg/kg or 200 mg/kg was the earliest sampling interval, 0.25 hours and 4 hours, respectively The plasma half-life of low- and high-dose rats was slightly shorter in males than females, ~20-25 hours and ~34 hours, respectively.

Table A.3 Subchronic, Chronic and Other Toxicity Profile for Metconazole Technical[1]			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Effects on rat/mice liver enzymes WL136184* *cis only isomer	44721626 (1991) 0, 300 ppm in diet (mice) and 0, 1000 ppm in diet (rats) for seven or 28 days Acceptable/Non-guideline	Increased liver weight, cytochrome P450, ethoxycoumarin O-deethylase, ethylmorphine N-demethylase, and lauric acid 11-hydroxylase in both rats and mice. No effect on ethoxyresorufin O-deethylase, palmitoyl-CoA oxidation, or peroxisome proliferation (in terms of peroxisome number or morphology).
	14-day Mechanistic Study	46665402 (2005) 0, 30, 300, 1000 ppm in diet (mice) for 14 days. F: 4.5, 48, 151 mg/kg/day Acceptable/*Non-guideline*	Increased liver weight (300 and 1000 ppm); increased hepatic drug metabolizing enzymes (300 and 1000 ppm) after 7 days; enlarged livers (1000 ppm) at days 3, 7 and 14; hepatic hypertrophy and vacuolation (300 and 1000 ppm) at day 14; increased ALT and AST activities at 1000 ppm (day 14); increased lipid peroxide (300 and 1000) at day 14; increased PCNA labeling at 1000 ppm at day 3 and 7.
870.7600	In Vivo Dermal Penetration Study	46808450 (1990) Acceptable/Non-guideline	Dermal absorption= 16% (72 hrs)
[1] cis/trans ratio is 85:15. All studies used cis/trans mixture unless otherwise noted.			

12.4 Appendix 4.: Executive Summaries of Toxicity Studies

Subchronic Toxicity

870.3100 28-Day Oral Toxicity - Rat

In a 28-day oral toxicity study (MRID 44721515), seven Fisher F344 rats/sex/dose were fed a diet of Metconazole (94.5% a.i.; 85% cis:15% trans; nominal 80:20, batch 88-10) at dose levels of 0, 30,100, 1000 or 3000 ppm (equivalent to (m/f): 0, 2.7/3.1, 9.1/10.1, 90.2/97.0, and 261.2/287.4 mg/kg bw/day). Hematology and blood chemistry parameters were measured at 28 days. Urine samples were analyzed after a water loading in week 4. Gross examinations were performed on all animals and nine tissues were examined microscopically in the control and high dose groups. Only the livers and adrenals were examined in all dose groups.

Administration of metconazole had no effect on survival during the 28 day study period. Overall body weight gain was decreased in males at 1000 ppm (↓27%) and in both sexes at 3000 ppm (males ↓71%, females ↓58%). At week 4, bodyweight in males at 1000 and 3000 ppm were statistically significantly reduced compared to the controls (↓14% and ↓34%, respectively) and in females at 3000 ppm, the mean bodyweight was 19% lower than the control group. Food consumption was reduced 10-30% in these groups. At 3000 ppm, a slight reduction in mean cell hemoglobin concentration and erythrocyte mean diameter was observed. Platelet counts at 3000 ppm were reduced 20%. Increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (γ-GT) activities were observed at the highest dose. Glucose levels were reduced 15-30% in both sexes at the high dose. Cholesterol decreased 25% in both sexes at 3000 ppm and a 23% reduction in cholesterol was observed in males at 1000 ppm. Urinalysis revealed no treatment-related changes. Dose-related changes in absolute liver weights were observed in females at 1000 ppm and 3000 ppm (↑21% and ↑67%, respectively). Slight increases in absolute liver weights were observed in males at 1000 and 3000 ppm (↑4% and ↑8%, respectively). Relative spleen weights (↑23%, ↑33%) and relative kidney weights (↑5.8%, ↑11.8%) were statistically significantly higher at 3000 ppm than the control group in males and females, respectively. Macroscopic examination showed enlarged and pale livers in both sexes at 1000 ppm and 3000 ppm. Enlarged livers were also observed in 3/7 males at 100 ppm. Junctional ridge thickening and/or ulceration of the forestomach was observed in 4/7 males at the highest dose. The primary target organ was the liver as revealed by increased incidences of fatty vacuolation and hepatocellular hypertrophy in both sexes at 1000 and 3000 ppm. No microscopic abnormalities were observed in the liver at 100 ppm. Increased incidences of hyperkeratosis were observed in the forestomach of males at 3000 ppm which correlated with the macroscopic findings. Most animals at 3000 ppm showed adrenal cortical vacuolation. **The LOAEL is 1000 ppm (90.5 mg/kg/day), based on decreased body weight, increased liver and kidney weights, hepatocellular vacuolation and hypertrophy. The NOAEL is 100 ppm (9.1 mg/kg/day).**

This 28-day oral toxicity study in the rat is classified as acceptable/guideline and satisfies the guideline requirement for a 28-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats

870.3100 90-Day Oral Toxicity - Rat

In a 90-day oral toxicity study (MRID 44721517), WL148271 (94.5% pure with a cis/trans ratio of 81:19, batch # 88-10) was administered in diet to 10 F344 rats/sex/dose at dose levels of 0, 30, 100, 300, 1000 or 3000 ppm (equivalent to 0, 1.9, 6.4, 19.2, 64.3 and 192.7 mg/kg/day in males and 0, 2.1, 7.2, 22.1, 71.4,and 208.0 mg/kg bw/day in females). Two satellite groups (10/sex/group) were fed 0 or 3000 ppm for 13 weeks, followed by a 7 week recovery period.

There were no treatment-related effects on mortality. Increased food spillage was observed at the high dose in both sexes and occasionally at 1000 ppm. Food consumption was reduced in both sexes at 1000 ppm (males 12%, females 9%, both $p<0.01$) and 3000 ppm (males 33%, females 22%, both $p<0.01$). Overall body weight was reduced in males at 1000 ppm (9%,$p<.0.01$) and in both sexes at 3000 ppm (males 35%, females 19%, both $p<0.01$). Discharge and alopecia were observed in most high dose (3000 ppm) animals in both sexes, but not in the control animals. The eyes of lower dose animals were not examined. Hematological findings revealed changes in parameters consistent with mild hypochromic microcytic anemia at the high dose in both sexes. Decreased hemoglobin (4%, $p<0.01$), mean corpuscular hemoglobin (2.7%, $p<0.01$) and mean corpuscular hemoglobin concentration (2%, $p<0.01$) were also observed in females at 1000 ppm. Elevated white blood cell counts were observed in females at 300 ppm and above. Some recovery was observed in the satellite high dose group; however mean corpuscular volume, platelet count and plateletcrit remained low in males. Clinical chemistry revealed statistically significant ($p<0.01$) increases in plasma alkaline phosphatase (m 35%, f 42%), gamma-glutamyl transpeptidase, aspartate aminotransferase (m 77%, f70%) and alanine aminotransferase (m136%, f 94%) in both sexes at 3000 ppm. Alanine aminotransferase was also elevated in males (13.6%, $p<0.01$) at 1000 ppm. Cholesterol was decreased in males at 1000 ppm (36%, $p<0.01$) and 3000 ppm (48%, $p<0.01$) and triglyceride levels were down 69% ($p<0.01$) in males a 1000 ppm and in both sexes (m 96% and f 70%) at 3000 ppm. The decreased cholesterol and triglycerides is indicative of perturbations in hepatic lipid metabolism. Increased adjusted liver weight ($p<0.01$) was observed in the male and female at 1000 ppm (31% and 20%, respectively) and at 3000 ppm (11% and 53%, respectively). Increased spleen weights were reported in females at 300 and above and in both sexes at 3000 ppm. Decreased relative adrenal weights were also observed in males at 3000 ppm (11%, $p<0.05$). Histopathological changes in the liver were observed in all males at 1000 and in both sexes 3000 ppm including centrilobular hepatocyte hypertrophy and fatty vacuolation. An increased incidence of fatty vacuolation (4/10, $p<0.05$) was observed in males at 300 ppm and a single incidence of centrilobular hypertrophy was in this group. In the satellite group, a reduction in the incidence of fatty vacuolation was observed in high-dose males (4/10, $p<0.01$), but remained statistically significant in females, 6/10 ($p<0.05$). Increased incidences of pigmented Kupffer cells was also observed in the high dose group (9/10 males, 10/10 females). In the spleen, decreased hematopoiesis was observed in all high dose animals. Pigment deposit was observed in 9/10 males and all females at 3000 ppm and white pulp was reduced in the high-dose males (3/10, $p<0.001$)) and females (9/10, $p<0.001$). Forestomach focal hyperplasia was observed in the forestomach of 6 males and 2 females at the high dose. Moderate or slight adrenal cortical vacuolation was observed in all males and 6 females at 3000 ppm. **The NOAEL for this study is 100 ppm (6.4 mg/kg/day) and the LOAEL is 300 ppm (19.2 mg/kg/day) based on**

increased hepatocellular fatty vacuolation and increased spleen weight in females. This 90-day oral toxicity study in the rat is acceptable/guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

870.3100 90-Day Oral Toxicity - Mouse

In a 90-day oral toxicity study (MRID 44721519, Metconazole (95.3% pure, WL148271, Batch 89-01) was administered to 12 Crl:CD-1 (ICR)BR mice/sex/dose in diet at dose levels of 0, 30, 300, 3000 ppm (equivalent to 0, 4.6, 50.5 and 341.1 mg/kg bw/day in males and 6.5, 60.7 and 446.2 mg/kg bw/day in females). The high dose was reduced from 3000 ppm to 2000 ppm beginning on week two, due to significantly reduced food consumption and body weight in this dose group.

