Date: January 26-2007

MEMORANDUM

SUBJECT: Petition No: 5F6971; Tetraconazole: Human-Health Risk Assessment for Proposed Uses on Soybean, Sugar Beet, Peanut, Pecan, and Turf.

PC Code: 120603
DP Nos: 321751 (Petition No: 60063-12, turf, pecan, sugar beet and peanuts) and 331476 (Petition No: 60063-12, soybean).

FROM: Mary Clock-Rust, Biologist
Thomas Bloem, Chemist
P.V. Shah, Ph.D., Toxicologist
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509P)
And
Mark I. Dow, Ph.D., Biologist
Alternate Risk Integration Assessment Team (ARIA)
Risk Integration Minor Use and Emergency Response Branch (RIMUERB)
Registration Division (RD) (7505P)

THRU: Dana Vogel, Acting Chief
RAB1
HED (7509P)

TO: Lisa Jones, Risk Manager Reviewer
RD (7505P)

Under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act, as amended, Isagro S.P.A. and Sipcam Agro U.S.A. have requested registration of the fungicide tetraconazole. Currently, tetraconazole is registered for use on sugar beets in seven states: CO, MI, MN, MT, ND, NE, and WY. The registrant proposes to expand this use to all 50 states and add additional uses on turf, soybeans, pecans, and peanuts. The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed uses of tetraconazole in/on pecan, sugar beet, soybean, peanuts and turf.

A summary of the findings and an assessment of human health risk resulting from the proposed and registered uses of tetraconazole are provided in this document. The hazard characterization was provided by PV Shah and Guruva Reddy (RAB1); the residue chemistry review and dietary exposure assessment were provided by Tom Bloem (RAB1); the occupational/residential exposure assessment was provided by Mark Dow (RIMUERB); the risk assessment was provided by Mary Clock-Rust (RAB1) and the drinking water assessment was provided by Iwona Maher of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Background
Tetraconazole (1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy)propyl]-1*H*-1,2,4-triazole) is a broad spectrum systemic fungicide. It is absorbed by the root, stem, and leaves, with subsequent translocation to all portions of the plant. Triazole fungicides primarily function by interfering with cell growth, particularly the ability to build cell walls.

Tetraconazole is currently registered for application to sugar beet (regional registration) and soybean (Section 18 registration) with tolerances ranging from 0.05-3.0 ppm (40 CFR 180.557). Tolerances as a result of secondary residues are also established in/on poultry (temporary tolerances as a result of the soybean Section 18 registration) and ruminant commodities (0.0003-4.0 ppm).

Proposed Uses
The petitioner is proposing Section 3 registrations for application of tetraconazole to sugar beet (national registration), soybean, pecan, peanut, and turf. In conjunction with these requests, the petitioner proposed the establishment of the following tolerances for residues of tetraconazole *per se*:

Soybean, seed	0.1 ppm
Soybean, refined oil	0.5 ppm
Soybean, aspirated grain fractions	0.5 ppm
Poultry meat	0.01 ppm
Poultry liver	0.01 ppm
Poultry byproducts	0.01 ppm
Poultry fat	0.05 ppm
Poultry egg	0.01 ppm
Pecan	0.05 ppm
Peanuts (nutmeat)	0.03 ppm
Peanut meal	0.03 ppm
Peanut oil	0.1 ppm

The HED-recommended tolerances appear at the end of the Executive Summary.

Hazard Characterization

Tetraconazole Metabolites
HED has determined that three toxicologically different groups of compounds are of concern following application of tetraconazole (see Attachment 1 for structures). The implications for risk assessment of these groups are discussed below.

<u>Free triazole metabolites</u> (includes 1,2,4-triazole (T), triazolyl alanine (TA), triazolyl acetic acid (TAA), triazolyl hydroxypropionic acid (THP), and/or all labile conjugates of these compounds):
HED has previously addressed the toxicity of T, TA and TAA in D322215 (HED Risk Assessment Document; M. Doherty *et al.,* 7-Feb-2006). Please refer to this document for information concerning the toxicity of these free triazole metabolites.

The free triazole risk assessment mentioned above pertains to exposure to T, TA, and TAA from the conazole/triazole fungicides. Tetraconazole results in the formation of these compounds as well as THP.

THP is a residue of concern in rotational crops and livestock (included as a residue of concern in livestock based on the identification in rotational crops and therefore as a potential residue in feed). Based on the proposed application rates and the results of the confined rotational crop studies, HED has concluded that residues in rotational crops will be negligible; therefore, residue of THP will be negligible and the previous free-triazole risk assessment is acceptable.

Metabolites in common with propiconazole (M14360-ketone, M14360-CP(C-1)-alcohol, and M14360(C-1)-alcohol):

The tetraconazole plant metabolism, livestock metabolism, and/or confined rotational crop studies resulted in the identification of M14360-ketone, M14360(C-1)-alcohol, and M14360-CP(C-1)-alcohol (structurally similar to M14360(C-1)-alcohol); these compounds are also metabolites/degradates of propiconazole (identified as CGA-91304 and CGA-91305 in the propiconazole risk assessment). These common metabolites/degradates will be referred to as CGA-91304/CGA-91305 from hereon. HED concluded that the toxicity of these metabolites/degradates are accounted for in the propiconazole toxicity database (because they are identified in the propiconazole mouse and rat metabolism studies); whereas they were not identified in the tetraconazole rat metabolism study, and are therefore not accounted for in the tetraconazole toxicity database.

Although the identification of common metabolites/degradates often trigger the need for an aggregate risk assessment, this is not necessary at this time for the following reasons:

- Residue of CGA-91304/CGA-91305 in/on plant and livestock commodities resulting from application of tetraconazole is expected to be negligible in comparison to the magnitude of these residues following application of propiconazole.
- Since exposure to these compounds resulting from tetraconazole is insignificant, the propiconazole risk assessment can act as a 'worst-case' risk assessment for CGA-91304/CGA-91305, since they were included in the residues of concern for the propiconazole risk assessment.

However, if and when application of tetraconazole results in significant exposure to CGA-91304/CGA-91305, at that time it will be necessary to include the magnitude of these compounds resulting from application of tetraconazole in the propiconazole risk assessment.

Parent Tetraconazole
Tetraconazole has low acute toxicity via the oral, dermal, and inhalation routes. It is a slight eye irritant, but is not a dermal irritant or a dermal sensitizer. The liver and kidney are the primary target organs of tetraconazole. In the subchronic, chronic, and reproduction rat studies, subchronic and carcinogenicity mouse studies, and the chronic dog study increases in liver weight, increases in liver serum enzymes, or gross and microscopic liver pathology were noted at various doses, providing evidence of liver toxicity.

In all of the above studies, except the subchronic mouse study, increases in kidney weight or gross pathology and cortical tubular hypertrophy (dog) were noted at various doses, indicating renal toxicity.

Certain changes in multiple organs were seen in the database that may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

Long-term dietary administration of tetraconazole resulted in an increased incidence of combined benign and malignant liver tumors in mice of both sexes. The levels of the doses tested were adequate. No tumors were noted in male or female rats after long-term dietary administration of tetraconazole. The

HED Cancer Assessment Review Committee (November 10, 1999) classified tetraconazole as **"likely to be carcinogenic to humans"** by the oral route based on the occurrence of liver tumors in male and female mice, in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999). The CARC recommended that a low dose extrapolation model be applied to the experimental animal tumor data and that quantifications of risk be estimated for male and female mouse liver tumors for tetraconazole. Tetraconazole did not show evidence of mutagenicity in *in vitro* or *in vivo* studies.

Oral rat and rabbit developmental studies showed no increased susceptibility of the fetus to tetraconazole *in utero*. Maternal toxicity and developmental toxicity occur at the same dose level of 100 mg/kg/day in the rat study. No developmental toxicity was seen in the rabbit study with the maternal toxicity level noted at the highest dose tested (30 mg/kg/day).

A two-generation rat reproduction study also revealed no increased susceptibility to offspring. Decreased litter weight and mean pup weight and increased liver weight were noted at a dose of 35.5 mg/kg/day (males) and 40.6 mg/kg/day (females) while parental toxicity resulted in decreased body weight gain and food consumption during pre-mating, increased relative liver and kidney weights, hepatocellular hypertrophy and gastric irritation in males and females at 35.5 and 40.6 mg/kg/day, respectively.

No evidence of neurotoxicity was noted in any oral study. No acute or subchronic neurotoxicity studies were submitted.

Rat metabolism data indicate that tetraconazole is well absorbed from the gastro-intestinal tract and almost 100% of the administered dose was recovered in urine (52-76%) and feces (12-36%) and less than 6% (2.8-5.8%) of the administered dose remained in the carcass/tissues within 72 hours post-dosing. There was no major difference in absorption and elimination of tetraconazole between sexes and dose levels. Position of labeling [^{14}C-phenyl or ^{14}C-triazole] resulted in slight differences in the blood time to reach maximum (T_{max}) levels and $T_{1/2}$ lives between sexes and doses. Males had slightly higher T_{max} levels than females. Metabolic identification revealed triazole as the major urinary and fecal metabolite.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision
The liver and kidney are the primary target organs of tetraconazole. After exposure to tetraconazole, the dog appears to be the most sensitive species with regard to nephrotoxicity, while the rat and mice appear to be more susceptible to hepatotoxicity. Subchronic studies in rats and mice resulted in treatment-related hepatotoxicity noted in rats and hepatotoxicity and limited evidence of nephrotoxicity noted in mice. Chronic exposure to tetraconazole in dog produced hepatotoxicity at the highest dose tested. Hepatotoxicity was also observed in rats and mice after chronic exposure to tetraconazole. In rats, chronic exposure to tetraconazole did not produce any tumors where as in mice, it produced benign and malignant liver tumors.

Certain changes in multiple organs were seen in the database that may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

An endpoint of concern for acute dietary risk assessment for the general population was not identified. Therefore, this risk assessment was not performed. However, the endpoint for dietary risk assessment for females 13-50 years of age is based on increased incidence of supernumerary ribs seen in a rat developmental toxicity study. The acute reference dose (aRfD)/acute population-adjusted dose (aPAD) is 0.225 mg/kg/day (FQPA safety factor = 1x; see below)**.**

The chronic toxicity study in dogs is the basis for the chronic dietary reference dose (RfD). Absolute and

relative kidney weights and histopathological changes in the male kidney were seen at the LOAEL of 2.9 mg/kg/day. The cRfD/chronic population-adjusted dose (cPAD) is 0.0073 mg/kg/day.

The results of the 2-generation reproduction toxicity study were the basis for short- and intermediate-term incidental oral risk assessment, short-term dermal and inhalation risk assessment. At the LOAEL of 40.6 mg/kg/day, decreased litter weight and mean pup weight in litters of all generation before weaning and increased relative liver weights at weaning in both sexes of all litters was observed. The dose for risk assessment is the NOAEL of 5.9 mg/kg/day.

The dose and endpoint for intermediate- and long-term inhalation and dermal risk assessments were based on the results of the chronic toxicity study in dogs (the same study was used as the basis for the cRfD). The oral NOAEL is 0.73 mg/kg/day. Effects were the same as those described above for the cRfD.

It is recommended that the 10X FQPA safety factor for the protection of infants and children be reduced to 1X since there is no evidence of increased susceptibility and there are no concerns or residual uncertainities for pre and/or post-natal toxicity. In addition, dietary, drinking water and residential exposure assessments are not expected to underestimate exposure, the toxicity database for tetraconazole is complete, and a developmental neurotoxicity (DNT) study is not required.

Drinking Water Exposure
Tetraconazole is persistent in the environment and has moderate to slight mobility in soils. Laboratory and field half-lives ranged from 107 days to more than 1 year; however, the dissipation of tetraconazole applied directly to foliage (i.e. sugar beet leaves) is much more rapid. Foliar dissipation studies suggest that tetraconazole is taken up quickly and extensively metabolized in plants yielding tetraconazole acid, tetraconazole alcohol, triazolylalanine and triazolylacetic acid as metabolites. Successive applications of tetraconazole are expected to result in year-to-year soil accumulation. Tetraconazole has potential to reach surface water via runoff and spray drift, but its tendency to reach ground water is expected to be reduced due to its lack of mobility in soil.

EFED provided modeled ground (Screening Concentration In Ground Water (SCIGROW)) and surface [Pesticide Root Zone Model (PRZM 3.12) and Exposure Analysis Modeling System (EXAMS 2.98.04)] water concentrations for tetraconazole *per se*. The water estimates were incorporated directly into the dietary exposure analysis.

Dietary Exposure
Based on the plant metabolism, livestock metabolism, and confined rotational crop studies, HED identified the following three groups of compounds differentiated by toxicity: (1) free triazole compounds, (2) non-free triazole metabolites in common with propiconazole, and (3) tetraconazole and remaining non-free triazole metabolites. The following text is a summary of these risk assessments for each group.

Free Triazole Metabolites: HED has determined that T, TA, TAA, THP and all labile conjugates of these compounds are residues of concern in plant, livestock, and rotational crops following application of tetraconazole. The formation of the free triazole metabolites is a common aspect of the conazole/triazole class of fungicides and the toxicity and potential exposure to all registered/proposed conazole/triazole fungicides registrations as of 1-September-2005 were previously evaluated by HED (D322215, M. Doherty *et al.,* 7-Feb-2006). HED concludes that this previous free triazole risk assessment is adequate for the current petition.

The free triazole risk assessment mentioned above pertains to exposure to T, TA, and TAA from the conazole/triazole fungicides. Tetraconazole results in the formation of these compounds as well as THP. THP is a residue of concern in rotational crops and livestock (included as a residue of concern in livestock based on the identification in rotational crops and therefore as a potential residue in feed). Based on the proposed application rates and the results of the confined rotational crop studies, HED has concluded that residues in rotational crops will be negligible; therefore, residue of THP will be negligible and the previous free-triazole risk assessment is acceptable.

Tetraconazole: Acute, chronic, and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03) which incorporates the food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). These analyses were conducted in support of the proposed application of tetraconazole to soybean (Section 3 Registration), sugar beet (Nationwide Section 3 Registration), peanut (Section 3 Registration), and turf (Section 3 Registration). The following paragraphs are summaries of the acute, chronic, and cancer analyses.

Acute Dietary Risk: The Tier 1 acute dietary analysis (food and water; drinking water estimate derived from the proposed turf application scenario) resulted in an exposure estimate for females 13-49 years old that was less than HED's level of concern (2.7% aPAD; see Table 5.2a). Since the dietary risk estimate from turf drinking water resulted in an unacceptable cancer risk alone (see below) and HED is recommending that the turf use not be established, the acute analysis was repeated with exclusion of the turf use (the drinking water estimate was derived from the pecan application scenario). The resulting risk estimate for females 13-49 years old does not exceed HED's level of concern (<1% aPAD; see Table 5.2b). An acute endpoint of concern was not identified for the general population including infants and children.

Chronic Dietary Risk: The chronic analysis (food and water; drinking water estimate derived from the proposed turf application scenario) was partially refined through the incorporation of empirical processing factors, average field trial residues, and average residues from the feeding studies (100% crop treated assumed). The resulting risk estimates were less than HED's level of concern (≤76% cPAD; all infants <1 year old were the most highly exposed population subgroup; see Table 5.2a). Since the dietary risk estimate from turf drinking water resulted in an unacceptable cancer risk alone (see below) and HED is recommending that the turf use not be established, the chronic analysis was repeated with exclusion of the turf use (the drinking water estimate was derived from the pecan application scenario). The resulting exposure estimates do not exceed HED's level of concern (≤10.1% cPAD; all infants <1 year old were the most highly exposed population subgroup; see Table 5.2b).

Cancer: Dietary cancer risk was calculated two ways to explore risk mitigation options: 1) risk based on exposure from drinking water only, and 2) risk based on exposure from food and drinking water estimates from all non-turf uses.

First, dietary cancer risk was calculated based on drinking water sources alone (*i.e.,* all food sources were excluded), using drinking water estimates based on the proposed turf use. Using only the water estimates from application to turf (golf courses only), the cancer risk for the U.S. population was **4 x 10^{-6}**.

Second, the dietary cancer risk assessment was performed based on food exposure and drinking water estimates from all proposed non-turf uses (sugar beet, peanut, soybean and pecan). The refined dietary cancer risk assessment was performed using empirical processing factors, average field trial residues, average residues from the feeding studies, projected percent crop treated estimates, and the drinking water estimate derived from the pecan application scenario (4.97 ppb; 8 x 0.125 lb ai/acre; highest estimate when turf is excluded). **The resulting exposure estimates yielded a cancer risk for the U.S. population of 3 x 10^{-6}.** A complete commodity analysis indicates that drinking water contributes 78% of the total exposure, soybean oil contributes 18% of the total exposure, and the remaining food commodities contribute 4% of the total exposure.

Cancer risks presented in this assessment are expressed to one significant figure. However, it should be noted that, in general, the precision which can be assumed for cancer risk estimates is best described by rounding to the nearest integral order of magnitude on the log scale, e.g., 3.16 x 10^{-7} to 3.16 x 10^{-6}, expressed as 10^{-6}. Risks are generally reported to one significant figure in HED risk assessments to allow better characterization of *changes* in risk which might result from potential risk mitigation. This rounding procedure indicates that risks should generally not be assumed to exceed the benchmark level of concern of 10^{-6} until the calculated risks exceed approximately 3 x 10^{-6}. Discretion should be used in interpreting the significance of these calculated risks with consideration given to the precision in the risk estimates.

Residential Exposure
As stated above, since the dietary risk estimate from turf drinking water (alone) resulted in unacceptable cancer risk, HED is recommending that the turf use not be established. No residential exposure is expected if the turf use is excluded.

Occupational Exposure
HED is recommending that the turf use not be established. HED's risk estimates for the proposed uses excluding turf are discussed below.

Occupational Handler Risk
A variety of uses are proposed for tetraconazole. Based upon the proposed agricultural uses, HED believes that the most highly-exposed occupational pesticide handlers (*i.e.,* mixers, loaders, applicators) are the following:

- mixer/loader using open-pour loading of liquids for aerial spraying
- applicator using open-cab ground-boom sprayer
- applicator using open-cab airblast sprayer
- aerial applicator (pilot)

Short- (1-30 days) and intermediate-term (1-6 months) dermal and inhalation exposures were assessed. No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the

Pesticide Handler's Exposure Database (PHED; v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline," that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves, as well as with a single layer of work clothing and the use of protective gloves or other personal protective equipment (PPE) as might be necessary. The proposed product labels involved in this assessment direct applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves made of any waterproof material such as nitrile, butyl, neoprene and/or barrier laminate.

Provided that mixer/loaders supporting aerial operations wear protective gloves, all estimated MOEs are >100, and the proposed uses do not exceed HED's level of concern for occupational pesticide handlers.

Occupational Post-application Risk
There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities. Short-term exposures are expected. Post-application worker exposure was estimated using the highest transfer coefficient (TC) of 6800 cm^2/hr (for commercial sod farming). This TC was obtained from an interim TC policy developed by HED's Science Advisory Council for Exposure (ExpoSAC) using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database SOP # 3.1.

For all proposed use sites **except turf**, estimates of exposure and risk result in MOEs greater than 100. Therefore, the proposed uses on pecan, peanut, sugar beet and soybean do not exceed HED's levels of concern.

Occupational Cancer Risk
Excluding turf uses, the next highest cancer risk estimate is for mixer/loaders supporting aerial application, with a cancer risk estimate of **6×10^{-6}.** HED's level of concern for occupational cancer risk is 1×10^{-4} to 1×10^{-6}. Therefore, estimated cancer risks for all proposed uses (except turf) do not exceed HED's level of concern.

Aggregate Risk
As stated above, since the dietary risk estimate from turf drinking water (alone) resulted in unacceptable cancer risk, HED is recommending that the turf use not be established. Aggregate risk is only relevant if there are residential uses. No residential exposure is expected if the turf use is excluded.

HED Recommendations
As stated earlier, risk estimates resulting from the proposed turf use exceed HED's level of concern. Therefore, HED does not recommend establishing a registration on turf.

Provided the petitioner submits revised Sections B and F, HED concludes that the toxicology, residue chemistry, and occupational/residential exposure databases are sufficient to permit a conditional registration for application of tetraconazole to sugar beet, peanut, pecan and soybean and establishment of the tolerances listed in the table below for residues of tetraconazole *per se*. An unconditional registration may be established upon the submission of the storage stability and field trial data outlined below.

Commodity	HED-Recommended Tolerance (ppm)
Beet sugar, root	0.05
Beet, sugar, dried pulp	0.15

Beet, sugar, molasses	0.15
Peanut	0.03
Peanut, oil	0.10
Pecan	0.04
Soybean, seed	0.15
Soybean, refined oil	0.80
Aspirated grain fractions	1.0
Poultry, meat	0.01
Poultry, fat	0.05
Poultry meat byproducts	0.01
Eggs	0.02
Cattle, meat	0.01
Cattle, liver	0.20
Cattle, fat	0.02
Cattle, meat byproducts (except liver)	0.01
Milk	0.01
Milk, fat	0.25
Goat, meat	0.01
Goat, liver	0.20
Goat, fat	0.02
Goat, meat byproducts (except liver)	0.01
Hog, meat	0.01
Hog, liver	0.05
Hog, fat	0.01
Hog, meat byproducts (except liver)	0.01
Horse, meat	0.01
Horse, liver	0.20
Horse, fat	0.02
Horse, meat byproducts (except liver)	0.01
Sheep, meat	0.01
Sheep, liver	0.20
Sheep, fat	0.02
Sheep, meat byproducts (except liver)	0.01

Summary of Data Needs

●Revised labels excluding all turf uses
●Revised Section F
●Revised Section B:

(1) pecan: revised label should be submitted which indicates a PHI of 30 days, spray volumes of >100 GPA for ground applications and >10 GPA for aerial applications, and removes references concerning the addition of a surfactant to the spray solution;

(2) peanut: Revised label should be submitted which prohibits the feeding of peanut hay to livestock and removes references concerning the addition of a surfactant to the spray solution;

(3) sugar beet: Revised label should be submitted which removes references concerning the addition of a surfactant to the spray solution; and

(4) soybean: Revised Section B which is consistent with the use directions provided in the email dated 20-June-2006 from Mel Graben (Isagro USA) to Lisa Jones (EPA/OPP/RD), Based on advice from the ChemSAC (minutes of 7-Jun-2006) and the magnitude of the residue studies, the following revisions should be included on the label:
(a) since the magnitude of the residue studies employed a final application at the R5 crop growth stage, replace the proposed restriction, "Do not apply Domark at or after growth stage R6 (full seed)" with, "Do not apply after soybean growth stage R5 (beginning seed)";
(b) since the magnitude of the residue studies did not include an adjuvant in the spray solutions, information concerning the addition of a adjuvant to the spray solution should be removed from the label; and
(c) include the following restriction, "Do not use on vegetable soybean varieties grown for their immature pods."

●Storage Stability Data: HED requests that the petitioner submit additional data determining the storage stability of T in soybean seed, AGF, meal, and hulls (487 days).
●Field Trial Data: HED requests that the petitioner reanalyze the soybean field trial and processing samples using a method capable of quantitatively determining residues of tetraconazole *per se* (storage stability data are also required).

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

Tetraconazole is registered for application to sugar beet (regional registration) and soybean (Section 18 registration). The petitioners request Section 3 registrations for sugar beet (national registration), pecan, soybean, peanut, and turf. The registered sugar beet and soybean application scenarios are nearly identical to that being currently recommended with the exception that the registered soybean Section 18 application scenario does not include a restriction prohibiting application to soybean intended for the fresh market. The proposed labels include a 24-hour REI and indicate that as a resistance management strategy, tetraconazole should be applied in alternate applications or in combination with non-DMI fungicides. Table 2.1 is a summary of the proposed application scenarios.

Table 2.1. Proposed Application Scenarios.					
Formulation	Single Rate (lb ai/acre)	No. Apps.	RTI (days)	PHI (days)	Comments
PECAN					
Eminent® 125SL Fungicide (water soluble liquid; 1 lb ai/gallon; EPA Reg. No. 60063-12))	0.125	8	14-21	14	-ground, aerial, and chemigation applications are permitted in spray volumes sufficient to provide complete coverage -addition of a surfactant is acceptable
SOYBEAN					
Domark® 230ME Fungicide (1.9 lb ai/gallon; label dated 19-Jun-2006)	0.075	2	15-21	not specified	-ground (10-20 GPA) and aerial (minimum of 5 GPA) applications are permitted (chemigation prohibited); addition of an adjuvant, including a nonionic surfactant at 0.125% (v/v), is acceptable -applications are to be made from the R3 (beginning pod) to R6 (full seed) growth stages -the harvesting of treated immature soybeans for consumption is prohibited -crops other than soybean or sugar beet may not be grown within 120 days from the last application -the grazing or feeding of forage or hay to livestock is prohibited.
SUGARBEET					
Eminent® 125SL Fungicide (1 lb ai/gal; EPA Reg. No. 60063-12))	0.10	2	21-28	14	-addition of a surfactant is acceptable -ground, (5-150 gallons per acre (GPA)), aerial (5-10 GPA), and chemigation applications are permitted -crops other than sugar beet must not be grown within 120 days following the last application
PEANUT					
Eminent® 125SL Fungicide (1 lb ai/gal; EPA Reg. No. 60063-12))	0.10	4	14	14 days before digging	-addition of a surfactant is acceptable -ground, (5-150 gallons per acre (GPA)), aerial (5-10 GPA), and chemigation applications are permitted -crops other than peanuts must not be grown within 120 days following the last application
TURF					
Eminent® 125SL Fungicide (1 lb ai/gal; EPA Reg. No. 60063-12))	1.4	N.S.	N.S.	N/A	-groundboom and high-pressure hand wand application mainly expected

N.S.: Not specified.

HED requests that the petitioners submit revised labels with the following changes:

Turf: Revised label should be submitted excluding all uses on turf.

Pecan: Revised label should be submitted which indicates a PHI of 30 days, spray volumes of >100 GPA for ground applications and >10 GPA for aerial applications, and removes references concerning the

addition of a surfactant to the spray solution.

Peanut: Revised label should be submitted which prohibits the feeding of peanut hay to livestock and removes references concerning the addition of a surfactant to the spray solution.

Sugar Beet: Revised label should be submitted which removes references concerning the addition of a surfactant to the spray solution.

Soybean: Revised Section B which is consistent with the use directions provided in the email dated 20-June-2006 from Mel Graben (Isagro USA) to Lisa Jones (EPA/OPP/RD). Based on advice from the Chemistry Science Advisory Council (ChemSAC; minutes of 7-Jun-2006) and the magnitude of the residue studies, the following revisions should be included on the label: **(1)** since the magnitude of the residue studies employed a final application at the R5 crop growth stage, replace the proposed restriction, "Do not apply Domark at or after growth stage R6 (full seed)" with, "Do not apply after soybean growth stage R5 (beginning seed)"; **(2)** since the magnitude of the residue studies did not include an adjuvant in the spray solution, information concerning the addition of a adjuvant to the spray solution should be removed from the label; and **(3)** include the following restriction, "Do not use on vegetable soybean varieties grown for their immature pods."

2.2 Tetraconazole Structure and Nomenclature

Table 2.2.1 is a summary of the tetraconazole nomenclature and Table 2.2.2 is a summary of the physical/chemical properties. Chemical structures for degradation products are show in Attachment 1.

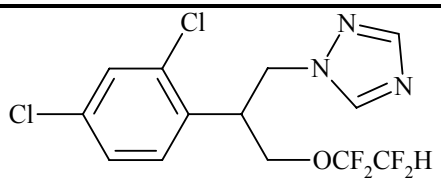
Table 2.2.1. Test Compound Nomenclature.	
Chemical Structure	
Common name	Tetraconazole
Company experimental name	None Specified in Submission
IUPAC name	(±)-2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propyl-1,1,2,2-tetrafluoroethyl ether
CAS name	1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy) propyl]-1*H*-1,2,4-triazole
CAS #	112281-77-3
End-use product/EP	Domark™ 230 ME® Fungicide (1.9 lb ai/gal, new end-use product registration 80289-T); Eminent® 125SL Fungicide (1 lb ai/gal, EPA Reg. No. 60063-12))

Table 2.2.2. Physicochemical Properties of the Technical Grade Tetraconazole.		
Melting point/range	Not applicable - test substance is a viscous liquid	MRID 44268104; D259842, B. Kitchens, 04/11/2000.
pH	5.48 in DI H_2O 5.47 for saturated solution at 20°C	
Density	1.4382 g/ml at 20°C 1.4252 g/ml at 30°C	
Water solubility (PAI >94.16%)	159.31 mg/L at 25°C	
Solvent solubility	not available	
Vapor pressure (PAI >99.65%)	0.13 x 10^2 Pa at 35.5°C 0.58 x 10^2 Pa at 46.5°C 2.985 x 10^2 Pa at 60°C	MRID 44305301; D259842, B. Kitchens, 04/11/2000.
Dissociation constant (K_a)	0.158 - 0.316	MRID 46055603; D294198, B. Kitchens, 01/26/2004.
Octanol/water partition coefficient (PAI >99.65%)	log P_{ow} = 3.53 at 25°C	MRID 44305301; D259842, B. Kitchens, 04/11/2000.
UV/visible absorption spectrum	not available	

3.0 Hazard Characterization/Assessment

On May 13, 2004, the HED Hazard Identification Assessment Review Committee (HIARC) re-reviewed the recommendations of the toxicology reviewer for tetraconazole with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments established previously September 14, 1999 (when tetraconazole was first evaluated by HIARC). The potential for increased susceptibility of infants and children from exposure to tetraconazole was also addressed as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

On November 10, 1999, the HED Cancer Assessment Review Committee met to consider and evaluate the carcinogenic potential of tetraconazole. The conclusions of the HIARC and CARC and hazard assessment team are reflected in this risk assessment.

3.1 Hazard and Dose-Response Characterization

3.1.1. Database Summary

The toxicology database for tetraconazole is complete and deemed adequate for evaluating risk assessments and for FQPA evaluation. The toxicology data requirements (40 CFR 158.340) for tetraconazole's food uses are complete. The DNT study is not required.

3.1.1.1. Studies Available and Considered

Acute- oral, dermal, inhalation, eye irritation, skin irritation, dermal sensitization
Subchronic- 21/28 day dermal toxicity in rat, oral 90-day rat, oral 90-day mouse
Chronic- oral rat (combined chronic/carcinogenicity), oral carcinogenicity in mice and oral dog
Reproductive/developmental- oral developmental rat and rabbit, rat reproduction/fertility
Other- mutagenicity studies (*in vitro and in vivo*), metabolism/pharmacokinetics studies and liver enzyme induction studies (2 studies).

3.1.1.2. Mode of Action, Metabolism and Toxicokinetic Data

Tetraconazole is a systemic fungicide and is a member of the conazole/triazole class of pesticides. Like all other triazoles, tetraconazole belongs to the SBI (Sterol Biosynthesis Inhibitors) group; it acts by inhibiting the metabolic pathway leading to fungal sterol production, thus blocking the lanosterol demethylation reaction. Its inhibitory action, in fungi, causes an accumulation of anomalous 14C-methylated sterols, a corresponding reduction of ergosterol, which badly affects fungal cell membranes making them no longer functional.

3.1.1.3. Sufficiency of Studies/Data

The toxicity database is complete for tetraconazole and is adequate for risk assessment evaluations and determination of the FQPA safety factor. All studies evaluated were deemed acceptable and met guideline criteria.

3.1.2. Toxicological Effects - Data Summary and Toxicity Profile

Tetraconazole has low acute toxicity via the oral, dermal, and inhalation routes. It is a slight eye irritant, but is not a dermal irritant or a dermal sensitizer.

The liver and kidney are the primary target organs of tetraconazole. In the subchronic, chronic, and reproduction rat studies, subchronic and carcinogenicity mouse studies, and the chronic dog study increases in liver weight, increases in liver serum enzymes, or gross and microscopic liver pathology were noted at various doses, providing evidence of liver toxicity.

In all of the above studies, except the subchronic mouse study, increases in kidney weight or gross pathology and cortical tubular hypertrophy (dog) were noted at various doses, indicating renal toxicity.

Certain changes in multiple organs were seen in the database that may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

Long-term dietary administration of tetraconazole resulted in an increased incidence of combined benign and malignant liver tumors in mice of both sexes. The levels of the doses tested were adequate. No tumors were noted in male or female rats after long-term dietary administration of tetraconazole. The HED Cancer Assessment Review Committee (November 10, 1999) classified tetraconazole as **"likely to be carcinogenic to humans "** by the oral route based on the occurrence of liver tumors in male and female mice, in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999). For the quantification of human cancer risk, the Committee recommended a linear low-dose extrapolation approach based on the incidence of combined liver tumors in male or female mice, whichever is more potent.