There were no compound related effects on mortality or clinical signs. Overall food consumption was impaired in the high dose group in both sexes (-9% males, -14% females, $p<0.05$). This resulted in reduced body weight gain of 61% ($p<0.001$) and 51% ($p<0.001$) in males and females respectively at 2000 ppm. Hematological findings showed slightly decreased values in hematocrit, mean cell volume and cell hemoglobin at 2000 ppm indicative of mild microcytic anemia. In high-dose females, increased leukocytes and neutrophils, and decreased lymphocyte counts were observed. The primary target organ at the high dose was the liver corroborated by increased liver weight (males 113% $p<0.001$,females 121%, $p<0.001$) , hepatocellular hypertrophy and vacuolation, increased alanine aminotransferase (ALT; males 455%, $p<0.001$, females 508%, $p<0.001$) and aspartate aminotransferase levels (AST; males 172%, $p<0.001$, females 146%, $p<0.001$) decreased bilirubin (males 46%, females 28%, both $p<0.001$) and cholesterol (males 65%, females 60%, both $p<0.001$). At 300 ppm, increased relative liver weight was observed at 300 ppm in both sexes (males 22%, females 24%, both $p<0.001$) and increased spleen weight (30%, $p<0.01$) in females. In males at 300 ppm, increased AST (61, $p<0.001$) and ALT (61%, $p<0.01$) levels were reported. Elevated AST levels were reported in males at 30 ppm (32%, $p<0.05$), however no other clinical or histopathological findings support evidence of toxicity at this dose level. **The LOAEL is 50.5 mg/kg/day, based on increased aminotransferase (ALT and AST) levels, increased liver and spleen weight, hepatocellular hypertrophy and decreased cholesterol. The NOAEL is 4.6 mg/kg/day.**

This 90-day oral toxicity study in the mouse is acceptable (guideline) and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the mouse.

870.3150 90-Day Oral Toxicity - Dog

In a 90-day oral toxicity study (MRID 44721521), Metconazole (WL148271, 95.3% a.i., batch 899-01, batch 2 and 5)] was administered to groups of beagle dogs (5/sex/group) in diet at dose levels of 0, 60, 600 or 6000 ppm (equivalent to 0, 2.5, 24.4 or 225.2 mg/kg bw/day in males and 0, 2.6, 24.3 or 206.6 mg/kg bw/day in females).

There were no treatment-related mortalities or clinical signs of toxicity observed during the study. Decreased food consumption was observed at 600 ppm in females (↓14%) and in males and females at 6000 ppm. (↓14% and ↓31%, respectively). Body weight gains were decreased during the treatment period in both sexes at the high dose (males ↓60%, females ↓98%) and in

females at 600 ppm (↓29%). Ophthalmoscopic examinations revealed cataracts in all high dose animals. No incidences of cataracts were observed in the lower dose groups. Hematological findings included reduced hemoglobin and red blood cell counts, and decreased packed cell volumes in both sexes at 6000 ppm. Reticulocyte counts were increased at week 13 in both sexes at 6000 ppm (males ↑33%, females ↑31%) and in males at 600 ppm (↑42%). Increased platelet counts were observed at weeks 6 and 13 in high dose males (↑64% and ↑72%, respectively) and in males at 600 ppm (↑23% and ↑21%, respectively). Alterations in clinical chemistry included increased alkaline phosphatase and gamma glutamyl transferase activities in high dose animals. Decreased albumin (both sexes) and glucose (females only) were also observed at 6000 ppm. Bilirubin was detected in the urine of 3 of 5 males at 6000 ppm, but not at the lower dose levels. Group mean relative liver weights were higher in males at 6000 ppm compared to the controls. In females, statistically significant increases in mean relative spleen weights and relative thyroid weights were observed at 6000 ppm. Increases in mean absolute adrenal (males, 600 and 6000 ppm), liver (both sexes, 6000 ppm) and spleen (females, 6000 ppm) weights were observed, but the increases did not reach statistical significance. A comparison of the absolute and relative organ weights shows evidence of treatment-related effects in the liver and spleen. Treatment-related histopathological findings were restricted to the high dose animals and included hepatocyte hypertrophy in all high dose animals, increased hematopoiesis in the spleen of males and females and in the kidney, an increased incidence of tubular pigment was observed in both sexes with an increase in the incidence of tubular vacuolation in females only. High dose males also showed an increased incidence of thymic involution. Histopathological examinations of the eyes showed cataracts degeneration in all high dose animals. The cataracts were more severe in females than males. **The LOAEL is 600 ppm (24.3 mg/kg/day), based on decreased food consumption and body weight gain (females), and elevated platelets and reticulocyte counts in males. The NOAEL is 60 ppm (2.5 mg/kg/day).**

This 90-day oral toxicity 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 species.

870.3200 21-Day Dermal Toxicity- Rat

In a 21-day dermal toxicity study (MRID 46808439), Metconazole (84.3% cis, 14.4% trans; Lot No. AS 2122a) was applied to the shaved skin of ten Fischer 344 rats/sex/dose at dose levels of 0, 250, 500 or 1000 mg/kg bw/day, approximately 6 hours/day for 21 consecutive days.

Dermal observations were performed daily 0.5 to 2 hours following administration of the test material. General health checks were performed twice daily and body weights and food consumption were measured weekly. Blood was collected for hematology and clinical chemistry measurements at the end of the study. Ocular examinations were performed on all animals on days -9 and 21. All animals survived to the scheduled sacrifice. No treatment-related clinical signs were observed during the study. The test material had no effect on mean body weight, body weight gain or food consumption up to the highest dose tested (1000 mg/kg/day). Ophthalmic examinations showed no treatment-related effects. There were no toxicologically significant hematology and clinical chemistry findings and gross pathology revealed no treatment-related

effects. Increased relative liver weights were reported in high dose male animals (↑7%, $p<0.05$) and females at 500 and 1000 mg/kg/day (↑9% and 15%, respectively, $p<0.01$) compared to the control groups. A 13% decrease in relative thymic weight was observed in males at 500 and 1000 mg/kg/day compared to the controls. These changes in organ weights were not considered adverse since no treatment-related changes in histopathology were reported.
No LOAEL was identified in this study. The dermal and systemic NOAEL is 1000 mg/kg/day.

This 21-day dermal toxicity study in the rat is acceptable (guideline) and satisfies the guideline requirement for a 21/28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat
In a developmental toxicity study (MRID 44721522), Metconazole (95.3% a.i., batch 89-01 Ref. ST89/088, *cis:trans* 83.7:16.3) was administered to 25 (Crl:CD^R (SD) BR VAF/Plus strain) female rats/dose by gavage at dose levels of 0, 12, 30 or 75 mg/kg bw/day from days 6 through 15 of gestation.

There were no mortalities observed during the duration of the study. Post-dosing salivation was observed in some dams at 75 mg/kg/day, which was first evident during the second week of treatment. No other clinical signs of toxicity were observed. A slight reduction in food consumption (10%) was observed on GD 6-7 in the 30 and 75 mg/kg/day group. This correlated with poor body weight gain during the initial two days of treatment and resulted in an overall decrease in body weight gain during the treatment period at 30 and 75 mg/kg/day (↓12% and ↓18%, respectively). There was no increase in pre-implantation loss at any dose and the numbers of corpora lutea and implantation sites at all doses were similar to the control group.
The maternal LOAEL is 30 mg/kg bw/day, based on decreased body weight gains during the treatment period. The maternal NOAEL is 12 mg/kg bw/day.