Tetraconazole did not show evidence of mutagenicity in *in vitro* or *in vivo* studies.

Oral rat and rabbit developmental studies showed no increased susceptibility of the fetus to tetraconazole *in utero*. Maternal toxicity and developmental toxicity occur at the same dose level of 100 mg/kg/day in the rat study. No developmental toxicity was seen in the rabbit study with the maternal toxicity level noted at the highest dose tested (30 mg/kg/day). In the developmental toxicity study in rats, the maternal toxicity was manifested as decreased body weight gain, food consumption, increased water intake, increased liver and kidney weights. Developmental toxicity in rats consisted of increased incidence of supernumerary ribs. Increased incidences of hydroureter and hydronephrosis seen at 100 mg/kg/day exceeded the high end value of the historical control range.

A two-generation rat reproduction study also revealed no increased susceptibility to offspring. Decreased litter weight and mean pup weight and increased liver weight were noted at a dose of 35.5 mg/kg/day in males and 40.6 mg/kg/day in females while parental toxicity resulted in decreased body weight gain and food consumption during pre-mating, increased relative liver and kidney weights, hepatocellular hypertrophy, and gastric irritation in males and females at the LOAEL of 35.5 mg/kg/day (males) and 40.6 mg/kg/day (females).

No evidence of neurotoxicity was noted in any oral study. No acute or subchronic neurotoxicity studies were submitted.

Rat metabolism data indicate that tetraconazole is well absorbed from the gastro-intestinal tract and almost 100% of the administered dose was recovered in urine (52-76%) and feces (12-36%) and less than 6% (2.8-5.8%) of the administered dose remained in the carcass/tissues within 72 hours post-dosing. There was no major difference in absorption and elimination of tetraconazole between sexes and dose

levels. Position of labeling [^{14}C-phenyl or ^{14}C-triazole] resulted in slight differences in the blood time to reach maximum (T_{max}) levels and $T_{1/2}$ lives between sexes and doses. Males had slightly higher T_{max} levels than females. Metabolic identification revealed triazole as the major urinary and fecal metabolite.

Table 3.1.2a. Acute Toxicity of Tetraconazole.

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
870.1100 (81-1)	Acute Oral (rat)	44268112	LD_{50} = 1031 mg/kg	III
870.1200 (81-2)	Acute Dermal	44335501	LD_{50} > 2000 mg/kg	III
870.1300 (81-3)	Acute Inhalation	44305302	LC_{50} > 3.66 mg/L	IV
870.2400 (81-4)	Primary Eye Irritation	44335502	Slight eye irritant	III
870.2500 (81-5)	Primary Skin Irritation	44335503	not a dermal irritant	IV
87.2600 (81-6)	Dermal Sensitization	44268113	not a dermal sensitizer	NA

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 4-Week Oral toxicity rodents (rat)	44751304 (1988) Acceptable/non-guideline 0, 70, 200, or 500 mg/kg/day via gavage	NOAEL was not established. LOAEL = 70 mg/kg/day, based on decreased body weight gains in and increased liver weights both sexes, and increased kidney weights in males and ovary weights in females.
870.3100 4-Week Oral toxicity rodents (rat)	44751305 (1988) Acceptable/nonguideline 0, 40, 160, 640, 2500 or 10000 ppm M: 0, 4.4, 17.5, 68.4, 229 mg/kg/day; F: 0, 3.8, 16.1, 62.3, 217 mg/kg/day	NOAEL = not established (M), 3.8 (F) mg/kg/day LOAEL = 4.4/15.3 (M/F) mg/kg/day, based on increased liver weights, enlarged livers and enlarged centrilobular hepataocytes.
870.3100 4-Week Oral toxicity rodents (rat)	44751306 (1989) Acceptable/nonguideline 0, 2, 5, 15 or 40 ppm M: 0, 0.21, 0.52, 1.57 or 4.19 mg/kg/day	NOAEL = 4.19 mg/kg/day(M) LOAEL was not established.
870.3100 90-Day oral toxicity rodents (rat)	44335504 (1988) Acceptable/guideline 0, 10, 60, or 360 ppm M : 0, 0.7, 4.1, or 23.9 mg/kg/day F: 0, 0.9, 5.5, or 28.7 mg/kg/day	NOAEL = 4.1/5.5 mg/kg/day (M/F) LOAEL = 23.9/28.7 (M/F) mg/kg/day, was based upon increased body weight gains in males, decreased body weight gains in females, increased absolute and liver weights in both sexes, enlarged livers in males, enlarged centrilobular hepatocytes in males and females.
870.3100 90-Day oral toxicity rodents (mice)	44778701 (1989) Acceptable/guideline 0, 5, 25, 125, or 625 ppm M : 0, 1, 4, 16, or 85 mg/kg/day F: 0, 1, 4, 20, or 103 mg/kg/day	NOAEL = 4 mg/kg/day (M/F) LOAEL = 16/20 mg/kg/day, based on single liver cell degeneration in males, and increased SGPT and SGOT, decreased BUN levels, increased absolute and relative liver weights and presence hepatocellular single cell necrosis in females.
870.3150 90-Day oral toxicity in nonrodents (dog)	NA	NA

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3200 21/28-Day dermal toxicity (rabbit)	44751307 (1992) Acceptable/guideline 0, 250, 100 or 2000 (formulation) mg/kg/day Actual a.i 0, 30.1, 120.4 or 241 mg/kg/day	Systemic Toxicity NOAEL = 241 (a.i) mg ai/kg/day LOAEL was not established Dermal Toxicity NOAEL= not established LOAEL = 30 (a.i) mg/kg/day, based on dermal irritation.
870.3250 90-Day dermal toxicity	NA	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental in rodents (rat)	44335505 (1990) Acceptable/guideline F: 0, 5, 22.5, or 100 mg/kg/day (GD 2-15)	Maternal NOAEL = 22.5 mg/kg/day LOAEL = 100 mg/kg/day, based on decreased body weight gain, and food consumption and increased water intake, and increased liver and kidney weights. Developmental NOAEL = 22.5 mg/kg/day LOAEL = 100 mg/kg/day, based on increased incidence of small fetuses, supranumerary ribs and hydroureter and hydronephrosis.
870.3700b Prenatal developmental in nonrodents (rabbit)	44335506 (1990) Acceptable/guideline F: 0, 7.5, 15, or 30 mg/kg/day	Maternal NOAEL = 15 mg/kg/day LOAEL = 30 mg/kg/day, based upon decreased body weight gain. Developmental NOAEL = 30 mg/kg/day LOAEL was not established
870.3800 Reproduction and fertility effects (rats)	44305306 (1991) Acceptable/guideline 0, 10, 70, and 490 ppm M: 0, 0.7, 4.9, and 35.5 mg/kg/day F: 0, 0.8, 5.9, and 40.6 mg/kg/day	Parental/Systemic NOAEL = 4.9/5.9 mg/kg/day (M/F) LOAEL = 40.6/35.5 mg/kg/day (M/F), based on decreased body weight gain and food consumption during pre-mating, increased relative liver and kidney weights, hepatocellular hypertrophy, and gastric irritation in males and females. Reproductive NOAEL = 40.6/35.5 mg/kg/day (M/F) LOAEL = Not established. Offspring NOAEL = 5.9 mg/kg/day LOAEL = 35.5/40.6 mg/kg/day (M/F), based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters.

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined chronic toxicity/carcinogenicity rodents (rat)	44305304 (1992) Acceptable/guideline M: 0, 10, 80, 640 or 1280 ppm F: 0, 10, 80, 640 ppm M: 0, 0.4, 3.4, 27.7, or 59 mg/kg/day F: 0, 0.6, 4.4, or 39.4 mg/kg/day	NOAEL = 3.4/4.4 mg/kg/day (M/F) LOAEL = 27.7/39.4 (M/F), based upon histopathology of the bone (osseous hypertrophy of the cranium/parietal bone), pale and thickened incisors, and decreased absolute and relative adrenal and pituitary weights in males; decreased body weight (at terminal sacrifice) in females. Dosing was considered adequate. No treatment-related increases in tumor incidence was observed.
870.4100b Chronic toxicity dogs	44305303 (1990) Acceptable/guideline M & F: 0, 22.5, 90 or 360 ppm. M: 0, 0.73, 2.95 or 12.97 mg/kg/day F: 0, 0.82, 5.9, or 40.6 mg/kg/day	NOAEL = 0.73/0.82 (M/F) mg/kg/day LOAEL = 2.95/3.33 (M/F), based upon increased absolute and relative kidney weights and histopathological changes in the male kidney.
870.4300 Carcinogenicity mice	44305305 (1998) Acceptable/guideline 0, 10, 90, 800, or 1250 ppm M: 0, 1.4, 12, 118, or 217 mg/kg/day F: 0, 1.6, 14.8, 140, or 224 mg/kg/day	NOAEL = 1.4/1.6 (M/F) mg/kg/day LOAEL = 12/14.5 (M/F), based upon increased liver weights and hepatocellular vacuolation in both sexes and increased kidney weights in males. Dosing was considered adequate based on above findings. Treatment-related increased incidence of combined benign and malignant liver tumors in both sexes.
Gene Mutation 870.5265 reverse gene mutation assay in bacteria	44335511 (1987) Acceptable/guideline 125-2000 µg/plate ± S9 activation.	Cytotoxicity was evident for the majority of strains at ≥1000 µg/plate -S9 and at 2000 µg/plate +S9. There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5300 forward gene mutation assay in mammalian cells	44335508 (1988) Acceptable/guideline 5-125 µg/mL ± S9 activation.	Cytotoxicity was observed in all trials at ≥ 100 µg/mL +/- S9. There was no indication that M 14360 induced a mutagenic response, either in the presence of absence of S9 activation.

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5375 in vitro mammalian cytogenetic assay	44335507 (1989) Acceptable/guideline 0.5-250 µg/mL ± S9 activation.	Cytotoxicity was observed at ≥31.3 µg/mL -S9 (6-hr. treatment and 24-hr. cell harvest or 24 hrs. of continuous treatment before sampling); ≥15 µg/mL -S9 (48 hrs of continuous treatment before sampling) and at ≥15.6 µg/mL +S9 (6-hr. treatment and a 24-hr. cell harvest). Not clastogenic with or without S9 activation, at any dose tested.
Other Effects 870.5395 in vivo mammalian cytogenetic assay	44335509 (1989) Acceptable/guideline 0, 185, 370 or 740 mg/kg	Did not induce micronucleated polychromatic erythrocytes (MPEs) in bone marrow at any dose. The test material was not cytotoxic to the target tissue.
Other Genotoxic Effects 870.5550 UDS synthesis in mammalian cell culture	44335510 (1989) Acceptable/guideline 0.25-512 µg/mL ± S9 activation	Cytotoxicity was evident in all trials at ≥64 µg/mL +/-S9. The positive controls induced significant and dose-related increases in UDS. No evidence of genotoxic effect under any test condition.
870.6200a Acute neurotoxicity screening battery	NA	NA
870.6200b Subchronic neurotoxicity screening battery	NA	NA
870.6300 Developmental neurotoxicity	NA	NA
870.7485 Metabolism and pharmacokinetics (rat)	44305307 (1993) Acceptable/guideline M & F: 14C-phenyl]tetraconazole or [14C-triazole]tetraconazole were given single gavage dose of 5 or 60 mg/kg.	About 92.0-100.7% of the administered dose was recovered in urine, feces, and tissues within 72 hours of dosing. Absorption of [14C]tetraconazole from the G.I. tract of rats was evident in both low- and high-dose animals based on the high level of urinary excretion, which ranged from 50.7-71.0% by 48 hours post-dose. Only minor differences were noted in the pattern of excretion between the sexes, labels, and dose levels. About 3-6% of the dose was recovered in the carcass/tissues. Differences were noted maximum blood concentrations between the doses, sexes and label. No differences were noted in the half-life.

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics (rat)	45068403 (1992) Acceptable/guideline for excretion, distribution and metabolic identification portion of the study. Single oral doses of [14C] triazole ring labeled M-14360 administered at dose levels of 5 or 60 mg/kg, urine and feces were collected from five rats/sex/dose for 168 hours at which time these animals were killed and their tissues and organs were harvested. The remaining five animals/sex/group were killed at peak blood levels of radioactivity occurring at 8-28 hours of post dosing and their tissues and organs were harvested. Radioactivity was measured in urine, feces, blood, tissues, organs, carcasses and cage washes from all animals.	Total recovery of radioactivity ranged from 95% to 102% of the administered dose. Most of the dose (75%) was recovered in the urine after 7 days. Feces accounted for 15 to 18% of the administered dose. Triazole was the major metabolite identified in the urine and feces. In the urine M-14360 acid along with minor metabolite of M-14360 alcohol and its glucuronide conjugate (M3) were isolated. In the feces minor amounts of parent M-14360, the acid and alcohol were isolated. Data suggest M-14360 or its metabolites do not accumulate in the tissues following single oral administration. 95-98% of the urinary and fecal metabolites were identified. There is a qualitative and quantitative difference in the metabolites in the males and females and the dose levels. Male rats produced more triazole than females (65-67% of the AD vs. 48% in females) in the urine, while urine of females had more of M-14360 acid. The same pattern was also seen in the multiple dosing studies, although the differences were not pronounced. In the multiple dosing studies, triazole (3.2-3.9% of the AD for males and females at the low dose vs. 6.5-6.8% for the high dose), M-14360 acid, M-14360 alcohol, M-14360, M6 and others were reported while in the single dosing only triazole (5.6-10.4% of the administered low and high doses in both sexes), M-14360 acid and M-14360 were reported. Based on the results, the study authors postulated that cleavage of M-14360 to yield triazole appears to be a major step through glutathione mediated path. A metabolic pathway was proposed where the initial step is the formation of an aldehyde intermediate of M-14360 following dealkylation of the fluoro-alkyl group of the molecule.

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics (rat)	44268114 (1990) Acceptable/guideline for single dose excretion and distribution Single oral doses of 14C-Tetraconazole phenyl labeled or triazole ring labeled were administered at dose levels of 5 or 60 mg/kg, urine, feces and expired air were collected for 168 hours and radioactivity in blood, tissues, organs, carcass and cage washes were determined.	Total recovered radioactivity ranged from 99% to 114% for the phenyl label and 96% to 109% for the triazole label of the administered dose (AD). Most of the radioactivity was recovered in the urine, particularly the triazole label. In the triazole study, males excreted the radio label into the urine more and faster than in the females. Compared to the phenyl label, more of the triazole label was excreted at both doses in the urine. Radioactivity in the tissues was minimal and accounted for less than 1% in the phenyl label. For the triazole label 0.9% to 1.4% radioactivity was recovered in tissues. In the feces, more phenyl label (21-32%) than in the triazole label (12-16% of the AD) radioactivity was excreted. Male rats generally excreted the radiolabel into the feces faster than in the females for both labels.
870.7485 Metabolism and pharmacokinetics (rat)	44268119 (1994) Acceptable/guideline for excretion and distribution of triazole labeled M-14360 following repeated oral administration. Groups of rats received single oral dose of nonradiolabeld M 14360 at 5 or 60 mg/kg for 14 days followed by single oral dose of [14C] triazole ring labeled M 41360; animals were placed metabolism cages where urine and feces were collected and radioactivity in blood, tissues, organs, carcass and cage washes were determined upon sacrifice.	The test material was readily absorbed and distributed in the body within 8 hours after dosing and about 100.9 ± 4.0% of the administered dose was recovered. Urine was the major route of excretion accounting for nearly 87% of the AD after 7 days of exposure. Most of the urinary radioactivity was excreted during the first 48 hours. Fecal elimination of the radioactivity was the next major route accounting for 12-16% of the AD after 7 days of exposure. Less than 1% of the AD was recovered in tissues. Sex has no effect on excretion and distribution.
870.7600 Dermal penetration	NA	NA

Table 3.1.2b. Subchronic, Chronic and Other Toxicity.		
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Non-guideline - rats Liver enzyme induction	44751310 (1998) Acceptable/nonguideline In diet at doses of 0, 10, 80, 640 ppm; the positive control was Phenobarbital (Na) salt, 75 mg/kg/day for 4 weeks.	Dietary administration of tetraconazole for 4 weeks results in liver enzyme induction at dose levels of 80 and 640 ppm. Induction at the 640 ppm dose level was similar to that induced by phenobarbital at 75 mg/kg/day.
Non-guideline - mice Liver enzyme induction	44751309 (1996) Acceptable/nonguideline In diet at doses of 0, 20, 800, 1250 ppm in the diet; the positive control was Phenobarbital (Na) salt, 75 mg/kg/day for 4 weeks.	Tetraconazole administration for 4 weeks results in liver enzyme induction. At doses ≥ 20 ppm in females an apparent increases in microsomal protein, cytochrome P450, and ethylmorphine N-demethylase were observed. At all dose levels in males and females, 7-pentoxyresorufin O-depentylase values were statistically elevated. At 800 and 1250 ppm, statistically significant findings were typically noted. However, dose-response increases were not apparent in these findings at the 1250 ppm level as compared to the lower 800 ppm level.