Post-implantation loss was significantly higher at 75 mg/kg/day compared to the control group. There were 79 resorptions (36 early, 43 late) at 75 mg/kg/day versus18 resorptions (15 early, 3 late) in the control group. No difference in post-implantation loss was observed at 30 mg/kg/day and below. Hydrocephaly was observed at 75 mg/kg/day (2 fetuses, separate litters) and was observed only at the high dose where clear maternal toxicity was evident. No malformations were observed at 30 mg/kg/day and lower. A statistically significant increase in visceral anomalies compared to the control was observed at 75 mg/kg/day which included cranial hemorrhage, dilated renal pelvis, dilated ureter and displaced testis. No increase in the incidence of visceral anomalies was observed at the lower dose levels. A dose-related increase in the incidence of extra lumbar ribs was observed at 12, 30 and 75 mg/kg/day compared to the control group. The incidence of lumbar ribs was statistically significant at 30 and 75 mg/kg/day (relative to control). At 12 mg/kg/day, although the fetal incidence of lumbar ribs fell within the historical control range, the litter incidence of lumbar ribs was outside the range for the historical controls. Other skeletal anomalies were observed at 30 and 75 mg/kg/day including increased incidence of cervical ribs and extra pre-sacral vertebra. Significant reduction in ossification of

sternebrae was also observed at 30 and 75 mg/kg/day. In addition, a treatment-related reduction in mean fetal weights was observed at 75 mg/kg/day compared to the controls. **The developmental LOAEL is 30 mg/kg bw/day, based on the increased incidence of skeletal anomalies including extra lumbar ribs, cervical ribs and extra pre-sacral vertebra. The developmental NOAEL is 12 mg/kg bw/day.**

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

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 46808443) KNF-474m (Metconazole; 98.99% a.i., lot number 9Z521) was administered to 22 mated female Crl:CD® (SD)IGS BR rats/dose by gavage in 1% (w/v) methylcellulose at dose levels of 0, 1, 4, 16, or 64 mg/kg bw/day on gestation days (GDs) 6 through 19. Dams were sacrificed and necropsied on GD 20. All fetuses were weighed, sexed, and examined externally; approximately one-half were subjected to visceral examination by fresh dissection with subsequent skeletal evaluation, and the remaining one-half were subjected to visceral examination by the Wilson method. All placentae were weighed individually and examined grossly. Dose selection was based on a range-finding study (MRID 46808442), and the analytical method and the homogeneity/stability of the low- and high-dose dosing formulations were previously verified (MRID 46808452).

One high-dose female was killed *in extremis* on GD 18 after exhibiting hunched posture, pale skin and eyes, and piloerection (all on GD 18) and a weight loss of 14 g during GD 16-18. A total of four high-dose females had red or bloody vaginal discharge or red vaginal staining noted in life and/or at necropsy during GD 16-20. High-dose females lost weight during GD 6-8 (-6 g vs. +8 g for controls) and had decreased body weight gain during GD 8-20 (18% less than controls), with resultant decreases in absolute body weight throughout treatment (-6 to –10%; $p<0.01$ or 0.05), which gradually increased in magnitude over time. Although mean gravid uterine weight of the high-dose group was significantly decreased (-10%), a decrease in the adjusted (for gravid uterus) GD 6-20 body weight gain (-73%; $p<0.01$) indicates that this was also a maternal effect. Correlated treatment-related decreases in food consumption were seen at the highest dose level throughout the dosing interval (-16% to -23%; $p\leq0.01$).

At 16 and 64 mg/kg bw/day, the mean placental weight was significantly increased ($p<0.05$ or 0.01) and the most prominent abnormal finding at necropsy was swollen placentae. All of the placentae from all of the surviving high-dose females were swollen, pale, and/or mottled; in addition, two high-dose dams had one or more placentae that were surrounded by clotted blood, and one high-dose dam had 5 placentae with numerous punctate foci and pale rims. Two 16-mg/kg bw/day dams had large numbers of abnormal placentae: 7/15 placentae were swollen in one dam and 16/16 placentae were swollen with mottled white areas in the other.

The maternal toxicity LOAEL for metconazole in Sprague-Dawley rats is 16 mg/kg bw/day, based on placental abnormalities (increased weight and swollen, mottled, and/or pale appearance). The maternal toxicity NOAEL is 4 mg/kg bw/day.

The previously mentioned increased placental weight and gross placental abnormalities at 16 and 64 mg/kg bw/day are also considered to be developmental effects. At 64 mg/kg bw/day, there was an increased mean percentage postimplantation loss (17.7% vs. 4.4% for controls; $p<0.001$) with greater numbers of early resorptions/dam (1.6 vs. 0.7; $p<0.05$) and late resorptions/dam (1.0 vs. 0; $p<0.001$) with 20/21 surviving high-dose dams having one or more resorptions (vs. 10/22 controls). The high-dose mean live litter size was decreased (-15%; $p<0.05$), and mean fetal weight was decreased in both sexes (males: -20%; females: –17%; $p<0.01$). There were no total litter resorptions or dead fetuses, and there was no treatment-related effect on fetal sex ratio.

The total numbers of fetuses (and litters) evaluated in the 0-, 1-, 4-, 16-, and 64-mg/kg bw/day groups were 329 (22), 320 (22), 329 (22), 337 (22) and 268 (21), respectively, and malformations were observed in a total of 0 (0), 2 (2), 1 (1), 2 (2), and 3 (3) fetuses (and litters) from these same respective groups. Treatment-related lipofuscin deposition was noted in the renal papilla, renal pelvis, and/or ureter(s) of 61 (20) high-dose fetuses (and litters), compared to no other incidences of this finding in any other group, and the high-dose group also had increased litter incidences of several minor cardiovascular anomalies (including ventricular septal defect [VSD], small VSD, absent/rudimentary innominate artery, and/or variation in origin of the subclavian artery), which were seen in a total of 2/22, 2/22, and 10/21 control, 4-, and 64-mg/kg bw/day litters. An increased incidence of fetuses with unossified sternebrae was seen in the high-dose litters, and the litters of this same group also had increased incidences of a constellation of axial skeletal anomalies (including cervical and lumbar rib(s) and other anomalies of the ribs and costal cartilage, 20 thoracolumbar vertebrae, and offset alignment of the pelvic girdle), which together are considered indicative of increased fetal and/or maternal stress.

The developmental toxicity LOAEL for metconazole in Sprague-Dawley rats is 16 mg/kg bw/day, based on placental abnormalities (increased weight, swollen, mottled, and/or pale appearance). The developmental toxicity NOAEL is 4 mg/kg bw/day.

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

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID 44721602), AC900768 (cis/trans Metconazole, 98.3% a.i., lot # AC 10575-61; cis/trans ratio 80:15) was administered to 25 female New Zealand White [HRa:(NZW)SPF] rabbits/dose in diet by gavage at dose levels of 0, 5, 10, 20 or 40 mg/kg bw/day from days 6 through 28 of gestation.

No relevant maternal clinical signs or treatment-related effects on survival were reported. Isolated incidences of localized alopecia were observed, but were not clearly attributed to treatment. Does at 40 mg/kg/day lost weight from gestation day (GD) 24-29 which resulted in an overall decrease (-15%) in bodyweight gain for this group. Food consumption was reduced 16% at 40 mg/kg/day on gestation days 24-29 and was slightly less than control group

throughout the treatment period, but at no time reached statistical significance. Gravid uterine weight was also reduced at 40 mg/kg/day. This decrease was associated with a statistically significant ($p<0.01$) increase in post-implantation loss and reduced fetal body weight compared to the control group. Other maternal findings at 40 mg/kg/day include increased liver weight, reduced hemoglobin, hematocrit and mean corpuscular volume. Reduced platelet counts and alkaline phosphatase levels were also observed at 40 mg/kg/day. **The maternal LOAEL is 40 mg/kg bw/day, based on a decrease in bodyweight gain, decreased food consumption, increased liver weight, statistically significant decreases in RBC parameters and elevated alkaline phosphatase levels. The maternal NOAEL is 20 mg/kg bw/day.**

Post-implantation loss observed at 40 mg/kg/day was associated with an observed increase in the number of does with any (early and late) resorptions and elevated rate of dead/resorptions per litter. Reduced, but not statistically significant, live litter size and fetal body weights were observed at 40 mg/kg/day compared to the control group. No treatment-related gross external, soft tissue or skeletal malformations or anomalies were observed at any dose. **The developmental LOAEL is 40 mg/kg bw/day, based on increase in early and late resorptions. The developmental NOAEL is 20 mg/kg bw/day.**

The developmental toxicity study in the rabbit is classified acceptable/guideline, and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit.

Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

In a 2-generation reproduction study (MRID 46808447*)* Metconazole (KNF-474m, 98.99% a.i., Lot number 9Z521) was administered to [(24Crj:CD(SD)[IGS]rats/sex/dose in the diet at target dose levels of 0, 30, 150, or 750 ppm (0, 1.97, 9.79 and 49.4 mg/kg bw/day and 0, 2.14, 10.78 and 53.2 mg/kg bw/day for males and females, respectively in the F_0 generation; 0. 2.13, 10.63 and 53.0 mg/kg bw/day and 0, 2.20, 11.21, and 55.5 mg/kg bw/day for males and females, respectively, in the F_1 generation). F_0 and F_1 male and female parental animals were administered test or control diet for at least 70 days prior to mating, throughout mating, gestation, lactation, and until necropsy. One litter was produced by each generation.