[1] Study requirement satisfied by chronic dog study

3.1.3 Dose-Response

The liver and kidney are the primary target organs of tetraconazole. After exposure to tetraconazole, the dog appears to be the most sensitive species with regard to nephrotoxicity, while rats and mice appear to be more susceptible to hepatotoxicity. Subchronic studies (90-day) in rats and mice resulted in NOAELs (4.1 and 4.0 mg/kg/day, respectively), with treatment-related hepatotoxicity noted in rats and hepatotoxicity and limited evidence of nephrotoxicity noted in mice. Subchronic toxicity study in dogs is not available. Chronic exposure to tetraconazole in dog produced hepatotoxicity at the highest dose tested (HDT; 12.97 mg/kg/day). Hepatotoxicity was also observed in rats and mice after chronic exposure to tetraconazole at doses of 59 and 12 mg/kg/day, respectively. In rats, chronic exposure to tetraconazole did not produce any tumors where as in mice, it produced benign and malignant liver tumors.

Certain changes in multiple organs were seen in the database that may be due to various mechanisms including possible liver-pituitary-thyroid homeostatic disruption or inhibition of steroid synthesis.

3.2 Absorption, Distribution, Metabolism, and Excretion

Several metabolism studies in rats are available to characterize pharmacokinetic and pharmacodynamics profile of tetraconazole following gavage administration. A series of rat metabolism studies with [^{14}C-phenyl]tetraconazole and [^{14}C-triazole]tetraconazole were conducted using a single dose of 5 or 60 mg/kg or pretreatment with tetraconazole at 5 or 60 mg/kg/day for 14 days followed by a radioactive dose. The results of these studies indicated that orally administered tetraconazole was rapidly absorbed, distributed and excreted in rats. The major route of excretion is via urine. Urinary excretion accounted for 70-95% of the administered dose in 7 days depending upon sex, dose and radiolabelling position. Fecal excretion accounted for 12-32% of the administered dose in 7 days depending upon sex, dose and radiolabelling position. Most of the excretion occurred in first 48 to 72 hours. Approximately, 52-76% and 12-36% of the administered dose excreted in urine and feces in 72 hours, respectively. Only minor differences were noted in pattern of excretion between the sexes, dose levels and radiolabelling position. In the [^{14}C-triazole] animals, urinary excretion was higher, while fecal excretion was lower when compared to the [^{14}C-phenyl] animals. Males excreted higher levels of radioactivity in the feces than females. Approximately, 1% of the administered dose remained in the tissues and carcass in 7 days, indicating no significant bioaccumulation of orally administered tetraconazole. Approximately, 2.8-5.8% of the administered dose remained in the tissues and carcass at 72 hours post-dosing. No major differences in absorption, metabolism and excretion were observed in single dose or repeated dose (pretreatment) studies.

Maximum blood concentrations in both sexes were delayed in the [^{14}C-triazole] animals compared to the [^{14}C-phenyl] animals; maximum blood concentrations were slightly higher in the males. Half-lives were shorter in the [^{14}C-triazole] animals compared to the [^{14}C-phenyl] animals. AUC (area-under-the curve) values were higher in the [^{14}C-triazole] animals when compared to the [^{14}C-phenyl] animals. [^{14}C-phenyl] males had lower median AUC values compared to females while the [^{14}C-triazole] males had higher median AUC values compared to females.

No parent compound was identified in urine and a small amount of parent compound was found in the feces. In the urine and fecal samples, triazole was the major metabolite for both dose levels and sexes. M-14360 acid along with minor metabolites of M-14360 alcohol and its glucuoronide conjugate (M3) were also isolated from the urine. In the feces minor amounts of the parent material, M-14360, the acid and alcohol were also isolated. In the multiple dosing, triazole, M-14360 acid, M-14360 alcohol, M-

14360, M6 and others were reported while in the single dosing only triazole, M-14360 acid and M-14360 were reported. It was postulated that metabolism of tetraconazole in the rat may involve cleavage of the molecule between the phenyl and the triazole ring followed by glutathione conjugation of the triazole ring. See Attachment 1 for metabolite structures.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for tetraconazole is adequate for evaluation of the FQPA safety factor. The following acceptable studies are available:

Developmental toxicity study in rats and rabbits
Two-generation reproduction study in rats

3.3.2 Evidence of Neurotoxicity

No acute or subchronic neurotoxicity studies are available for tetraconazole. The HIARC concluded that there is not a concern for neurotoxicity resulting from exposure to tetraconazole since there was no evidence of neurotoxicity in short-term studies in rats, mice and dogs; and long-term toxicity study in dogs. Dorsal compression of the brain was observed in the carcinogenicity studies in rats and mice; however, this effect is not indicative of neurotoxicity and may be attributed to cranial bone thickening.

3.3.3 Developmental Toxicity Studies

Rat: In a developmental toxicity study (MRID 44335505) M 14360 (94.6% ai) was administered to 120 pregnant BR VAF/Plus rats, at dose levels of 0, 5, 22.5, 100 mg/kg/day by oral gavage from days 2 through 15 of gestation. Treatment-related effects noted at 100 mg/kg/day consisted of decreased body weight gain (22%), and food consumption (≥ 23%, increased water intake (9-15%) and increased liver and kidney weights. There was a dose-related increase in the incidence of salivation in the main study and in the range-finding study, however, this effect was considered primarily due to bolus dosing and not treatment-related. No macroscopic changes were noted at post-mortem examination. Exposure to 5 mg/kg/day did not result in any significant maternal toxicity.

Therefore, the maternal toxicity LOAEL is 100 mg/kg/day based on decreased body weight gain (22%), and food consumption (≥ 23%, increased water intake (9-15%) and increased liver and kidney weights. The maternal toxicity NOAEL is 22.5 mg/kg/day.

Developmental toxicity was noted at 100 mg/kg/day and consisted of increased incidence of small fetuses, and supernumerary ribs. Increased incidences of hydroureter and hydronephrosis seen at 100 mg/kg/day exceeded the high end value of the historical control range.

Therefore, the LOAEL and NOAEL for developmental toxicity were 100 and 22.5 mg/kg/day, respectively.

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; §83-3a) in rats.

Rabbit: In a developmental toxicity study (MRID 44335506), M 14360 (94.6% ai) was administered to 16 New Zealand White rabbits/dosed by gavage at dose levels of 0, 7.5, 15, and 30 mg/kg/day from days 6 through 18 of gestation.

Compound-related maternal toxicity was limited to depressed body weight gain during the dosing period from days 6-18 of gestation. No treatment-related effects occurred in mortality, clinical signs, food

consumption, or cesarean parameters**.** The maternal LOAEL is 30 mg/kg/day, based on decreased body weight gain. The maternal NOAEL is 15 mg/kg/day.

No treatment-related effects in developmental parameters were noted. The developmental LOAEL is greater than 30 mg/kg/day. The developmental NOAEL is 30 mg/kg/day.

The developmental toxicity study in the rabbit is classified as acceptable/guideline and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

3.3.4 Reproductive Toxicity Study

In a two-generation reproduction study (MRID 44305306), M 14360 (94.6%) was administered to 28 Crl:CD® (SD) BR VAF/Plus rats/sex/dose (P adults) and 24 Crl:CD® (SD) BR VAF/Plus rats/sex/dose (F1 adults) in the diet at dose levels of 0, 10, 70, and 490 ppm (0, 0.7, 4.9, and 35.5 mg/kg/day for males or 0, 0.8, 5.9, and 40.6 mg/kg/day for females). The study design included a standard reproduction protocol with litters standardized to four animals per sex on Day 4 post-partum and with two matings of the P generation.

Parental toxicity included increased mortality of adult females in the P and F1 generations at 490 ppm, decreased body weight gain and food consumption at premating for P females and both F1 sexes at 490 ppm, increased absolute and relative liver weights of both P and F1 sexes at 490 (except absolute liver weights in F1 males), increased relative kidney weights in P females and both F1 sexes at 490 ppm, compound-related mortality of one P female at 70 ppm, increased relative liver weights of F1 females at 70 ppm, and increased incidence of centrilobular hepatocyte enlargement in both P and F1 sexes at 490 ppm. No concomitant liver pathology was noted in the F1 females at 70 ppm.

Offspring toxicity included decreased litter weight and mean pup weight of F_1A, F_1B, and F_2 litters at 490 ppm and increased relative liver weights of both sexes in all litters at 490 ppm. Increased relative liver weights of F_1B and F_2 female pups at 70 ppm were noted, but since no histopathology was performed on the weanling pups, verification of these changes as adverse could not be achieved.

Reproductive toxicity included increased incidences of peri-parturient mortality associated with dystocias at 490 ppm in P and F1 females and evidence of increased gestation intervals at 70 and 490 ppm in P females. Also, one F1 dam at 70 ppm and two F1 dams at 490 ppm showed a 24-day gestation period which further indicated an effect on the parturition process.

The LOAEL for parental toxicity was 490 ppm (35.5 mg/kg/day in males and 40.6 mg/kg/day in females) based on decreased body weight gain and food consumption during pre-mating, increased relative liver and kidney weights, hepatocellular hypertrophy, and gastric irritation in males and females. The NOAEL was 70 ppm (4.9 mg/kg/day in males and 5.9 mg/kg/day in females).

The LOAEL for offspring toxicity was 490 ppm (40.6 mg/kg/day) based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters. The NOAEL was 70 ppm (5.9 mg/kg/day).

The LOAEL for reproductive toxicity was 70 ppm (4.9 mg/kg/day for males and 5.9 mg/kg/day for females) based on increased mean gestation duration in P parental females and related evidence of compound toxicity on the parturition process. The NOAEL was 10 ppm (0.7 mg/kg/day for males and 0.8 for females).

The reproductive study in the rat is classified as **acceptable/guideline** and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

3.3.5 Pre-and/or Postnatal Toxicity

The HIARC concluded that there is no concern for pre- and/or postnatal toxicity resulting from exposure to tetraconazole (TXR No. 0052657).

3.3.5.1 Determination of Susceptibility

There is no evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to tetraconazole. In the developmental toxicity study in rats, developmental effects were seen at the same dose that induced maternal toxicity. In the developmental toxicity study in rabbits, no developmental toxicity was seen at the highest dose tested. In the two-generation reproduction study, offspring toxicity occurred at doses higher than the dose that induced parental/systemic toxicity.

3.3.5.2 Degree of Concern Analysis and Residual Uncertainties

Since there is no evidence of increased susceptibility, there are no concerns or residual uncertainties for pre and/or post-natal toxicity.

3.3.6 Recommendations for a Developmental Neurotoxicity (DNT) Study

The HIARC concluded that there is no need for the DNT Study (TXR No. 0052657). This decision was based on the following:

- No evidence of increased susceptibility to the developing fetus due to *in utero* and pre-natal and post-natal exposure to tetraconazole.
- No apparent neurotoxic effects in guideline studies. No oral toxicity studies showed evidence of neurotoxicity. No neurotoxicity studies were submitted.
- No CNS signs seen in developmental studies. No evidence of CNS signs or neurotoxicity was seen in any of the developmental or reproduction studies. LOAEL effects were increased incidence of small fetuses, supernumerary ribs, decreased litter weight and mean pup weight, and increased pup liver weight.
- No evidence of neuropathology in the subchronic and chronic oral toxicity studies.

3.4 Safety Factor for Infants and Children

It is recommended that the 10X FQPA safety factor for the protection of infants and children be reduced to 1X since there is no evidence of increased susceptibility and there are no concerns or residual uncertainities for pre and/or post-natal toxicity. In addition, the toxicity database for tetraconazole is complete and a DNT study is not required.

- The dietary food exposure assessment is not likely to underestimate exposure/risk.
- The dietary drinking water 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.
- The residential exposure assessment was conducted using standard assumptions which are based on carefully reviewed data.

3.5 Hazard Identification and Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – (Females 13-50)

Study Selected: Prenatal Oral Developmental/ Rat OPPTS 870.3700(§83-3a)

MRID No.: 44335505

Dose and Endpoint for Establishing aRfD: Developmental NOAEL = 22.5 mg/kg/day, based on increased incidence of supernumerary ribs at 100 mg/kg/day (LOAEL).

Comments on Study/Endpoint/Uncertainty Factors**:** The endpoint chosen, supernumerary ribs, was presumed to occur following a single exposure during the period of organogenesis. An UF of 100 was applied to account for inter-species extrapolation (10x) and intra-species variation (10x)

$$\textbf{Acute RfD} = \frac{\text{22.5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.225 mg/kg/day}$$

3.5.2 Acute Reference Dose (aRfD) - General Population

Study Selected: None

MRID No.: None

Dose and Endpoint for Establishing aRfD: None

Comments on Study/Endpoint/Uncertainty Factors**:** An effect of concern attributable to a single exposure (dose) was not identified from the oral toxicity studies including developmental toxicity studies in rats and rabbits.

3.5.3 Chronic Reference Dose (RfD)

Study Selected: Chronic Oral Toxicity (Feeding)/ Dog OPPTS 870.4100(§83-1b)

MRID No.: 44305303

Dose and Endpoint for Establishing RfD: NOAEL of 0.73 mg/kg/day based on increased absolute and relative kidney weights and histopathological changes in the male kidney at 2.95 mg/kg/day (LOAEL).

Uncertainty Factor(s): An UF of 100 was applied to account for inter-species extrapolation (10x) and intra-species variation (10x).

Comments about Study/Endpoint/Uncertainty Factor: The dose (NOAEL) in the chronic study is appropriate for the duration as well as the population of concern.

$$\textbf{Chronic RfD} = \frac{\text{0.73 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.0073 mg/kg/day}$$

3.5.4 Incidental Oral Exposure: Short-and Intermediate-term (1-30 days and 1-6 months)

Study Selected: 2-Gen Reproduction Toxicity Study – Rats (OPPTS 870.3800)

MRID No.: 44305306 & 44751308

Dose and Endpoint for Risk Assessment: Offspring NOAEL is 5.9 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters at the LOAEL of 40.6 mg/kg/day.

Comments about Study/Endpoint: The HIARC did not select the lower parental/systemic NOAEL (0.8 mg/kg/day), since the increased mortality in the F1 females were attributed to difficulty in parturition and thus not relevant for this risk assessment of infant and children. In contrast, the decrease in body weights in offspring is appropriate for this population of concern.

3.5.5 Dermal Absorption

A dermal absorption study on tetraconazole is not available. A dermal absorption factor of 12% was extrapolated by the ratio of the LOAEL of 30 mg/kg/day established in an oral developmental toxicity study in rabbits and the NOAEL of 241 mg/kg/day established in the 21-day dermal toxicity study in rabbits.

30/241 x 100 = 12% dermal absorption factor

The dermal absorption data for compounds structurally related to tetraconazole range from 2-40%. A comparison of the LOAEL (30 mg/kg/day) in an oral developmental toxicity study in rabbits to the NOAEL (241 mg/kg/day; HDT) in the 21-day dermal toxicity study results in a dermal absorption factor of 12%. HED has high confidence in the value obtained with the studies conducted with tetraconazole.

Dermal Absorption Factor: 12%

3.5.6 Dermal Exposure: Short-Term Exposure

Study Selected: 2-Gen Reproduction Toxicity Study - rat OPPTS 870.3800 (§83-4)

MRID No.: 44305306 & 44751308

Dose and Endpoint for Risk Assessment: Offspring NOAEL is 5.9 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters at a LOAEL of 40.6 mg/kg/day.

Comments about Study/Endpoint: No systemic toxicity was seen at 2000 mg/kg/day with the formulation product in the 21-day dermal study with rabbits. This study was not used as the basis for short-term dermal risk assessment because the test material was a formulation product and because the effects seen in the 2-generation reproductive toxicity study were not measured in the dermal study.

A 12% dermal absorption factor should be used in route-to-route extrapolation.

3.5.7 Dermal Exposure: Intermediate-Term and Long-term (1-6 months and > 6 months)

Study Selected: Chronic Oral Toxicity (Feeding)/ Dog OPPTS 870.4100(§83-1b)

MRID No.: 44305303

Dose and Endpoint for Risk Assessment: NOAEL of 0.73 mg/kg/day based on increased absolute and relative kidney weights and histopathological changes in the male kidney at 2.95 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This dose/end-point was selected due to the concern for nephrotoxicity seen in dogs. A 12% dermal absorption factor should be used in route-to-route extrapolation.

3.5.8 Inhalation Exposure: Short –Term (1-30 days)

Study Selected: 2-Gen Reproduction Toxicity Study - rat OPPTS 870.3800 (§83-4)

MRID No.: 44305306 & 44751308

Dose and Endpoint for Risk Assessment: Offspring NOAEL is 5.9 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters at a LOAEL of 40.6 mg/kg/day.

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

3.5.9 Inhalation Exposure: Intermediate-Term and Long-Term (1-6 months and > 6 months)

Study Selected: Chronic Oral Toxicity - dog (OPPTS 870.4100)

MRID No.: 44305303

Dose and Endpoint for Risk Assessment: NOAEL of 0.73 mg/kg/day based on increased absolute and relative kidney weights and histopathological changes in the male kidney at 2.95 mg/kg/day (LOAEL).

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

3.5.10 Margins of Exposures for Occupation/Residential Exposure Risk Assessments

Table 3.5.10. Summary of Levels of Concern for Risk Assessment.			
Route	**Short-Term (1 - 30 Days)**	**Intermediate-Term (1 - 6 Months)**	**Long-Term (> 6 Months)**
Residential			
Dermal	100	100	100
Inhalation	100	100	100
Incidental oral	100	100	100
Occupational Exposure			
Dermal	100	100	100
Inhalation	100	100	100

3.5.11 Recommendation for Aggregate Exposure Risk Assessments

Comparison of the complete toxicity profile across studies indicates that it is appropriate to aggregate risk estimates for short-term oral, dermal, and inhalation routes of exposure and for intermediate- and long-term dermal and inhalation exposures. For short-term aggregate exposure risk assessment, common toxicological endpoints of concern (decreased pup weights and increased liver weights) were selected via the oral, dermal, and inhalation routes. Therefore, these routes (oral, dermal and inhalation) can be combined for short-term exposure duration.

Common toxicological end-points of concern (nephrotoxicity) were also selected for intermediate- and long-term dermal and inhalation routes. Therefore, exposure from these routes can be combined.

3.5.12 Classification of Carcinogenic Potential

On November 10, 1999, in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July 1999; now final March, 2005), the HED Cancer Assessment Review Committee (CARC) classified Tetraconazole as **"likely to be carcinogenic to humans"** based on the occurrence of liver tumors in male and female mice. The CARC recommended that a low dose extrapolation model be applied to the experimental animal tumor data and that quantifications of risk be estimated for male and female mouse liver tumors for tetraconazole. The most potent unit risk will be used for the purpose of lifetime cancer risk assessment by the Agency. In this case, the most potent unit risk, Q1*, is that for male mouse liver benign and/or malignant combined tumor rates at 2.3×10^{-2} $(mg/kg/day)^{-1}$ in human equivalents.

3.5.13 Summary of Toxicological Doses and Endpoints for Tetraconazole Use in Human Health Risk Assessments

Table 3.5.13. Summary of Toxicological Doses and Endpoints for Tetraconazole for Use in 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	None	None	None	An endpoint of concern attributable to a single dose was not identified. An acute **RfD** was not established.
Acute Dietary Females 13-50 years of age	NOAEL=22.5 mg/kg/day	UF_A=10x UF_H=10x SF_{FQPA} = 1	aRfD=0.225 mg/kg/day aPAD= 0.225 mg/kg/day	**Developmental Toxicity Study in Rats** Developmental LOAEL=100 mg/kg/day based on increased incidence of small fetuses and supernumerary ribs.
Chronic Dietary (All Populations)	NOAEL=0.73 mg/kg/day	UF_A=10x UF_H=10x SF_{FQPA} = 1	cRfD = 0.0073 mg/kg/day cPAD = 0.0073 mg/kg/day	**Chronic oral toxicity - dog** LOAEL = 2.95/3.33 (M/F) mg/kg/day, based on absolute and relative kidney weights and histopathological changes in the male kidney.
Incidental Oral Short-Term (1-30 days) And Intermediate-term (1-6 months)	Offspring Toxicity NOAEL = 5.9 mg/kg/day	UF_A=10x UF_H=10x SF_{FQPA} = 1	LOC = 100 (occupational) LOC = 100 (residential)	**Reproductive toxicity - rat** Offspring LOAEL = 35.5 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters.

Dermal Short-Term (1-30 days)	Oral study Offspring Toxicity NOAEL = 5.9 mg/kg/day (dermal absorption rate = 12%)	UF_A=10x UF_H=10x SF_{FQPA} = 1	LOC = 100 (occupational) LOC = 100 (residential)	**Reproductive toxicity - rat** Offspring LOAEL = 35.5 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters.
Dermal Intermediate-Term (1-6 months) And Long-term (>6 months)	Oral study NOAEL=0.73 mg/kg/day (dermal absorption rate = 12%)	UF_A=10x UF_H=10x SF_{FQPA} = 1	LOC = 100 (occupational) LOC = 100 (residential)	**Chronic oral toxicity - dog** LOAEL = 2.95/3.33 (M/F) mg/kg/day, based on absolute and relative kidney weights and histopathological changes in the male kidney.
Inhalation Short- term (1-30 days)	oral study offspring NOAEL = 5.9 mg/kg/day (inhalation absorption rate = 100%)	UF_A=10x UF_H=10x SF_{FQPA} = 1	LOC = 100 (occupational) LOC = 100 (residential)	**Reproductive toxicity - rat** Offspring LOAEL = 35.5 mg/kg/day, based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters.
Inhalation Intermediate-term (1-6 months) And Long-term (>6 months)	oral study NOAEL = 0.73 mg/kg/day (inhalation absorption rate = 100%)	UF_A=10x UF_H=10x SF_{FQPA} = 1	LOC = 100 (occupational) LOC = 100 (residential)	**Chronic oral toxicity - dog** LOAEL = 2.95/3.33 (M/F) mg/kg/day, based on absolute and relative kidney weights and histopathological changes in the male kidney.
Cancer (Adults; dietary, dermal, inhalation)	Classification: **"Likely to be Carcinogenic to Humans."** $Q_1^* = 2.3 \times 10^{-2}$ $(mg/kg/day)^{-1}$ based on male mouse liver benign and/or malignant combined tumor rates.			

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). SF_{FQPA} = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. LOC = level of concern.

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.

4.0 Public Health and Pesticide Epidemiology Data

The following data bases have been consulted for the poisoning incident data on the active ingredient tetraconazole:

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. There were no reports for tetraconazole in the Incident Data System.

2) Poison Control Centers (PCCs) - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 2003 for all pesticides. There were no reports located in the PCC records from 1993 through 2003 involving tetraconazole.

3) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. There were no reports of cases related to tetraconazole.

4) National Pesticide Information Center (NPIC) - NPIC is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, tetraconazole was not reported to be involved in human incidents.

5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) performs standardized surveillance in nine states from 1998 through 2003. States included in this reporting system are Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas, and Washington. Out of 5,899 reported cases from 1998-2003, none involved tetraconazole.

Finally, no scientific literature was found concerning human poisoning or other adverse effects from

exposure to tetraconazole.

There were no reports of ill effects from exposure to tetraconazole in the available data bases. Therefore, no recommendations are made based on the limited information available.

5.0 Dietary Exposure/Risk Characterization

The following references apply to this section:

- Residue Chemistry Summary – Petition 5F6971. D321555, D325322, D329379, D330068, T. Bloem, 1/23/2007.
- Dietary Exposure Analysis- 321637, T. Bloem, 1/23/2007.
- Estimated Drinking Water Concentrations, D321622, D321742, D331420. I. Maher, 27-Nov-2006

5.1 Pesticide Metabolism and Environmental Degradation

A detailed summary of the plant and livestock metabolism studies and the confined rotational crop studies can be found in Appendix B (see Attachment 1 for structures).

5.1.1 Metabolism in Primary Crops

The petitioner submitted sugar beet, wheat, and grape (data presented for the raw agricultural commodity (RAC), wine, and wine sediment) metabolism studies conducted with [triazole-^{14}C]-tetraconazole and [phenyl-^{14}C]-tetraconazole and submitted a soybean metabolism study conducted with [triazole-^{14}C]-tetraconazole (only seed harvest); the metabolism studies employed foliar application with PHIs of 23-60 days. Total radioactive residues (TRRs) did not vary with the radio-label position for all the commodities excluding wheat grain where residues were significantly higher following treatment with the triazole label. TRRs were ≥0.2 ppm in/on all commodities excluding triazole- and phenyl-labeled sugar beet root (1.3x seasonal rate; TRRs = 0.007-0.008 ppm; not analyzed further) and phenyl-labeled wheat grain (2 x 0.11 lb ai/acre; TRRs = 0.091 ppm; analyzed further). The phenyl-labeled sugar beet study also employed a 6.7x application rate with TRRs in sugar beet root of 0.042 ppm (analyzed further).

Tetraconazole was the major identified residue in all analyzed crops (40-82% TRR) excluding triazole-labeled wheat grain and triazole-labeled soybean seed. The major residue identified in triazole-labeled wheat grain was TA (50% TRR; also identified in soybean seed at 14% TRR; not identified in the remaining crops) and the major residue identified in triazole-labeled soybean seed was the glucose conjugate of TA (75% TRR; not identified in the remaining crops). TAA was identified in wheat grain at 25% TRR and in sugar beet leaves at 6% TRR (not identified in the remaining crops) and T and THP were identified in sugar beet leaves at 6-7% TRR (not identified in the remaining crops). Several metabolites were identified in sugar beet root, sugar beet leaves, and wheat straw at combined concentrations of 6-23% TRR (0-day PHI samples excluded; M14360-acid, M14360-DFA, M14360-DCP-OH, M14360-alcohol (free and conjugated), M14360-hydroxydetriazolyl-O-malonydiglucoside, M14360-CP(C-1)-alcohol, M14360-ketone, and M14360(C-1)-alcohol. Total identified residues accounted for 40-95% of the TRR. The grape metabolism studies employed only parent as a reference standard and five unknowns were identified which accounted for a combined 7%, 39%, and 4% TRR in grape, wine, and wine sediment, respectively. HED notes that M14360-CP(C-1)-alcohol, M14360-ketone, and M14360(C-1)-alcohol (identified in wheat straw only at a combined ≤5% TRR) are identical or structurally similar to the propiconazole metabolites CGA-91304 and CGA-91305

The plant metabolism data indicate that tetraconazole is absorbed and distributed throughout the plant. Metabolism of tetraconazole in plants appears to proceed as follows: tetraconazole is oxidized to M14360-DFA followed by hydrolysis to M14360-alcohol which may form a conjugate or be oxidized to M14360-acid. M14360-acid may undergo ring separation to form T or to a lesser extent may undergo oxidative decarboxylation to M14360-ketone followed by reduction to M14360(C-1)-alcohol; the M14360-ketone and M14360(C-1)-alcohol may also undergo ring separation to form T. The free T is readily conjugated with the amino acid, serine/alanine, forming TA which is further metabolized to TAA or THP.

Conclusions: The HED Metabolism Assessment Review Committee (MARC) reviewed the sugar beet (triazole ring labeled study), grape (triazole and phenyl ring labeled studies), and wheat (triazole and phenyl ring labeled studies) metabolism studies (D264157, W. Donovan, 19-Apr-2000). The MARC tentatively concluded that the residue of concern in banana, peanut, and sugar beet was tetraconazole *per se*. This decision was not finalized due to uncertainty concerning the toxicity of the free triazole metabolites, incomplete identification of residues in wheat straw, and the lack of a phenyl-labeled sugar beet metabolism study. HED has subsequently determined that the free triazole metabolites are of toxicological concern (TXR No. 0052011) and received/reviewed the requested metabolism studies.

Based on the results of the metabolism studies and toxicological considerations, HED concludes that the residue of concern for tolerance enforcement in all crops is tetraconazole *per se* and the residues of concern for risk assessment are as follows: (1) shelled pea and bean (succulent and dried): tetraconazole and T, TA, TAA, and all labile conjugates of these compounds and (2) all remaining crops: tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360-hydroxydetriazolyl-O-malonyldiglucoside, and T, TA, TAA and all labile conjugates of these compounds.

HED excluded the non-free triazole metabolites as residues of concern in shelled pea and bean as they were not identified in the [triazole-^{14}C]-tetraconazole soybean seed metabolism study (TRR = 0.452 ppm; 95% of the TRR identified); the non-free triazole metabolites were included as residues of concern in the remaining crops based on toxicological considerations and their identification in the sugar beet root (19% TRR), sugar beet top (16-23% TRR), and wheat straw (3% TRR; not identified in grain; forage was not collected) and since the grape metabolism study included only parent as a reference standard (unknowns were 4-41% TRR in grape, wine, and wine sediment). HED did not include M14360-CP(C-1)-alcohol, M14360-ketone, and M14360(C-1)-alcohol as residues of concern due to differing toxicity of these compounds to parent (see below) and since they were only identified in wheat straw at a combined ≤5% TRR.

5.1.2 Metabolism in Livestock

The petitioner submitted ruminant and poultry metabolism studies conducted with [phenyl-^{14}C]-tetraconazole and [triazole-^{14}C]-tetraconazole (D263068, W. Donovan, 29-Feb-2000; D254411, W. Donovan, 18-May-2000; D279986, W. Donovan, 17-May-2002). Goats were dosed orally for 5 consecutive days at a dietary burden of 0.45 mg/kg/day; hens were dosed orally for 3 consecutive days at a dietary burden of 10 ppm (149x the maximum dietary burden). TRRs were highest in fat followed by liver and lowest in muscle; except for milk and ruminant muscle, the magnitude of the TRRs did not vary with the radiolabled position. For milk and ruminant muscle, TRRs were significantly higher following dosing with triazole-labeled tetraconazole. TRRs in the triazole- and phenyl-labeled milk reached a plateau by day three; a plateau of TRR levels was not reached for triazole- and phenyl-labeled eggs.

Tetraconazole was the principle residue in all commodities (42-105% TRR) excluding triazole-labeled milk and ruminant muscle where T was the principle residue (76-82% TRR). T was also identified in the triazole-labeled ruminant fat (13-28% TRR), ruminant kidney (49% TRR), ruminant and poultry liver (2-8% TRR), poultry muscle (5% TRR), and egg yolk and whites (2-3% TRR). Four additional minor metabolites were identified in ruminant and poultry tissue, egg, and milk: M14360-ketone in ruminant fat, ruminant kidney, ruminant liver, and ruminant muscle (2-4% TRR), M14360-DFA in milk, egg, poultry liver, and poultry muscle (<1-5% TRR), M14360-alcohol in ruminant liver (<0.1% TRR), and M14360-DCP-3OH in poultry liver and poultry muscle (~1% TRR). Based on the identified residues, the metabolic pathway in livestock is similar to that in plants; tetraconazole is oxidized to M14360-DFA followed by hydrolysis to M14360-alcohol. M14360-alcohol undergoes ring separation to form T or is oxidized to M14360-ketone which also may under go ring separation to form T. HED notes that M14360-ketone, which was identified in ruminant tissue (≤4.5% TRR), is structurally identical to the propiconazole metabolite CGA-91304.

Conclusions: The MARC reviewed the goat metabolism studies and tentatively determined that the residues of concern in livestock were tetraconazole and T (D264157, W. Donovan, 19-Apr-2000). This decision was not finalized due to uncertainty concerning the toxicity of T and due to the lack of a poultry metabolism study. HED has subsequently determined that the free triazole metabolites are of toxicological concern (TXR No. 0052011) and received/reviewed the poultry metabolism study. Since the MARC was disbanded prior to the submission and/or review of these data, a final conclusion pertaining to the residues of concern in livestock was not made by the MARC.