Parental systemic toxicity was evident at 750 ppm. During the pre-mating period of the F_0 generation, body weight and body weight gain were slightly, but significantly decreased compared to the control group during treatment weeks 1 and 2 in F_0 males (decrease of 5%) and during treatment weeks 6-10 in F_0 females (decrease of 4-5%). Reduced body weight gains were noted for two weeks after initiation of treatment in F_0 males (decrease of 11%) and throughout the pre-mating growth period and on gestation day 20 in F_0 females. In F_1 parental animals, body weight was significantly decreased for both sexes (decrease of 6-12% in F_1 males, decrease of 5-11% in F_1 females) compared to the control group throughout the pre-mating period and into the breeding period. This was partly due to significantly lower body weight at selection. Body weight gain of males at treatment weeks 1-4 (decrease of 10% weight gain, decrease of 10-15% food consumption during this time) and of females at treatment week 10 (decrease of 8%)

was significantly reduced. Higher incidences of centrilobular fatty change of hepatocytes were observed in high-dose F_0 and F_1 males [19/24 (79%) and 20/24 (83%), respectively] compared to 0/24 controls of both generations. A higher incidence [16/20 (80%)] of spleen congestion was observed in F_1 females compared to 0/24 control females. **The parental systemic LOAEL for KNF-474m in CD rats is 750 ppm (49.4 and 53.2 mg/kg/day for males and females, respectively) based on decreased body weight and decreased weight gain in male and female parental animals, increased incidence of fatty hepatocyte change in male parental animals, and increased incidence of spleen congestion in F_1 parental females. The parental systemic NOAEL is 150 ppm (9.79 and 10.78 mg/kg/day for males and females, respectively).**

Offspring toxicity was evident at 750 ppm as decreased viability index on lactation day 0 and reduced body weight in F_2 offspring. There was an increase in stillborn pups on lactation day 0 (16 high-dose group vs. 4 control) of the F_2 generation leading to the decreased viability index. Significantly reduced body weight was observed on lactation days 0, 14, and 21 in the F_2 offspring (decreases of 13%, 8%, 10% in males and 11%, 10%, 12% in females, respectively). **The offspring LOAEL for KNF-474m in CD rats is 750 ppm (49.4 and 53.2 mg/kg/day for males and females, respectively) based on decreased viability on lactation day 0 and decreased body weight in F_2 offspring. The offspring NOAEL is 150 ppm (9.79 and 10.78 mg/kg/day for males and females, respectively).**

Reproductive toxicity was evident at 750 ppm as prolonged duration of gestation and decreased gestation index driven by dystocia (maternal deaths during delivery). Prolonged duration of gestation and maternal deaths during delivery, were noted in both F_0 and F_1 females. Gestation length was significantly increased in F_0 females by treatment (23.0 days vs. 22.2 days in control) and corresponded with dystocia in five F_0 females and four F_1 females; all died during delivery, some with fetuses in the uterus. The deaths, along with two females of each generation that failed to produce live pups caused the gestation index to be decreased in both F_0 and F_1 females. Other reproductive parameters were not different from control. There were no effects of treatment on male reproductive parameters. **For female CD rats, the reproductive LOAEL for KNF-474m is 750 ppm (53.2 mg/kg/day) based on increased gestation length and decreased gestation index driven by dystocia. The NOAEL is 150 ppm (10.78 mg/kg/day). For male CD rats, the reproductive NOAEL is greater than or equal to 750 ppm (49.4 mg/kg/day), and the LOAEL is not identified.**

This study is Acceptable/Guideline and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800; OECD 416) in rats

Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In a chronic toxicity study (MRID 44721610) Metconazole (95.3% a.i., batch 89-01) was administered to four pure-bred beagles/sex/dose in diet at dose levels of 0, 30, 300, 1000 or 3000 ppm (equivalent to 0, 1.1, 12.0, 38.5 and 110 mg/kg bw/day in males and 0, 1.1, 10.0, 36.5 and 113.7 mg/kg bw/day in females) for 52 weeks.

There were no treatment-related mortalities in the study. One male in the 3000 ppm group was diagnosed with chronic enteritis and sacrificed at week 32 following a history of diarrhea and weight loss. Treatment-related clinical signs included opaque eyes in one male and one female in the high dose (3000 ppm) group at weeks 26 and 39, respectively. Decreased body weight gains were observed during weeks 1-13 in males at 1000 ppm (↓56%) and 3000 ppm (↓60%) and in females at 3000 ppm (↓45%). Body weight gains were similar in all treatment groups subsequent to week 13. A 10-15% decrease in food consumption was observed in the high dose animals during the initial 2 weeks of treatment. Hematology showed elevated platelet counts at weeks 13 and 26 (↑31% and 35%, respectively) and a statistically significant ($p<0.05$) trend for increased platelet counts in males were seen at week 52. Platelet counts were statistically significantly ($p<0.05$) higher in high dose females compared to the control group at weeks 13, 26 and 52 (↑44%, 45% and 35%, respectively). Elevated neutrophils counts (↑69%) in high dose males and elevated lymphocyte counts (↑91%) in high dose females were reported ($p<0.05$) compared to the control animals. Urinalysis revealed no treatment-related findings. Marked (9.1-15.5-fold) increases in alkaline phosphatase activity were observed in all high dose animals at weeks 13, 26 and 52. Elevated alkaline phosphatase activity was also seen in both sexes at 1000 ppm and reached statistical significance ($p<0.05$) in males at weeks 13, 26 and 52 (↑144%, 229% and 227%, respectively) and in females at week 52 (↑378%) compared to the controls. Clinical findings also indicated that albumin concentrations were decreased by treatment at the highest dose in males at weeks 13 and 26 (↓10% and 25%, respectively $p<0.05$) and in females at week 13 (↓9%, $p<0.05$) and week 52 (↓13%, $p<0.01$). Relative liver weights increased 13% and 28% in high dose males and females, respectively. Relative spleen and kidney weights increased 14% and 11%, respectively in high dose males compared to the control group.

The increased liver weights at the high dose correlated with the observed increased incidence of liver alterations in the high dose animals. Hepatocellular hypertrophy was observed in three males and all females at 3000 ppm. An increase in incidence (and severity) of Kupffer cell pigmentation was observed in all high dose animals and three females at 1000 ppm compared to the controls. Increased hematopoiesis was observed in the spleen of all high dose males and in two of the high dose females. Congestion and hemorrhage of the cecum was observed in a number of the test groups with increased incidences observed in both sexes at 1000 and 3000 ppm. **The LOAEL is 36.8 mg/kg/day, based on decreased body gain (weeks 1-13), increased alkaline phosphatase activity and Kupffer cell pigmentation at 1000 ppm. The NOAEL is 10.5 mg/kg/day (300 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 dogs.

870.4100b Chronic Toxicity - Dog

In a chronic toxicity study (MRID 44721610) Metconazole (95.3% a.i., batch 89-01) was administered to four pure-bred beagles/sex/dose in diet at dose levels of 0, 30, 300, 1000 or 3000 ppm (equivalent to 0, 1.1, 12.0, 38.5 and 110 mg/kg bw/day in males and 0, 1.1, 10.0, 36.5 and 113.7 mg/kg bw/day in females) for 52 weeks.

There were no treatment-related mortalities in the study. One male in the 3000 ppm group was diagnosed with chronic enteritis and sacrificed at week 32 following a history of diarrhea and weight loss. Treatment-related clinical signs included opaque eyes in one male and one female in the high dose (3000 ppm) group at weeks 26 and 39, respectively. Decreased body weight gains were observed during weeks 1-13 in males at 1000 ppm (↓56%) and 3000 ppm (↓60%) and in females at 3000 ppm (↓45%). Body weight gains were similar in all treatment groups subsequent to week 13. A 10-15% decrease in food consumption was observed in the high dose animals during the initial 2 weeks of treatment. Hematology showed elevated platelet counts at weeks 13 and 26 (↑31% and 35%, respectively) and a statistically significant ($p<0.05$) trend for increased platelet counts in males were seen at week 52. Platelet counts were statistically significantly ($p<0.05$) higher in high dose females compared to the control group at weeks 13, 26 and 52 (↑44%, 45% and 35%, respectively). Elevated neutrophils counts (↑69%) in high dose males and elevated lymphocyte counts (↑91%) in high dose females were reported ($p<0.05$) compared to the control animals. Urinalysis revealed no treatment-related findings. Marked (9.1-15.5-fold) increases in alkaline phosphatase activity were observed in all high dose animals at weeks 13, 26 and 52. Elevated alkaline phosphatase activity was also seen in both sexes at 1000 ppm and reached statistical significance ($p<0.05$) in males at weeks 13, 26 and 52 (↑144%, 229% and 227%, respectively) and in females at week 52 (↑378%) compared to the controls. Clinical findings also indicated that albumin concentrations were decreased by treatment at the highest dose in males at weeks 13 and 26 (↓10% and 25%, respectively $p<0.05$) and in females at week 13 (↓9%, $p<0.05$) and week 52 (↓13%, $p<0.01$). Relative liver weights increased 13% and 28% in high dose males and females, respectively. Relative spleen and kidney weights increased 14% and 11%, respectively in high dose males compared to the control group.