Based on the tentative conclusions made by the MARC, the results of the metabolism studies, and toxicological considerations, HED concludes that the residue of concern in livestock for tolerance enforcement is tetraconazole *per se* and the residues of concern for risk assessment are tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360(C-1)-alcohol (free and conjugated), M14360-hydroxydetriazolyl-O-malonyldiglucoside, and T, TA, THP, and TAA and all labile conjugates of these compounds. HED included as residues of concern the free triazole metabolites (excluding T) and non-free triazole metabolites as these were identified as significant residues in plants; T was included as it was a significant metabolite in the metabolism studies.

5.1.3 Metabolism in Rotational Crops

The petitioner submitted a confined rotational crop study conducted with [phenyl-^{14}C]-tetraconazole and [triazole-^{14}C]-tetraconazole (D263068, W. Donovan, 29-Feb-2000; D254411, W. Donovan, 18-May-2000; D267481, W. Donovan, 12-Oct-2000; D278236, W. Donovan, 22-Oct-2001; D282558, W. Donovan, 12-May-2002). Soil was treated with either phenyl- or triazole-labeled tetraconazole at 0.45 lb ai/acre and planted with carrot, lettuce, and wheat at plant-back intervals (PBIs) of 0, 120, and 365 days (≥4.5x/≥1.1x the proposed maximum single/seasonal application rate for rotated crops). The samples were harvested at maturity and analyzed for TRRs (carrot root and top, lettuce, and wheat forage, straw, and grain). TRRs were >0.01 ppm in/on all matrices. TRRs in the samples collected from the triazole plots were >6x the TRRs in samples collected from the phenyl plots for all commodities excluding wheat straw. For wheat straw, TRRs were similar for the two labels at the 30-day PBI and were 2-3x greater in wheat straw collected from the triazole plot at the 120- and 365-day PBIs.

The principle residues in samples collected from the [triazole-^{14}C]-tetraconazole treated field were TA or THP: TA - carrot root, wheat forage, and wheat grain (all PBIs) - 40-67% TRR (3-28% TRR in the remaining crops) and THP - carrot top, lettuce, and wheat straw (all PBIs) - 29-80% TRR (<1-26% TRR in the remaining crops). TAA was also identified as a significant residue in wheat forage, wheat straw, and wheat grain (2-57% TRR; <1% in the remaining crops) and tetraconazole was identified in all of the

crops at 1-11% TRR. Total identified residues accounted for 68-99% TRR.

The major residue identified in samples collected from the [phenyl-^{14}C]-tetraconazole treated field were tetraconazole and M14360-acid: tetraconazole - all crops (all PBIs) excluding 30- and 120-day PBI wheat grain - 40-81% TRR (15-16% TRR in 30- and 120-day PBI wheat grain); M14360-acid - 30- and 120-day PBI wheat grain - 20-23% TRR (<1-15% TRR in the remaining crops). M14360(C-1)-alcohol conjugate (<1-23% TRR all crops/PBIs) and M14360-DFA (<1-11% TRR all crops/PBIs) were identified as significant residues. M14360-alcohol-conjugate and M14360-ketone (free and conjugated) accounted for a combined <1-9% TRR (all crops all PBIs). Total identified residues accounted for 36-97% TRR. HED notes that M14360-ketone (free and conjugated; <1-8% TRR) and M14360(C-1)-alcohol-conjugate (<1-23% TRR) are structurally identical to the propiconazole metabolites CGA-91305 and CGA-91304.

Conclusions: The MARC reviewed the [triazole-^{14}C]-tetraconazole confined rotational crop study summarized above and tentatively determined that the residue of concern in rotational crops is tetraconazole *per se* (D264157, W. Donovan, 19-Apr-2000). This decision was not finalized due to uncertainty concerning the toxicity of the free triazole metabolites and due to the lack of a [phenyl-^{14}C]-tetraconazole confined rotational crop study. HED has subsequently determined that the free triazole metabolites are of toxicological concern (TXR No. 0052011) and received/reviewed the [phenyl-^{14}C]-tetraconazole confined rotational crop study. Since the MARC was disbanded prior to the submission and/or review of these data, a final conclusion pertaining to the residues of concern in rotational crops was not made by the MARC.

Based on the tentative conclusions made by the MARC, the results of the confined rotational crop studies, and toxicological considerations, HED concludes that the residue of concern in rotational crops for tolerance enforcement is tetraconazole *per se* and the residues of concern for risk assessment are tetraconazole, M14360-acid, M14360-DFA, M14360(C-1)-alcohol (free and conjugated), and TA, THP, and TAA and all labile conjugates of these compounds.

HED notes that the triazole- and phenyl- labeled confined rotational crop studies indicated that majority of the residues in rotational crops following application of tetraconazole are the free triazole metabolites. Since the toxicity of the free triazole; M14360(C-1)-alcohol (free and conjugated); and tetraconazole, M14360-acid, and M14360-DFA are different (see below) and based on the magnitude of M14360(C-1)-alcohol (free and conjugated; <1-23% TRR) and tetraconazole (15-81% TRR), M14360-DFA (<1-11% TRR), and M14360-acid (<1-23% TRR) in the phenyl-labeled confined rotational crops study, HED concluded that the non-free triazole metabolites should be included as residues of concern in rotational crops.

5.1.4 Analytical Methodology

The petitioner previously submitted gas chromatograph/electron-capture detector (GC/ECD) methods for the determination of residues of tetraconazole *per se* in plant and livestock commodities. HED has determined that these methods are adequate for tolerance enforcement (D280006, W. Donovan, 10-Jan-2002). Briefly, the methods involve extraction with acetone or hexane:acetone, solvent partition and column clean-up, and GC/ECD analysis. The GC/ECD methods were successfully validated by the Analytical Chemistry Branch in sugar beet top, sugar beet root, banana, peanut, milk, and liver (D264936 and D264683, P. Schermerhorn, 18-Dec-2001). The ACB-determined level of quantitation (LOQ) in sugar beet top was 0.1 ppm and in sugar beet root, banana, peanut, milk, and liver was 0.01 ppm. The GC/ECD method was also successfully radiovalidated in wheat grain, wheat straw, milk, and muscle (D278236, W. Donovan, 22-OCT-2001; D267481, W. Donovan, 12-Oct-2000). Adequate confirmatory methods using GC with mass spectrometry (GC/MS) were also submitted by Sipcam Agro USA

(D278236, W. Donovan, 22-Oct-2001). HED concludes that these methods are sufficient to enforce the recommended tolerances.

5.1.5 Environmental Degradation

Tetraconazole is persistent in the environment and does not have a single predominant route of dissipation. Laboratory and field half-lives ranged from 107 days to more than 1 year; however, the dissipation of tetraconazole applied directly to foliage (sugar beet leaves) is much more rapid. Foliar dissipation studies suggest that tetraconazole is taken up quickly and extensively metabolized in plants yielding tetraconazole acid, tetraconazole alcohol, triazolylalanine and triazolylacetic acid as metabolites (Tomlin, 2003). Tetraconazole is expected to have low volatility from soil and water surfaces and possesses moderate to slight mobility in soils. Successive applications are expected to result in year-to-year accumulation of residues in soil. Tetraconazole has potential to reach surface water via runoff and spray drift, but its tendency to reach ground water is expected to be reduced due to its lack of mobility in soil.

5.1.6 Comparative Metabolic Profile

Primary Crops, Livestock, and Rotational Crops: The plant, livestock, and rotational crop studies demonstrated a similar metabolic pathway although the relative amounts of parent and metabolites were different within and between plants and livestock. In general, tetraconazole is oxidized to M14360-DFA followed by hydrolysis to M14360-alcohol which may form a conjugate or be oxidized to M14360-acid. M14360-acid may then undergo ring separation to form T, TA, TAA, and /or THP or to a lesser extent may undergo oxidative decarboxylation to M14360-ketone followed by reduction to M14360(C-1)-alcohol; these compounds may also undergo ring separation to form T, TA, TAA, and/or THP. HED notes that M14360-CP(C-1)-alcohol, M14360-ketone, and/or M14360(C-1)-alcohol, which were identified in primary crops (wheat straw only at ≤5% TRR), livestock (ruminant tissue at ≤4.5% TRR) and rotational crops (lettuce, wheat forage, and wheat straw at 1-30% TRR), are structurally similar or identical to the propiconazole metabolites CGA-91305 and CGA-91304.

Rat Metabolism: Rat metabolism data indicate that tetraconazole is well absorbed from the gastro-intestinal tract and almost 100% of the administered dose was recovered in urine (~76%) and feces (~36%) and less than 6% of the administered dose remained in the carcass/tissues within 72 hours post-dosing. There was no major difference in absorption and elimination of tetraconazole between sexes and dose levels. Position of labeling [^{14}C-phenyl or ^{14}C-triazole] resulted in slight differences in the blood, time to reach maximum (T_{max}) levels and $T_{1/2}$ lives between sexes and doses. Males had slightly higher T_{max} levels than females. No parent compound was identified in urine and a small amount of parent compound was found in the feces. In the urine and fecal samples, triazole was the major metabolite for both dose levels and sexes. M-14360 acid along with minor metabolites of M-14360 alcohol and its glucuoronide conjugate (M3) were also isolated from the urine. In the feces minor amounts of the parent material, M-14360, the acid and alcohol were also isolated. In the multiple dosing, triazole, M-14360 acid, M-14360 alcohol, M-14360, M6 and others were reported while in the single dosing only triazole, M-14360 acid and M-14360 were reported. It was postulated that metabolism of tetraconazole in the rat may involve cleavage of the molecule between the phenyl and the triazole ring followed by glutathione conjugation of the triazole ring.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

HED has previously determined that the toxicological effects of T and combined TA and TAA are different from the of the remaining tetraconazole metabolites and different from each other (HED risk

assessment D322215, M. Doherty *et al.,* 7-Feb-2006).

The free triazole risk assessment mentioned above pertains to exposure to T, TA, and TAA from the conazole/triazole fungicides. Tetraconazole results in the formation of these compounds as well as THP. THP is a residue of concern in rotational crops and livestock (included as a residue of concern in livestock based on the identification in rotational crops and therefore as a potential residue in feed). Based on the proposed application rates and the results of the confined rotational crop studies, HED has concluded that residues in rotational crops will be negligible; therefore, residue of THP will be negligible and the previous free-triazole risk assessment is acceptable.

M14360-CP(C-1)-alcohol, M14360-ketone, and M14360(C-1)-alcohol were identified in the tetraconazole plant metabolism, livestock metabolism, and confined rotational crop studies and are structurally identical or similar to the propiconazole metabolites CGA-91304 and CGA-91305. Based on the magnitude of these residues in the tetraconazole plant metabolism, livestock metabolism, and confined rotational crop studies, only M14360(C-1)-alcohol was included as a residue of concern and only in rotational crops. However, they were identified in the propiconazole plant (≤32% TRR), livestock (16-79% TRR), rotational crop (≤2% TRR), mouse (≤30% TRR), and rat (≤3% TRR) metabolism studies (D319598, Y. Donovan *et al.,* 15-Aug-2006; TXR No. 0050446, A. Khasawinah, 26-Feb-2006). Based on the identification of M14360-ketone and M14360(C-1)-alcohol as significant residues in the propiconazole livestock and mouse metabolism studies (chronic endpoint based on a mouse study) and since these compounds were minor or not identified in the tetraconazole rat and livestock metabolism studies, HED concludes that the toxicity of M14360-CP(C-1)-alcohol, M14360-ketone, and M14360(C-1)-alcohol is likely to be more closely related to propiconazole than tetraconazole and residues of these compounds resulting from the application of tetraconazole should be included in the propiconazole risk assessment.

The tetraconazole chronic RfD is based on increased absolute and relative kidney weights and histopathological changes in the kidney from the chronic dog study (NOAEL=0.7 mg/kg/day, LOAEL =3.0 mg/kg/day). In addition, tetraconazole was classified "likely to be carcinogenic to humans" with Q1* based on liver tumors in male and female mice. No mechanism for either the kidney effects or the liver tumors is available. As speculated at the original MARC, the kidney effects may well be due to the tetrafluorethoxy moiety of the parent. Fluorinated anesthetics, e.g., methoxyflurane, have produced kidney toxicity in rats and humans. Thus, it would make sense to include M13460-DFA as a contributor to the dog toxicity endpoint. In regards to the remaining non-free triazole metabolites, these chemicals are dichlorophenyl carboxylic acids or may be metabolized to dichlorophenyl carboxylic acids. From the known high sensitivity of dogs to carboxylic acids (eg. 2,4-D, MCPA etc., chloro-phenoxy carboxylic acids produce kidney effects in dogs), HED is inclined to say that they also contribute to the kidney toxicity in the dog; thus, to the regulated chronic endpoint. Concerning the liver carcinogenicity endpoint in mice and the remaining non-free triazole metabolites, HED is inclined to include them in the cancer risk assessment. Based on the structural similarity to the parent tetraconazole and their probable liver toxicity (based on 2,4-D and MCPA), HED concludes that they cannot be excluded from the cancer risk assessment, especially in the absence of a known mode of action for liver carcinogenicity.

5.1.8 Pesticide Metabolites/Degradates of Concern

Table 5.1.8 is a summary of the HED's conclusions concerning the residues of concern for risk assessment and tolerance enforcement. HED notes the following:

●HED has previously determined that the toxicological effects of T and combined TA and TAA are different from each other and different from that of tetraconazole (HED risk assessment D322215, M. Doherty *et al.,* 7-Feb-2006). Furthermore, HED has determined that the toxic effect of M14360(C-1)-

alcohol is likely to be similar to propiconazole and residues of this compound resulting from the application of tetraconazole should be included in the propiconazole risk assessment. Finally, HED has determined that the toxic effects of the remaining compounds are likely to be similar to tetraconazole.
●The free triazole risk assessment mentioned above pertains to exposure to T, TA and TAA from the conazole/triazole fungicides. Tetraconazole results in the formation of these compounds as well as THP. THP is a residue of concern in rotational crops and livestock (included as a residue of concern in livestock based on the identification in rotational crops and therefore as a potential residue in feed). Based on the proposed application rates and the results of the confined rotational crop studies, HED has concluded that residues in rotational crops will be negligible; therefore, residue of THP will be negligible and the previous free-triazole risk assessment is acceptable.
●The free triazole metabolites (excluding T) and non-free triazole metabolites were included as residues of concern in livestock as these were identified as significant residues in plants; T was included as it was a significant metabolite in the livestock and plant metabolism studies. Since tetraconazole was the major residue in the majority of the feed commodities and based on the similar structure of parent to the non-free triazole metabolites, HED concludes that the tetraconazole *per se* transfer coefficients determined in the feeding studies are a satisfactory estimate of the transfer coefficients of the non-free triazole metabolites (*i.e.,* for the tetraconazole risk assessment, calculate livestock dietary burdens for non-free triazole residues of concern and use the tetraconazole transfer coefficient to estimate residues in livestock commodities).
●Syngenta developed a common moiety method for propiconazole which employs base hydrolysis followed by oxidation and for future magnitude of the MOR studies that a similar method would be appropriate for determination of the non-free triazole metabolites in the primary crops (non-free-triazole metabolites hydrolyzed/oxidized to 2,4-dichlorobenzoic acid); this method would not be appropriate for rotational crops as the residues of concern includes M14360(C-1)-alcohol whose toxicity is different from the remaining non-free triazole metabolites.

Table 5.1.8. Residues of Concern for Tolerance Expression and Risk Assessment.

Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Shelled Pea and Bean	tetraconazole*	tetraconazole
Remaining Plants	tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360-hydroxydetriazolyl-O-malonyldiglucoside	tetraconazole
Livestock	tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360(C-1)-alcohol (free and conjugated), M14360-hydroxydetriazolyl-O-malonyldiglucoside*	tetraconazole
Rotational Crops	tetraconazole, M14360-acid, M14360-DFA, M14360(C-1)-alcohol (free and conjugated)*	tetraconazole
Drinking Water	tetraconazole*	not applicable

* 1,2,4-triazole (T), triazolyl alanine (TA), triazolyl acetic acid (TAA), and all labile conjugates of these compounds are residues of concern for risk assessment. Separate assessments have been conducted to address risks associated with these compounds.

5.1.9 Drinking Water Residue Profile

The following information was obtained from EFED's drinking water memo (memo, I. Maher, D321622,

11/27/2006).

The metabolites identified in water photodegradation studies were found at low levels (a maximum of 15.6% of the applied radioactivity) and were generally considered less toxic than parent tetraconazole. On this basis, the HED MARC determined that the residue of concern in water is tetraconazole *per se* (Memo, W. Donovan, TXR # 0050095, 4/19/2000).

The Risk to Drinking Water Resources

As a result of its persistence, tetraconazole will likely contaminate surface water resources. It will reach surface water via surface runoff and spray drift. The areas of the U.S. where surface water is a source of residential drinking water and are co-located with high densities of golf courses may be at risk of contamination by tetraconazole use on turf. The northern part of Texas, where at least half of the population relies on surface water for drinking water, and the southern part of Oklahoma, where surface water is the only source of drinking water, may be contaminated with tetraconazole through spray drift and runoff from peanut agricultural areas. Drinking water from surface water in Colorado, Wyoming, California, and North Dakota may be at risk of tetraconazole contamination where sugar beets are grown. With tetraconazole accumulation in the soil due to successive application year to year, the potential for exposure to tetraconazole via drinking water may be even greater.

Because tetraconazole is persistent and moderately-to-slightly mobile, it may contaminate shallow ground water under some vulnerable conditions. Corresponding K_{oc} values of 1004, 769, 428, and 2036 mL/g were calculated for sand, loamy sand, clay, and clay loam soil, respectively. Peanuts preferably are grown on sandy loam soils with good drainage, but the U.S. peanut production regions have different soil types ranging from sandy soils to loams. In the sandy soils of coastal plains where peanuts are grown, tetraconazole may leach into the shallow ground water. Tetraconazole may reach the shallow ground water when applied on turf grown on sandy soil (*i.e.* Florida's golf courses).

The Uncertainties Associated with Tetraconazole Degradates

The risk assessment did not include tetraconazole degradates. Tetraconazole degradates were not analyzed in any of the terrestrial field studies. Registrant-submitted data for a common degradate, 1,2,4-triazole, are under review. In the soil photodegradation study 3.7% of 1,2,4-triazole was formed at 112 days post treatment. In the aqueous photolysis study 6.7% 1,2,4-triazole was formed at 30 days post-treatment.

Drinking Water Estimates

EFED provided modeled ground (SCIGROW) and surface (PRZM 3.12 and EXAMS 2.98.04) water concentrations for tetraconazole *per se*. Table 5.1.9 is a summary of the estimates provided by EFED. The water estimates were incorporated directly into the dietary exposure analysis via the water sources direct (all sources) and indirect (all sources) commodities. The water models and their description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Table 5.1.9. Summary of Ground and Surface Water Modeled Water Estimates.

Crop	state and application method modeled	ppb (µg/L)		
		peak	yearly	30-year annual average
ground water				
sugar beet		0.36		
Turf		10.0		
Peanut		0.72		
Soybean		0.27		

Pecan		1.79		
surface water				
sugar beet	Minnesota; aerial spray[1]	7.22	4.97	3.77
	Minnesota; ground spray[1]	6.33	4.40	3.20
	California; aerial spray[1]	2.12	1.43	1.30
	California; ground spray[1]	0.86	0.59	0.52
Peanut	North Carolina; aerial spray[2]	10.36	4.03	3.02
	North Carolina; ground spray[2]	10.02	3.83	2.78
Soybean	Mississippi; aerial spray[3]	1.29	0.59	0.47
	Mississippi; ground spray[3]	1.18	0.56	0.42
Pecan	Georgia; aerial spray[4]	20.01	7.26	4.97
	Georgia; ground spray[4]	19.46	6.79	4.41
Turf	Pennsylvania; aerial spray	118.00	77.13	59.90
	Pennsylvania; ground spray	87.40	57.55	41.03
	Florida; aerial spray	77.52	44.74	36.94
	Florida; ground spray	57.70	33.77	25.97
golf course turf	Pennsylvania; aerial spray[5]	40.12	26.22	20.37
	Pennsylvania; ground spray[5]	29.72	19.57	13.95
	Florida; aerial spray[5]	26.36	15.21	12.56
	Florida; ground spray[5]	19.62	11.48	8.83

[1] EXAMS EEC multiplied by 0.87 to account for percent of basin cropped (assumes 100% of the crop treated)

[2] EXAMS EEC multiplied by 0.67 to account for percent of basin cropped (assumes 100% of the crop treated)

[3] EXAMS EEC multiplied by 0.41 to account for percent of basin cropped (assumes 100% of the crop treated)

[4] EXAMS EEC multiplied by 0.85 to account for percent of basin cropped (assumes 100% of the crop treated)

[5] EXAMS EEC multiplied by 0.34 to account for percent of basin cropped (assumes 100% of the crop treated)

5.1.10 Food Residue Profile

Magnitude of the Residue - Primary Crops: The petitioner submitted soybean, pecan, peanut, and sugar beet field trial and/or processing studies and the following paragraphs are summaries of these data. HED notes that only tetraconazole *per se* residue data were provided for pecan, peanut, and sugar beet and the residues of concern for risk assessment in these crops includes tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360-hydroxydetriazolyl-O-malonyldiglucoside, and T, TA, TAA and all labile conjugates of these compounds (soybean magnitude of the residue studies provided residue data for all residues of concern). Since the field trial study was initiated prior to HED drawing conclusions pertaining to the residues of concern in plants, HED concludes that additional pecan, peanut, and sugar beet residue data depicting the magnitude of the residues of concern are unnecessary. For risk assessment, residues of the non-free triazole metabolites were estimated using residue ratios from the metabolism studies. Future magnitude of the residue studies should include data for the non-free triazole metabolites of concern. Issues concerning the magnitude of T, TA, and TAA residues in/on all proposed commodities are addressed in the Executive Summary of this memorandum.

Soybean (D321555, T. Bloem,1/23/07): The soybean field trials satisfy the geographical distribution specified in OPPTS 860.1500 and employed application of 230 g/L ME tetraconazole formulation at the proposed single/seasonal application rate. Soybean seed samples were harvested at maturity 42-84 days after the final application (soybean forage and hay samples were not collected). Residues of tetraconazole *per se* ranged from 0.005-0.069 ppm (highest average field trial (HAFT) = 0.068 ppm). The soybean seed samples were also blended based on U.S. EPA Region and were analyzed for T, TA, and TAA (analytical method included a hydrolysis procedure). A total of three blended soybean seed samples were produced; one each from Regions 2, 4 and 5. Residues of T, TA, and TAA ranged from <0.003 ppm, 0.340-1.050 ppm, and 0.10-0.027 ppm, respectively, in/on the regionally blended soybean seed samples.

The soybean seed processing study resulted in the following processing factors for tetraconazole *per se*: aspirated grain fraction (AGF) - 7.1-8.1x, hulls - 0.6x, meal - 0.1-0.2x, and refined oil - 3.8-5.4x. The hull, meal, and refined oil samples were also analyzed for T, TA, and TAA. Residues of T and TAA were less than the LOQ in the unprocessed seed and processed commodities; therefore, processing factors for T and TAA could not be calculated. Residues of TA were found to concentrate in meal (1.7-2.4x), remain constant in hulls (1.0x), and reduce in refined oil (0.02-0.05x).

The magnitude of the residue studies provided adequate method validation and concurrent recovery data for tetraconazole *per se*, T, TA, and TAA. The tetraconazole *per se* analytical method employed acetonitrile (ACN) extraction (radiovalidated enforcement method employs acetone extraction) and the T, TA, and TAA analytical method employed methanol:water extraction (included a hydrolysis procedure). The soybean seed metabolism study employed ACN extraction followed by acetone:water extraction (acetone water extract reduced to the aqueous phase and partitioned with ethyl acetate). The ACN extract recovered 50% of the total tetraconazole *per se* residue with the remaining 50% found in the ethyl acetate partition. All of the free triazole metabolites were found in the aqueous phase of the acetone:water extract. Therefore, based on the method validation data, concurrent recovery data, and the soybean seed metabolism study, HED concludes that the T, TA, and TAA method has been adequately validated (storage interval for TA and TAA has been validated; additional storage stability data for T are required). However, based on the soybean seed metabolism data, the tetraconazole *per se* analytical method may not be able to determine "weathered" tetraconazole *per se* residues in/on soybean seed and is not appropriate for data-collection purposes. HED request that the petitioner reanalyze the soybean seed and soybean seed processed samples using a method which is capable of quantitatively determining tetraconazole *per se* residues (storage stability data will also be required).

Pending reanalysis of the soybean seed and soybean seed processed samples for tetraconazole *per se* and provided the petitioner submits a revised Section B, HED concludes that currently available data are sufficient to support the following tolerances for residues of tetraconazole *per se*: soybean seed - 0.15 ppm, soybean refined oil - 0.80 ppm, and AGF - 1.0 ppm (tolerance spreadsheet was employed for the soybean seed tolerance). A revised Section F is requested. These tolerances accounted for the non-quantitative nature of the analytical method by multiplying the measured tetraconazole residue by two. HED notes that the proposed label prohibits the feeding of treated soybean forage and hay to livestock; therefore, forage and hay data are unnecessary.

Pecan (D331594, T. Bloem, 1/23/07): The pecan field trials satisfy the geographical distribution specified in OPPTS 860.1500 and employed application of Eminent® 125SL at the proposed single/seasonal application rate. Pecan nutmeat samples were harvested 30 days after the final application; residues of tetraconazole *per se* were <0.01-0.022 ppm in/on pecan nutmeat samples (validated storage interval and analytical method). Provided the petitioner submits a revised Section B, HED concludes that the available data support a tolerance for residues of tetraconazole in/on pecan of

0.04 ppm. Since all but one of the field trials resulted in residues <LOQ, the tolerance spreadsheet was not employed.

Sugar Beet (D327489, T. Bloem, 1/23/07): The petitioner originally proposed six foliar applications of the 1 lb ai/gal SL formulation at 0.10 lb ai/acre/application (RTI of 14-21 days; PHI of 14 days). The petitioner then reduced the maximum number of applications from six to three. The petitioner is currently reducing the maximum number of application from three to two and increased the RTI to 21-28 days. The following paragraphs are a summary of the available sugar beet residue data.

The petitioner submitted an adequate sugar beet field trial study conducted in the geographical regions suggested for a national sugar beet registration (D254411, W. Donovan, 18-May-2000). Mature sugar beet plants (tops with roots) were harvested 14 days following the last of six sequential broadcast spray applications of the 1 lb/gal SC formulation at 0.11 lb ai/acre/application (1x/3.2x the currently proposed single/seasonal application rate; 12-16-day RTI). Residues of tetraconazole *per se* were 0.013-0.103 ppm and 1.13-5.90 ppm in/on sugar beet root and leaves, respectively. The residue decline data suggest that residues of tetraconazole *per se* dissipated from 3.21 ppm (0-Day PHI) to 0.869 ppm (60-day PHI) in/on sugar beet tops. A meaningful decline trend was not observed in sugar beet roots. The sugar beet processing study indicated that residues of tetraconazole *per se* concentrate in sugar beet pulp (2.1x) and molasses (2.8x) and reduce in sugar (0.1x; D254411, W. Donovan, 18-May-2000).

The petitioner also submitted one side-by-side field trial comparing six and three applications of 1 lb ai/gal SC formulation at ~0.10 lb ai/acre/application (RTI = 14 days; 3.2x and 1.5x the proposed seasonal rate; D282558, W. Donovan, 17-May-2002). Samples were harvested 14 days after the final application and analyzed for residues of tetraconazole *per se*. Average residues of tetraconazole in sugar beet root following seasonal application rates of 0.60 lb ai/acre and 0.30 lb ai/acre were 0.038 ppm and 0.011 ppm (0.038 ÷ 0.011 = 3.4), respectively, and average residues in sugar beet top following application rates of 0.60 lb ai/acre and 0.30 lb ai/acre were 1.71 ppm and 0.790 ppm (1.71 ÷ 0.790 = 2.2), respectively. The ChemSAC determined that, based on the consistency of tetraconazole residues in/on sugar beet following six applications at 0.10 lb ai/acre together with the results of the side-by-side residue data, the reduction in the application rate from six to three applications at 0.10 lb ai/acre was acceptable (no additional field trial data required; minutes of 15-May-2002).

HED concludes that additional sugar beet field trial data to support the current request to reduce the maximum number of applications from three to two and increase the RTI to 21-28 days are unnecessary for the following reasons: (1) a sugar beet top tolerance is unnecessary since it is not a human food commodity and is being eliminated as a feed commodity from OPPTS 860.1000 (communication from J. Stokes, HED); and (2) based on the currently available field trial data and the LOQ for sugar beet root (LOQ = 0.01 ppm), HED concludes that if additional field trial data were conducted at the proposed rate, tetraconazole *per se* residues in/on sugar beet root would be ≈ LOQ. Therefore, based on the currently available data, HED concludes that the following tolerances for residues of tetraconazole *per se* are appropriate: sugar beet root - 0.05 ppm; sugar beet dried pulp - 0.15 ppm; and sugar beet molasses - 0.15 ppm.

Peanut (D327489, T. Bloem,1/23/07): The petitioner originally proposed four foliar applications of the 1 lb ai/gal SL formulation at 0.20 lb ai/acre/application (RTI of 14 days; PHI of 14 days; D259321, W. Donovan, 18-May-2000). The petitioner is currently requesting four foliar applications of the 1 lb ai/gal SL formulation at 0.10 lb ai/acre/application (RTI of 14 days; PHI of 14 days). The field trial data submitted with the original petition employed seven foliar applications at 0.10 lb ai/acre (RTI = 12-16 days; PHI = 14 days) and resulted in tetraconazole residues in/on peanut nutmeat of ≤0.034 ppm (validated storage interval and analytical method). The peanut nutmeat processing study resulted in

processing factors for peanut meal and refined oil of 1.12x and 3.34x, respectively (259321 W. Donovan, 18-May-2000). The original peanut petition recommended for peanut nutmeat and peanut refined oil tolerances for residues of tetraconazole *per se* of 0.05 ppm and 0.15 ppm.

Therefore, the currently-available field trial data employed an application rate 1.8x the proposed rate. Since tetraconazole *per se* residues in/on peanut nutmeat from the field trials were only slightly greater than the LOQ (LOQ = 0.01 ppm; residues were ≤0.034 ppm) and since the label will include a restriction prohibiting the feeding of peanut hay to livestock, HED concludes that the available data support peanut nutmeat and peanut refined oil tolerances for residues of tetraconazole *per se* of 0.03 ppm and 0.10 ppm, respectively. A revised Section F is requested.

Table 5.1.10a. Summary of Tetraconazole *per se* Residue Data.

Commodity	Total Rate (lb ai/acre)	PHI (days)	Residue of Tetraconazole *per se* (ppm)[2]						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
soybean seed	2 x 0.090	42-84	40	0.0053	0.0689	0.0680	0.0186	0.0230	0.0140
pecan nutmeat	8 x 0.129-0.139	30	10	<0.01	0.022	0.018	0.005	0.007	0.005
sugar beet root	6 x 0.107	14	22	0.011	0.103	0.086	0.030	0.040	0.027
sugar beet top	6 x 0.107	14	22	0.869	5.90	4.90	2.14	2.43	1.10
Peanut	7 x 0.10	14	22	<0.01	0.034	0.033	0.005	0.013	0.010

[1] HAFT = highest average field trial

[2] mean, median, and standard deviation calculated assuming ½ LOQ for residue <LOQ

Table 5.1.10b. Summary of T, TA, TAA Residue Data.

Commodity	Total Rate (lb ai/acre)	PHI (days)	Analyte	Residues (ppm)[3]						
				n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
soybean seed[2]	2 x 0.090	42-84	T	6	<0.003	<0.003	<0.003	<0.003	--	--
			TA	6	0.340	1.050	1.010	0.368	0.574	0.339
			TAA	6	(0.010)	(0.027)	(0.026)	(0.016)	(0.018)	0.006

[1] HAFT = highest average field trial

[2] blended samples from Regions 2 (2 field trials), 4 (3 field trials), and 5 (15 field trials)

[3] the LOQ/LOD for T are 0.01 ppm/0.003 ppm and for TA and TAA are 0.03 ppm/0.01 ppm; values between the LOQ and LOD are presented in parentheses

Table 5.1.10c. Summary of Processing Factors.