The increased liver weights at the high dose correlated with the observed increased incidence of liver alterations in the high dose animals. Hepatocellular hypertrophy was observed in three males and all females at 3000 ppm. An increase in incidence (and severity) of Kupffer cell pigmentation was observed in all high dose animals and three females at 1000 ppm compared to the controls. Increased hematopoiesis was observed in the spleen of all high dose males and in two of the high dose females. Congestion and hemorrhage of the cecum was observed in a number of the test groups with increased incidences observed in both sexes at 1000 and 3000 ppm. **The LOAEL is 36.8 mg/kg/day, based on decreased body gain (weeks 1-13), increased alkaline phosphatase activity and Kupffer cell pigmentation at 1000 ppm. The NOAEL is 10.5 mg/kg/day (300 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 dogs.

Carcinogenicity

870.4200a Carcinogenicity Study - rat

In a carcinogenicity study (MRID 44721611) Metconazole (95.3% a.i., 79.8% cis, 15.5% trans; Lot 89-01) was administered to 50 Fischer 344 rats/sex/dose in diet at dose levels of 0, 100, 300 or 1000 ppm (equivalent to 0, 4.6, 13.8, 46.5 mg/kg bw/day in males and 0, 5.5, 16.6, 56.2 mg/kg bw/day in females) for two years.

There were no treatment-related effects on mortality or cause of death. Food consumption was reduced in high-dose males during the first 8 weeks of treatment and in high-dose females during the initial 11 weeks of treatment. Reductions in food consumption contributed to decreased bodyweights in males during the initial 13 weeks of treatment at 1000 ppm. Bodyweights were reduced in females at 1000 ppm throughout the treatment period, compared to the control animals. During the treatment period, mean bodyweight gains were reduced 6% in males and 9% in females at the high dose. Hematological evaluations revealed statistically significant decreases in erythrocyte mean diameter in high-dose males at 12, 18 and 24 months and females at 1000 ppm at 12 months. Erythrocyte morphological changes were observed in high-dose males at 24 months, indicative of mild hemolytic anemia. Statistically significant ($p<0.01$) increases in relative liver weight at 1000 ppm were observed in males and females (12% and 13%, respectively). Increased relative spleen weight at the high dose were observed in males (16%) and females (21%, $p<0.05$). Relative adrenal weight was also increased (11%) in males at 1000 ppm. Histopathological findings revealed increased incidences of hepatocellular vacuolation in males at 1000 ppm and centrilobular hypertrophy and pigment deposition were observed in males at 300 ppm and above. An increased incidence in eosinophilic foci (females, high dose) and clear-cell foci (both sexes at high dose) in the liver were also observed. In the spleen, an increase in the incidence of histiocytic foci was reported in the high dose animals. Adrenal cortical vacuolation was observed in males at 300 and 1000 ppm. An increase in the incidence of forestomach lesions was also observed in the treated animals. Neoplastic findings included pituitary adenoma at 300 ppm, islet cell adenoma at 100 ppm and mononuclear cell leukemia at 100 and 300 ppm in both sexes and in females at 1000 ppm. The increased incidences of pituitary and islet cell tumor were within historical control range and are not considered to be treatment-related. The incidence of mononuclear cell leukemia for high-dose females (30%) fell outside the in-house historical control range (7 studies, 5-28%), but within the NTP historical control frequency of 6-31% for Fisher 344 females. **The LOAEL for systemic toxicity is 300 ppm (13.8 mg/kg/day) , based on increased adrenal cortical vacuolation, increased hepatocellular hypertrophy and hepatocellular vacuolation. The NOAEL for systemic toxicity is 100 ppm (4.6 mg/kg/day)..**

At the doses tested, there was not a treatment related increase in tumor incidence mononuclear cell leukemia when compared to controls. The incidence of mononuclear cell leukemia fell outside the in-house control range, but within the reported NTP range for non-treated Fischer 344 rats. Dosing was considered adequate based on increased liver and spleen weights and the marked hepatic effects of hepatocellular hypertrophy and vacuolation at the high dose.

This carcinogenicity study in the rats is acceptable (guideline) and satisfies the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in rats.

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study (MRID 44721612) WL148271(cis/trans ratio 84:16 metconazole, 95.3% a.i., batch/lot 42/89-579) was administered to 51 mice (Crl:CD-1(ICR)BR strain)/sex/dose in diet at dose levels of 0, 30, 300 or 1000 ppm (equivalent to 0, 4.4, 43.6 or 144.9 mg/kg bw/day for males and 0, 5.2, 53.0 or 179.2 mg/kg bw/day for females) for 91

weeks. In addition, 12 mice/sex/dose were administered the technical for an interim sacrifice at week 52.

Treatment had no adverse effect on survival. An increased incidence of swollen abdomens was observed in the high dose groups beginning at approximately week 50. Food consumption was significantly reduced during the first week of treatment in high-dose males (14%) and females (10%) relative to the control animals and continued, to a lesser degree, throughout the treatment period. Decreased terminal body weights were observed in males in the high dose group (7%) and in females at 300 and 1000 ppm (8% and 13%, respectively). During the first week of treatment, high-dose animals lost weight which resulted in an overall reduction in body weight gain for this group. Subsequent to week 1, the body weight gains for the high-dose animals were similar to the control group. Hematology revealed elevated leukocytes in males at 300 ppm (+35%) and above and in females at 1000 ppm (+228%). Increased levels on neutrophils and lymphocytes were also observed in the high dose animals. Clinical chemistry findings included decreased cholesterol (-33% males, -47% females) and triglycerides (-17% males, -22% females). Aspartate- and alanine aminotransferase levels were significantly increased in females (21% and 15%, respectively) at 300 ppm and in both sexes at the high dose. All high-dose animals showed increased liver weights and reduced spleen weights relative to the controls at the interim and terminal sacrifice. Relevant gross pathology findings in the liver included enlargement, thickening, multiple masses and pale areas/foci in high dose animals. Small, pale spleens were observed in high dose males (5/12) and in females at 300 ppm (1/12) and 1000 ppm (6/12). Histopathological findings revealed liver toxicity including hepatocyte vacuolation and hypertrophy at 300 and 1000 ppm at week 52 and 91. The incidence of liver vacuolation at 300 ppm was 20/51 in males and 36/51 in females compared to 11/50 for both male and female control animals at week 91. The incidence of liver hypertrophy at 300 ppm was 13/51 and 8/51 in male and female mice respectively at week 91. There were no incidences of liver hypertrophy in the control animals. These findings were accompanied by single cell necrosis, pigment deposit, oval cell and multifocal hyperplasia, and biliary proliferation at week 91 in high-dose animals. Spleen atrophy with prominent trabeculae and stroma were observed at 300 ppm (9/49 males, 15/50 females) and above. Adrenal corticomedullary pigmentation was observed in high dose males and in females at 300 ppm (49/51) and above. **The LOAEL is 43.6 mg/kg/day, based on decreased cholesterol and triglycerides, increased liver weight, elevated aminotransferases (AST/ALT), liver vacuolation and hepatocellular hypertrophy and necrosis, spleen atrophy and adrenal pigmentation. The NOAEL is 4.4 mg/kg/day.**

Neoplastic findings were noted in the liver where an increase in the incidence of hepatocellular adenomas was seen in females at 300 and 1000 ppm and in males at 1000 ppm. At the interim sacrifice, a single incidence of liver adenoma was observed at each dose in the male mice and 73% (8/11) of the high dose females showed liver adenomas. Overall, the incidences of liver adenomas in males were 11/62, 17/63, 16/63 and 35/62 at 0, 30, 300 and 1000 ppm, respectively. In females, the overall incidences of liver adenomas were 0/62, 1/63, 4/63 and 50/63 for 0, 30, 300 and 1000 ppm, respectively. Hepatocellular carcinoma was observed in one high dose female (1/11) at the interim sacrifice. The total (interim plus terminal sacrifice) incidences of liver carcinoma were 4/62, 4/63, 7/63 and 7/62 for males at 0, 30, 300 and 1000 ppm, respectively. The incidences of liver carcinoma in females were 0/62, 1/63, 0/63 and 20/63 at 0,

30, 300 and 1000 ppm, respectively. Statistical analysis showed a significant increase in the number of tumor bearing male animals at 1000 ppm (38/63, $p<0.001$) and in females at 300 ppm (4/63, $p<0.05$) and 1000 ppm (52/63, $p<0.001$). At the doses tested, there were treatment-related increases in tumor incidences hepatocellular adenoma and carcinomas when compared to controls. The CD-1 mouse in-house historical control values for liver adenomas are 10-33% (males) and 0-2% (females) and 2-8% (males) and 2-18% females for liver carcinomas. Dosing was considered adequate based on increased liver weight, elevated aminotransferase enzyme levels, liver vacuolation, hypertrophy and necrosis.

This carcinogenicity study in the mouse is acceptable and satisfies guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

Mutagenicity

Gene Mutation

870.5500 *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay MRID 44721613 Guideline/Acceptable	In an Ames assay, cis/trans metconazole was not mutagenic with and without metabolic activation when tested in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538 and *Escherichia coli* WP2 uvrA at concentrations up to 5000 µg/plate.
870.5300 *in vitro* Mouse Lymphoma Mutagenesis Assay MRID 44721615 Guideline/Acceptable	In a mutagenicity study, mouse lymphoma cells L5178Y/TK+/- treated with cis metconazole up to 70 µg/ml (without S9) showed no statistical increase in the mutation frequency in two separate experiments. In the presence of S9, a statistically significant increase in the mutation frequency was observed at 50 µg/ml, but not at higher doses (90 µg/ml). No increase in mutation frequency was observed when the experiment was repeated. Since the results were not reproducible, cis metconazole is not mutagenic in this assay .

Cytogenetics

870.5375 *in vitro* Cytogenetics Test MRID 44721616 Guideline/Acceptable	In an *in vitro* chromosome study, the exposure of CHO-K1 cells with cis/trans metconazole in the absence of S9 mix did not induce chromosomal aberrations at a dose up to 50 µg/ml after 24 or 48 hours of exposure. In the presence of S9, an increase in chromosomal aberrations relative to the negative controls was observed at 50 µg/ml at 24 hours in two experiments. The increase in aberrations was observed in the absence of cytotoxicity. Cis/trans metconazole is

	clastogenic in CHO cells in the presence of S9

870.5375 *in vitro* Cytogenetics Test MRID 44721617 Guideline/Acceptable	In an *in vitro* chromosome studies, the exposure of human lymphocytes to cis metconazole up to 750 µg/ml for 3, 24 or 48 hours in the presence and absence of S9 mix showed no increase in metaphase chromosome damage relative to the negative controls

870.5395 *in vivo* Mammalian Erythrocyte Micronucleus Test: Mouse MRID 44721618 Guideline/Acceptable	In an *in vivo* test bone marrow micronucleus test, mice were exposed to cis/trans metconazole up to the limit dose of 2000 mg/kg. No statistically or biologically significant increase in micronucleated polychromatic erythrocytes was observed at dose levels exhibiting bone marrow toxicity

Other Genotoxicity

870.5550 *in vivo/in vitro* Mammalian UDS test Rat MRID 44721620 Guideline/Acceptable	In studies to evaluate the potential to induce *in vivo /in vitro* unscheduled DNA synthesis, rats were treated with cis/trans metconazole at doses up to 2000 mg/kg bwy. Hepatocytes were isolated, cultured and labeled in the presence of ^{3}H-thymidine. Analysis revealed no significant dose-related increase in nuclear grain count (associated with induced unscheduled DNA synthesis) with cis/trans metconazole

Neurotoxicity

870.6200 Neurotoxicity – Rat

In a neurotoxicity study (MRID 46808440), groups of young adult Crl:CD (SD)IGS BR rats (10/sex/dose) were administered metconazole (98.99%, Lot 9Z521) in diet at doses of 0, 50, 170 or 500 ppm (corresponding to 0, 4.84, 15.69 or 47.08 mg/kg/day in males and 0, 5.10, 17.62 or 49.82 mg/kg/day in females) and observed for 28 days. Neurobehavioral assessments (including in-hand observations, functional observational battery and motor activity testing) were performed on 10 animals/sex/group on the week prior to treatment and each week thereafter. Body weight and food consumption were recorded weekly. At study termination, all animals were euthanized and perfused *in situ* for neuropathological examination including brain weight and anatomical measurements of the length and width of cerebral hemispheres. Of the perfused animals, 5 animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Cholinesterase activity was not determined.

There were no treatment-related effects on clinical signs or mortality. Decreased bodyweight was observed in males at 170 and 500 ppm and in females at 500 ppm during the first week of treatment. A marked decrease (↓41%) in bodyweight gain was seen in high dose females during the initial week of treatment compared to the control group. Bodyweight gain during the 4 weeks of treatment was lower in females at 170 and 500 ppm compared to the controls (↓12% and ↓19%, respectively). In addition, decreased food consumption (accompanied by an increase in food scatter) was observed in high dose females.

Functional observational battery (FOB) and motor activity testing revealed no treatment-related effects at any dose. Brain weights, anatomical measurements and microscopic neuropathology examinations were unaffected by treatment. Administration of metconazole in the diet up to concentrations of 47.82 and 49.82 mg/kg/day in male and female rats, respectively, showed no evidence of neurotoxicity.

Based on the effects seen in this study, the systemic toxicity LOAEL was 15.69 mg/kg bw/day in males and 17.62 mg/kg/day in female rats based on decreased body weight gain and decreases in food consumption and food efficiency. The systemic toxicity NOAEL was 4.84 mg/kg bw/day in males and 5.10 mg/kg/day in female rats. **The neurotoxicity NOAEL was > 500 ppm (47.08 mg/kg/day in males, 49.82 mg/kg/day in females)**

Metabolism

870.7485 Metabolism - Rat

In a metabolism study (MRID 44721623) Metconazole (>99 % a.i., batch S1106/1, [cyclopentyl-^{14}C] WL148271) was administered as a single dose of 2 mg/kg by gavage to 2 Fischer 344 rats/sex in the preliminary CO_2 study and 5 rats/sex in the main study. One rat/sex was administered DMSO as a vehicle control.

Nearly 94% of the administered radioactivity was eliminated by day 3 post-dose. The primary route of elimination was in feces with 86.1% and 82.1% of the administered dose eliminated in the feces by 48 hours in males and females, respectively. Urine was a minor route of elimination with approximately 15% of the administered dose eliminated via urine in males and 26% in females. Little or no radioactivity was detected in the respired air in a preliminary study. No significant differences in bodyweight, food consumption or water consumption were observed. Measurement of the ^{14}C-residues in tissues showed low or no detectable concentrations of ^{14}C-metconazole equivalent residues in most tissues with the exception of the GI tract, liver and adrenals. Moderate levels of radiolabeled residues were detected in the GI tract (0.750 ppm males, 0.559 ppm females) and were primarily associated with GI content. An approximately 10-fold sex difference in ^{14}C-residues was detected in the liver with 0.157 ppm detected in males and 1.63 ppm detected in females. Substantial concentrations of ^{14}C-residues were detected in the adrenal glands in both sexes (2.88 ppm males, 1.67 ppm females). The profiles of the radiolabeled metabolites from feces, urine and liver were similar in males and females. The chromatographic profiles were similar to those observed in previous studies in rats dosed with high dose [triazole-^{14}C] *cis* metconazole (MRID 44721624) or [cyclopentyl-^{14}C]*cis/trans*

metconazole (MRID 447216252). The major metabolites identified in the feces were categorized as monohydroxy-metabolites and carboxy-metabolites. The monohydroxy-metabolites were products of the oxidation of the methylene group, the methyl groups or the phenyl group. The carboxy-metabolites were generated from the further oxidation of the methyl groups. No further analyses of the fecal extracts were performed. Analysis of the urine metabolites showed similar (qualitative) profiles in males and females with a higher proportion of the carboxy metabolite M12 excreted in the urine of males compared to females (11% versus 22%, respectively). The reason for the difference in M12 excretion is unclear. Only a very limited characterization of the liver metabolites was performed.

This metabolism study in the rat is classified acceptable/guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7485 Metabolism - Rat

In a metabolism study (MRID 44721624) [triazole-^{14}C] Metconazole (>98% a.i., batch 1084/1, WL136184) was administered to six male Fischer 344 rats by a single oral gavage dose of 200 mg/kg. The animals were housed in metabolic cages and urine and feces were collected at 24 hour intervals for a total of seven days.

Elimination of the radioactivity was rapid with 70% of the administered dose excreted with 72 hours. Little or no labeled parent compound was detected in the excreta. Greater than 95% of the dose was eliminated by day 7 and major route of excretion (75%) was via the feces. The total recovery of radioactivity in the urine was 20%. The metabolites identified in the excreta primarily represent products of the oxidation of the methyl groups on the cyclopentane ring. Some cleavage of the compound was also observed. The six classes of metabolites identified were: monohydroxy-metabolites, hydroxyphenyl-metabolites, carboxy-metabolites, multihydroxy-metabolites, mixed function metabolites and sulfated conjugates of metabolites.

This metabolism study in the rat is classified acceptable/guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rat.

870.7485 Metabolism - Rat

In a metabolism study (MRID 44721622) [cyclopentyl-^{14}C]WL148271 (cis:trans Metconazole, >99% a.i.; SCP/1, batch # S1164/1) was administered to five Fischer 344 rats/sex by gavage in a single dose at 164 mg/kg (target dose: 200 mg/kg). Two Fischer 344 strain rats/sex were treated with dose vehicle (DMSO) only.

The major objectives of this study were to measure the rates and routes of elimination of metconazole after a single high dose and to measure the retention and distribution of the test material. Partial metabolite profiling of the urine and feces was also performed. The study showed that the elimination of administered radioactivity was rapid with 94.9% and 93.9% of the administered dose eliminated 5 days after dosing in male and female rats, respectively. A sex-related difference in the proportion of radioactivity eliminated in feces and urine was observed. The predominant route of elimination was via the feces, accounting for 81.3% of the administered radioactivity in males and 65.5% in females. Elimination via urine accounted for

most of the remaining radioactivity with 13.6% and 28.4% of the administered dose excreted in the urine in males and females, respectively. Analysis of the distribution of radioactivity 5 days after dosing showed the highest level of radioactive residues in the adrenals, liver and GI tract. The residue levels in these tissues were slightly higher in males than females. The major excreted metabolites were identified and categorized as hydroxy metabolites from the oxidation of the benzylic methylene, methyl groups or phenyl group of the cyclopentane ring and carboxy metabolites from the further oxidation of the methyl groups.

This metabolism study in the rat is classified as acceptable/guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats

870.7485 Metabolism - Rat

In a metabolism study (MRID 44721625), labeled [cyclopentyl-^{14}C]WL136184 (98.2% a.i., batch # S.1190/2), was administered via stomach cannula as a single dose to three bile-cannulated Fischer 344 rats/sex in at dose level of 2 mg/kg.

The mean total recovery of the radiolabeled dose was 95.5% and 97.2% in male and female rats respectively. Biliary excretion was rapid with at least 50% of the dose excreted in the bile within the first 6 hours with 79% (male) and 83% (female) of the administered dose excreted in the bile at 48 hours. Urinary excretion accounted for 4.3% of the dose in males and 12.1% of the dose in females. Fecal excretion of radioactivity was low in both sexes accounting for 0.2% and 0.3% of dose in male and females, respectively. The retention of radioactivity in the gastro-intestinal tract and carcass was notably higher in male rats (combined retention 12.1%) than in females (1.2%).

This metabolism study in the rat is classified acceptable/guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7485 Metabolism - Rat

In a metabolism study (MRID 46808449), KNF-474m (Metconazole, unlabeled purity = 98.99%, labeled purity = 98.9%, radiolabeled at carbon 1 of the cyclopental ring) was administered to groups of three male and three female F344/DuCrj rats for plasma kinetic studies at concentrations of 2 mg/kg bw or 200 mg/kg bw by gavage. For plasma pharmacokinetic studies, blood was drawn 0.25, 0.5, 1, 2, 4, 8, 24, 48, and 72 hours after treatment with 2 mg/kg test material and 0.5, 1, 2, 4, 8, 24, 48, 72, 96, and 120 hours after treatment with 200 mg/kg test material. In tissue distribution studies, nine male and nine female rats were treated with 2 mg/kg bw radiolabeled test material and three rats/sex were sacrificed 0.5, 24, and 72 hours after treatment and 12 male and 12 female rats were treated with 200 mg/kg bw radiolabeled test material by gavage were sacrificed 4, 24, 72, and 120 hours after treatment. In a repeat dose study, groups of six male and six female rats received 14 daily gavage doses of 2 mg/kg bw unlabeled test material and were sacrificed 0.5 and 72 hours after receiving a single radiolabeled 2 mg/kg bw of radiolabeled test material.

Neither excreta nor expired air were collected in this study so an accurate determination of absorption cannot be made. However, tissue distribution data suggest maximum absorption for male and female rats treated with 2 mg/kg bw radiolabeled KNF-474m was ~14% and ~17%, respectively, 30 minutes after treatment while tissue distribution data from male and female rats

treated with 200 mg/kg bw radiolabel suggest maximum absorption was ~22% and ~29% four hours after treatment, respectively. Absorption was rapid at both dose concentrations but appeared saturated at 200 mg/kg bw.

The time to maximum plasma concentration for male and female rats treated with either 2 mg/kg or 200 mg/kg was the earliest sampling interval, 0.25 hours and 4 hours, respectively. The plasma half-life of low- and high-dose rats was slightly shorter in males than females, ~20-25 hours and ~34 hours, respectively. The ratio of $AUC_{(0-\infty)}$ between dose groups of both males and females was close to the 100-fold increase in dose. The $AUC_{(0-\infty)}$ for male and female rats were nearly proportional between doses while T_{max} was 0.25 hours at the low-dose and 4 hours at the high-dose suggesting absorption saturation occurred at the high-dose. The data also suggest that systemic exposure for female rats was greater than for males, accumulation of the test material did not occur in either sex, and that elimination from the plasma was monophasic and followed first order kinetics.

The highest concentrations of radiolabel found in low-, high, and repeat-dose male and female rats were in the gastrointestinal tract while the highest tissue concentrations were found in the liver. With the exception of the residual carcass, all other tissues contained <1% of the administered dose. The tissue distribution in the low-, high-, and repeat-dose studies was similar regardless of dose, frequency, or time of collection. These data suggest that a target organ was not identified and that accumulation of the radiolabel did not occur.

Excretion studies were not done, however, increased radiolabel concentrations in the GI tract and liver, and very low concentrations of radiolabel in the kidneys and lung suggest that the feces were the primary elimination route. Metabolite identification studies were not done.

This metabolism study in the rat is classified Acceptable/Guideline. The study does satisfy the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] when combined with the other submitted metabolism studies (MRIDs 44721622-5) examining absorptions, excretion and major metabolite identification in rats.

870.6700 Dermal Absorption- Rat

In a dermal penetration study (MRID 46808450), WL148271 (Metconazole, unlabeled purity 95-96%, Lot Number ST 89/008, and radiolabeled (labeled in the cyclopentyl region) purity 99%, Lot Number S1116) was applied to the shaved backs of 20 female CDF(F-344)/CRLBR rats at a single concentration of 354 $\mu g/cm^2$ (2.5 mg/animal applied to a 3 cm diameter area). Four treated rats were sacrificed after four hours of exposure and four were sacrificed after eight hours. An additional group of 8 animals (for per duration) were washed at 8 hours and terminated at 24 and 72 hours after treatment. The chemical was formulated as an emulsifiable concentrate at the commercial concentration in order to mimic the exposure of the operators involved in mixing and diluting the pesticide and those working in the formulation plant. Female animals were selected because the endpoint of concern for risk assessment for this compound is developmental toxicity. Results of the analyses are provided in Table 1.

Table 1. Dermal Absorption Rate Summary[1] Metaconozol In Vivo Rat Dermal Absorption Study								
Dose level ($\mu g/cm^2$)	Mean percentage of Dose Absorbed & In/On Skin							
	4 h		8 h		24 h[4]		72[4]	
	Abs [2]	Skin [3]	Abs.	Skin	Abs.	Skin	Abs.	Skin
354	1.10	15.68	1.66	12.21	3.39	8.115	7.553	8.761

[1] Data summarized by reviewer from page 28 Table 7.2 of the study report, MRID 46808450.
[2] Abs= radioactivity absorbed (sum of adrenals, carcass and excreta)
[3] Amount of radioactivity in/on skin after skin wash (application site and residual skin).
[4] Washed at 8 hours, terminated at 24 and 72 hours

Overall recovery of radioactivity ranged from 95% to 101% of the administered dose with most recovered radioactivity contained in the application site wash solutions (ranging from 81-88% of the administered dose). Amount of radioactivity absorbed ranged from 1% at 4 hours to 7.6% at 72 hours. Mean recoveries in excreta increased both with exposure time and study duration. Initially, most absorbed radioactivity was eliminated in the urine but from 24 hours on the majority was recovered in the feces. Amount of radioactivity in blood, plasma and carcass increased during the first 24 hours and then remained steady. Material remaining in/on the skin ranged from 9-15% of the applied radioactivity. The concentration of radiolabel in/on skin steadily declined over 72 hours to ~8.6% of the administered dose while systemic absorption increased to ~7.6%. The pattern of increased absorption at 24 and 72 hours post wash tends to indicate that the material remaining in/on the skin continues to be absorbed after wash at 8 hours. Mean penetration of radioactivity (absorption plus application site after washing) reached a maximum of about 16% at 72 hours (following an 8 hour exposure). Since only a single dose was analyzed, it is not possible to determine whether the skin is at or approaching saturation at the applied dose.

The single dose analyzed in this study represents the concentration of the emulsifiable concentrate and was selected to mimic the exposure mixer/loaders and persons working in the formulation plant. Presumably, field workers would be exposed to a more dilute formulation. Based on typical dermal absorption patterns, lower doses usually correspond to higher dermal absorption as a percent of dose; higher doses typically correspond to lower dermal absorption. Consequently, since the study dose per unit area for the emulsifiable concentrate is likely to be greater than the expected exposure dose per unit area of the dilute formulation for field workers, a higher percent absorption would be expected for field workers. Use of female rats appears to be appropriate given the effect of concern.

The study was conducted in 1990 and does not meet current OPPTS 870.7600 Guidelines for a dermal penetration study. However, the study does provide useful information on the dermal penetration of radiolabeled WL14827. This study in the rat is considered acceptable/non-guideline.

Special/Other Studies

Mechanistic Study- Mouse and Rat- 28 day

In a mechanistic study (MRID 44721626), metconazole (94.2% a.i., *cis* isomer, ST90/369, batch 12) was administered to16 male CD1 mice/dose in diet at dose levels of 0 or 300 ppm (equivalent to 0 and 58.3 mg/kg/day) and was administered to16 male Fisher 344 rats/dose at a dose level of 0 or 1000 ppm (equivalent to 0 and 86.7 mg/kg/day) for 28 days. Animals were

sacrificed 7 or 28 days after initiation of treatment. The livers were isolated, weighed and the liver homogenates and microsomal fractions were analyzed for xenobiotic metabolizing enzymes. Liver sections were examined by light and electron microscopy for treatment-related organelle and ultrastructural changes. All animals were monitored for body weight, food consumption and clinical signs of toxicity throughout the study. Phenobarbitone (0.05%) was fed to 8 mice and 8 rats in the diet for 28 days and was used as the positive control for xenobiotic enzyme induction.

There were no significant changes in bodyweight or food consumption in mice treated with 300 ppm metconazole compared to the control animals. Relative mouse liver weights were higher at 300 ppm on day 7 (↑22.4%) and day 28 (↑12.7%) than in the control group. The increased liver weights were associated with midzonal vacuolation (3/6 mice, day 28). In addition, single incidences of cytoplasmic vacuolation were observed at day 7 and day 28 and a single incidence of (slight) centrilobular hypertrophy was observed in the mouse at day 28. Liver biochemistry findings showed a statistically significant decrease in mouse liver homogenate DNA content (day 7 only) and significant increases in microsomal protein and CYP450 content as well as increased EMND and ECOD activities at day 7 and 28 compared to the control group. LA-12-H activity was also elevated at day 28. Electron microscopy of liver sections showed no evidence of an increase in peroxisome numbers or morphology in mice treated with metconazole or phenobarbitone.

In the rat, body weight was slightly reduced on day 7 (↓5%, $p<0.05$) and food consumption was lower (↓6%, $p<0.05$) on days 3-7 in metconazole-treated animals. Relative liver weights were higher at 1000 ppm at day 7 (↑9%, $p<0.01$) and day 28 (↑4%, $p<0.05$) compared to the control animals. No difference in liver protein, liver DNA content or homogenate palmitoyl-CoA oxidation was observed in rats fed metconazole for 7 or 28 days. Statistically significant increases in rat microsomal protein levels were seen in treated animals at days 7 and 28 (↑117% , and ↑139% control, respectively). Increased levels of CYP450 were statistically significant ($p<0.001$) at day 7 (154% control) and day 28 (140% control) as were activity levels of microsomal enzymes EMND (149% control, day 7; 141% control, day 28) and ECOD (173% control, day 7; 178% control, day 28). No statistically significant changes in the activity levels of hydroxylases LA-11 and LA-12 were observed in rats fed metconazole for 7 or 28 days. No treatment-related histopathological findings in the liver were observed at day 7. At day, 28, 5/6 rats showed slight or moderate midzonal vacuolation, which was statistically significant ($p<0.05$) when incidences of differing severities of vacuolation were compared to the controls. Electron microscopy of liver sections showed no evidence of peroxisome proliferation in metconazole- or phenobarbitone-fed rats. This study showed a significant induction of xenobiotic metabolizing enzymes after 7 days at dose levels that produced liver tumors in a mouse carcinogenicity study (MRID 44721612). No evidence of peroxisome proliferation was observed.

This mechanistic study in the mouse and rat is classified acceptable, non-guideline.

Mechanistic Study- Rat- 14 day

In a 14-day mechanistic study (MRID 46665403) Metconazole (98.53%, Lot #92521; cis 82.68%, trans 15.85%) was administered to 18 Crj:CD-1 (ICR) female mice/dose in diet at dose levels of 0, 30, 300, 1000 ppm (equivalent to 0, 4.49, 47.6 or 151 mg/kg bw/day). The animals

were evaluated at 3, 7 or 14 days for the effects of the test material on drug-metabolizing enzyme induction, cell proliferation, and reactive oxygen species (ROS) production in the liver.

There were no treatment-related deaths or clinical signs during the study. Body weight and food consumption were similar to the controls in all treatment groups. Enlarged livers were observed in nearly all animals at 1000 ppm after 3, 7 and 14 days of treatment (6/6, 6/6, and 5/6, respectively). Absolute and relative liver weights were significantly higher (↑35-52% and 46-58%, respectively) in the 1000 ppm group at all time points compared to the controls. Liver weights increased 11-18% at 300 ppm compared to the control groups, but did not reach statistical significance. The increase in liver weights was accompanied by an induction of hepatic drug-metabolizing enzymes observed after 7 days of treatment with dose-dependent and statistically significant increases in microsomal protein content, cytochrome P-450 content, and ethoxycoumarin O-dealkylase (ECOD) and pentoxyresorufin O-dealkylase (PROD) activities at 300 and 1000 ppm. ECOD activity was elevated 2.1- and 3.1-fold at 300 and 1000 ppm, respectively compared to the control group after 7 days of treatment. Marked elevation in PROD activity was observed at 300 and 1000 ppm (3.8- and 4.5-fold increases, respectively) at day 7 compared to the controls. Western blot analysis showed a significant induction in the levels of the P-450 isozymes CYP1A (↑4.5-fold), CYP2B (↑11.5-fold) and CYP3A (↑3.9-fold) at 1000 ppm relative to the controls. CYP2B and CYP3A were also significantly elevated at 300 ppm compared to the control group (↑4.0- and 2.5-fold, respectively). Induced hepatic cell proliferation was observed at 1000 ppm as demonstrated by an increase in PCNA labeling index after 3 and 7 days of treatment (↑8.5- and 6-fold, respectively). No significant differences in PCNA labeling index were observed between the treated and control groups by day 14. Blood biochemistry findings showed significantly elevated glutamic oxaloacetic transaminase (↑94%) and glutamic pyruvic transaminase (↑154%) at 1000 ppm. Other blood chemistry findings included dose-related decreases in total cholesterol (↓26% and 56%) and total bilirubin (↓22% and 33%) at 300 and 1000 ppm, respectively. Lipid peroxide (LPO) and 8-hydroxydeoxyguanosine (8-OHdG) were measured as markers of oxidative stress. After 14 days of treatment, LPO levels were significantly higher in the 300 and 1000 ppm groups (↑2.6- and 2.3-fold) compared to the control group indicating membrane lipid peroxidation, possibly via the generation of reactive oxygen species. No significant changes in 8-OHdG levels were observed at any dose, indicating no oxidative DNA damage was detected in the livers of the treated animals. Histopathology of the liver showed hepatocellular hypertrophy and hepatocellular vacuolation in nearly every animal (6/6 and 5/6, respectively) at 1000 ppm. Similar, but less severe liver histopathology findings were observed in the 300 ppm group. Based on the results, it is suggested that metconazole is a hepatic drug-metabolizing enzyme inducer, has the potential to induce cell proliferation and may exert a cytotoxic effect on hepatocytes through oxidative stress. **The NOAEL for this study is 30 ppm (4.49 mg/kg/day) based on increased incidence of hepatocellular hypertrophy, increased P-450 content, increased ECOD and PROD activities and increased LPO observed at 300 ppm (47.6 mg/kg/day).**

This mechanistic study in the mouse is classified acceptable, non-guideline.