Analyte	crop	Commodity	Processing Factor
Tetraconazole	soybean	AGF	7.1-8.1
		hulls	0.6
		meal	0.1-0.2
		refined oil	3.8-5.4
	sugar beet	pulp	2.1
		molasses	2.8
		sugar	0.1
	peanut	meal	1.12
		refined oil	3.34

Triazole (T)	soybean	all commodities	<LOQ in the RAC and processed commodities; therefore calculation of a processing factors was not possible
TAA	soybean	all commodities	
TA	soybean	hulls	1.0
		meal	1.7-2.4
		refined oil	0.02-0.05

Magnitude of the Residue - Livestock: Based on the beef cattle, diary cattle, hog, and poultry tetraconazole *per se* maximum dietary burdens (MDB) of 0.17 ppm, 0.11 ppm, 0.04 ppm, and 0.07 ppm, respectively, and the results of adequate ruminant and poultry feeding studies, HED concludes that the livestock tolerances for residues of tetraconazole *per se* are appropriate (see Appendix B for details). HED notes that this review recommends lowering the currently established milk, cattle, goat, horse, and sheep tolerances. This is due to the elimination of sugar beet tops as a ruminant feed commodity in OPPTS 860.1000 Table 1 (communication from J. Stokes, HED) and the label restrictions prohibiting the feeding of peanut hay and soybean forage and hay to livestock.

The residue of concern in livestock for tolerance enforcement is tetraconazole *per se,* and the residues of concern for risk assessment are tetraconazole, M14360-alcohol (free and conjugated), M14360-acid, M14360-DFA, M14360-ketone (free and conjugated), M14360(C-1)-alcohol (free and conjugated), M14360-hydroxydetriazolyl-O-malonyldiglucoside, and T, TA, THP, and TAA and all labile conjugates of these compounds. The livestock feeding studies determined residues of tetraconazole *per se* following dosing with tetraconazole. Since tetraconazole was the major residue in the majority of the feed commodities and based on the similar structure of parent to the non-free triazole metabolites, HED concludes that the tetraconazole *per se* transfer coefficients determined in the feeding studies are a satisfactory estimate of the transfer coefficients of the non-free triazole metabolites (*i.e.,* for the tetraconazole risk assessment, calculate livestock dietary burdens for non-free triazole residues of concern and use the tetraconazole transfer coefficient to estimate residues in livestock commodities). Issues concerning the magnitude of T, TA, and TAA residues in livestock are addressed in the Executive Summary.

Magnitude of the Residue - Rotational Crops: As stated above, the residue of concern in rotational crops for tolerance enforcement is tetraconazole *per se* and the residues of concern for risk assessment are tetraconazole, M14360-acid, M14360-DFA, M14360(C-1)-alcohol (free and conjugated), and TA, THP, and TAA and all labile conjugates of these compounds. HED determined that the toxicity of the free triazole metabolites, M14360(C-1)-alcohol (free and conjugated), and the remaining non-free triazole metabolites are different from each other. Therefore, when evaluating the magnitude of the residue in rotational crops, HED will determine the magnitude of M14360(C-1)-alcohol (free and conjugated); combined tetraconazole, M14360-acid, and M14360-DFA; and combined TA, THP, and TAA.

The petitioner submitted a field rotational crop study which monitored for residues of tetraconazole *per se* in spring wheat (straw and grain), peas (seed), potato (tuber), canola (seed), and sugar beet (root and top) planted 7-9 days following application of tetraconazole to bare soil at 0.112, 0.223, 0.669, and 1.34 lb ai/acre (D278236, W. Donovan, 22-Oct-2001). These application rates represent ≥0.3x, ≥0.6x, ≥1.7x, and ≥3.4x the maximum proposed single/seasonal application rate for crops which are rotated. Residues of tetraconazole were <0.02 ppm (<LOQ) in all samples except spring wheat straw harvested from the plots treated at 0.669 lb ai/acre and 1.34 lb ai/acre (<0.02-0.05 ppm). Based on these data and the tetraconazole to combined M14360-acid and M14360-DFA and tetraconazole to M14360(C-1)-alcohol residue ratios from the confined study of ≥0.7x and ≥2x, respectively, HED concludes that residues of M14360(C-1)-alcohol (free and conjugated) and combined residues of tetraconazole, M14360-acid, and M14360-DFA will be insignificant in/on rotational crops planted at the proposed 120-day PBI (tolerance and inclusion

of rotational crop residues in the tetraconazole risk assessment are unnecessary). Issues concerning the magnitude of TA, THP, and TAA residues in/on the rotational crops are addressed in the Executive Summary.

5.1.11 International Residue Limits

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for tetraconazole in/on the requested crops or livestock commodities.

5.1.12 HED Recommendations

Table 5.1.12 is a summary of the HED-recommended tolerances.

Table 5.1.12. HED-Recommended Tolerances.

Commodity	HED-Recommended Tolerance (ppm)
Beet, sugar, root	0.05
Beet, sugar, dried pulp	0.15
Beet, sugar, molasses	0.15
Peanut	0.03
Peanut, oil	0.10
Pecan	0.04
Soybean, seed	0.15
Soybean, refined oil	0.80
Aspirated grain fractions	1.0
Poultry, meat	0.01
Poultry, fat	0.05
Poultry meat byproducts	0.01
Eggs	0.02
Cattle, meat	0.01
Cattle, liver	0.20
Cattle, fat	0.02
Cattle, meat byproducts (except liver)	0.01
Milk	0.01
Milk, fat	0.25
Goat, meat	0.01
Goat, liver	0.20
Goat, fat	0.02
Goat, meat byproducts (except liver)	0.01
Hog, meat	0.01
Hog, liver	0.05
Hog, fat	0.01
Hog, meat byproducts (except liver)	0.01
Horse, meat	0.01
Horse, liver	0.20
Horse, fat	0.02
Horse, meat byproducts (except liver)	0.01
Sheep, meat	0.01

Table 5.1.12. HED-Recommended Tolerances.	
Commodity	HED-Recommended Tolerance (ppm)
Sheep, liver	0.20
Sheep, fat	0.02
Sheep, meat byproducts (except liver)	0.01

5.2 Dietary Exposure and Risk

Based on the plant metabolism, livestock metabolism, and confined rotational crop studies, HED identified the following three groups of compounds differentiated by toxicity: (1) free triazole compounds, (2) non-free triazole metabolites in common with propiconazole, and (3) tetraconazole and remaining non-free triazole metabolites. The following text is a summary of these risk assessments for each group.

Free Triazole Metabolites: HED has determined that T, TA, TAA, THP and all labile conjugates of these compounds are residues of concern in plant, livestock, and rotational crops following application of tetraconazole. The formation of the free triazole metabolites is a common aspect of the conazole/triazole class of fungicides and the toxicity and potential exposure to all registered/proposed conazole/triazole fungicides registrations as of 1-September-2005 were previously evaluated by HED (D322215, M. Doherty *et al.,* 7-Feb-2006). HED concludes that this previous free triazole risk assessment is adequate for the current petitions for the following reasons:

- The soybean, peanut, and sugar beet petitions were proposed prior to 1-September-2005.
- The soybean petition included T, TA, and TAA magnitude of the residue data for soybean seed and soybean seed processed commodities. The dietary exposure analyses conducted as part of the free triazole risk assessment incorporated soybean residue estimates greater than those expected based on these data.
- The pecan petition was received after 1-September-2005 and, therefore, the previous free triazole risk assessment did not consider the potential formation of free triazole metabolites in/on pecan following application of tetraconazole (the tetraconazole pecan field trial studies did not include free triazole residue data). HED performed a dietary exposure assessment assuming a pecan free triazole residue estimate of 10 ppm (only pecan was included in the assessment; 100% crop treated). The resulting exposure estimates were ≤0.9% the acute/chronic PAD. Based on the tetraconazole *per se* pecan residue data following treatment at the proposed rate (≤0.022 ppm; PHI = 30 days) and the tetraconazole to free triazole residue rations from the metabolism studies T (≥0.07x), HED concludes that residues of the free triazole residue will be significantly below 10 ppm (0.022 ppm ÷ 0.07 = 0.31 ppm). Therefore, HED concludes that although the free triazole residues resulting from the application of tetraconazole to pecans may be greater than the residue estimates used in the previous dietary exposure analyses, they will not be of a value that results in pecan being a significant contributor to the exposure estimates.
- The free triazole risk assessment mentioned above pertains to exposure to T, TA, and TAA from the conazole/triazole fungicides. Tetraconazole results in the formation of these compounds as well as THP. THP is a residue of concern in rotational crops and livestock (included as a residue of concern in livestock based on the identification in rotational crops and therefore as a potential residue in feed). Based on the proposed application rates and the results of the confined rotational crop studies, HED has concluded that residues in rotational crops will be negligible; therefore, residue of THP will be negligible and the previous free-triazole risk assessment is acceptable.

Metabolites in Common with Propiconazole: The tetraconazole plant metabolism, livestock metabolism, and/or confined rotational crop studies resulted in the identification of M14360-ketone, M14360-CP(C-1)-alcohol, and M14360(C-1)-alcohol. HED concluded that the toxicity of these compounds is likely to be similar to propiconazole and not to tetraconazole. Based on the magnitude of these residues relative to the other identified compounds in the tetraconazole metabolism and confined rotational crop studies, HED concluded that only M14360(C-1)-alcohol was a residue of concern and only in rotational crops following application of tetraconazole (not of concern in plants or livestock). However, HED notes that the magnitude of these compounds following application of tetraconazole may be such that they are of concern when compared to the magnitude of the propiconazole residues. HED recently completed a

propiconazole risk assessment (D319598, Y. Donovan *et al.,* 15-Aug-2006) and concludes that a revised propiconazole risk assessment is unnecessary for the following reasons:

●For the commodities which tetraconazole and propiconazole have in common (plant and livestock), the propiconazole *per se* tolerances are higher than the tetraconazole *per se* tolerances indicating that the residue ratio which lead to the exclusion of M14360-ketone, M14360-CP(C-1)-alcohol, and/or M14360(C-1)-alcohol as residues of concern for tetraconazole would also be applicable to propiconazole.

●M14360-ketone and M14360(C-1)-alcohol were significant residue in the propiconazole livestock metabolism studies (ruminants =31% TRR; poultry - =79% TRR) but were insignificant residues in the tetraconazole livestock metabolism studies (M14360-ketone was identified in ruminant tissue at =4.5% TRR; M14360-CP(C-1)-alcohol and M14360(C-1)-alcohol were not identified).
●Based on the tetraconazole field rotational crop study, HED concludes that residues of M14360(C-1)-alcohol will be insignificant in rotational crops following application of tetraconaozle at the currently proposed rates.

Acute, chronic, and cancer dietary risk assessments were conducted using the DEEM-FCID™, ver. 2.03 which incorporates the food consumption data from the USDA's CSFII; 1994-1996 and 1998. These analyses were conducted in support of the proposed application of tetraconazole to soybean (Section 3 Registration), sugar beet (Nationwide Section 3 Registration), peanut (Section 3 Registration), and turf (Section 3 Registration). The following paragraphs are summaries of the acute, chronic, and cancer analyses.

Acute Dietary Risk: The Tier 1 acute dietary analysis (food and water; drinking water estimate derived from the proposed turf application scenario) resulted in an exposure estimate for females 13-49 years old less than HED's level of concern (2.7% aPAD; see Table 5.2a). Since the dietary risk estimate from turf drinking water resulted in an unacceptable cancer risk alone (see below) and HED is recommending that the turf use not be established, the acute analysis was repeated with exclusion of the turf use (the drinking water estimate was derived from the pecan application scenario). The resulting risk estimate for females 13-49 years old does not exceed HED's level of concern (<1.0% aPAD; see Table 5.2b). An acute endpoint of concern was not identified for the general population including infants and children.

Chronic Dietary Risk: The chronic analysis (food and water; drinking water estimate derived from the proposed turf application scenario) was partially refined through the incorporation of empirical processing factors, average field trial residues, and average residues from the feeding studies (100% crop treated assumed). The resulting risk estimates were less than HED's level of concern (≤76% cPAD; all infants <1 year old were the most highly exposed population subgroup; see Table 5.2a). Since the dietary risk estimate from turf drinking water resulted in an unacceptable cancer risk alone (see below) and HED is recommending that the turf use not be established, the chronic analysis was repeated with exclusion of the turf use (the drinking water estimate was derived from the pecan application scenario). The resulting exposure estimates do not exceed HED's level of concern (≤10.1% cPAD; all infants <1 year old were the most highly exposed population subgroup; see Table 5.2b).

Cancer: Dietary cancer risk was calculated two ways to explore risk mitigation options: 1) risk based on exposure from drinking water only, and 2) risk based on exposure from food and drinking water estimates from all non-turf uses.

First, dietary cancer risk was calculated based on drinking water sources alone (*i.e.,* all food sources were excluded), using drinking water estimates based on the proposed turf use. Using only the water estimates from application to turf (golf courses only), the cancer risk for the U.S. population was **4×10^{-6}**.

Second, the dietary cancer risk assessment was performed based on food exposure and drinking water estimates from all proposed non-turf uses (sugar beet, peanut, soybean and pecan). The refined dietary cancer risk assessment was performed using empirical processing factors, average field trial residues, average residues from the feeding studies, projected percent crop treated estimates, and the drinking water estimate derived from the pecan application scenario (4.97 ppb; 8 x 0.125 lb ai/acre; highest estimate when turf is excluded). **The resulting exposure estimates yielded a cancer risk for the U.S. population of 3 x 10^{-6}.** A complete commodity analysis indicates that drinking water contributes 78% of the total exposure, soybean oil contributes 18% of the total exposure, and the remaining food commodities contribute 4% of the total exposure.

Cancer risks presented in this assessment are expressed to one significant figure. However, it should be noted that, in general, the precision which can be assumed for cancer risk estimates is best described by rounding to the nearest integral order of magnitude on the log scale, e.g., 3.16 x 10^{-7} to 3.16 x 10^{-6}, expressed as 10^{-6}. Risks are generally reported to one significant figure in HED risk assessments to allow better characterization of *changes* in risk which might result from potential risk mitigation. This rounding procedure indicates that risks should generally not be assumed to exceed the benchmark level of concern of 10^{-6} until the calculated risks exceed approximately 3 x 10^{-6}. Discretion should be used in interpreting the significance of these calculated risks with consideration given to the precision in the risk estimates.

Projected Percent of Crop Treated Information
The following information was obtained from the BEAD memo, *Projected Percent Crop Treated for the Fungicide Tetraconazole,* J. Alsadek, DP# 332043, 12/13/2006.

EPA estimates projected percent crop treated (PPCT) for a new pesticide use by assuming that the percent crop treated (PCT) during the pesticide's initial five years of use on a specific use site will not exceed the average PCT of the market leader (*i.e.,* the one with the greatest PCT) on that site.

The PPCTs for peanuts are calculated by averaging the PCTs of the leading fungicides for the three most recent available years. The PPCT for sugar beets showed a 55 percent use of tetraconazole as the market leader for the year 2000, based on its registration on sugar beets in seven states (Colorado, Michigan, Minnesota, Montana, Nebraska, North Dakota, and Wyoming). Therefore, the NASS data were adjusted to find the acres treated in each of the seven states, summing them up, then dividing by the sum of the planted acres in these same states, and multiplying by 100 to get, on average, market leader for sugar beets to be used in chronic dietary risk assessment and acute risk too.

The PPCTs for soybeans were based on a modified approach. Due to the recent discovery of a new and important disease on soybeans (Asian soybean rust), historical information was not considered useful for estimating PCT for soybeans. PCT estimates were obtained for future market leaders from soybean crop specialists. The estimates were obtained via telephone and four list server responses enlisted by USDA. The five crop specialists' PCT estimates for a market leader ranged from 10 to 38%. For a conservative estimate we utilized only the maximum projected values provided by each respondent, which ranged from 15 to 38%. These values translated into average and maximum PPCT values of 27 and 38%, respectively.

Projected Percent of Crop Treated Information for Dietary Risk Assessment
Peanuts: Chronic-77%; Acute-88%
Soybeans: Chronic-27%; Acute-38%
Sugar Beets: Chronic-70%; Acute-70%

Table 5.2a. Summary of the Acute and Chronic Dietary Exposure and Risk (all commodities; drinking water included).						
Population	aPAD (mg/kg/day)	Exposure (mg/kg/day)[1]	%aPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	no acute endpoint identified for these population subgroups			0.073	0.001724	24
All Infants (< 1 year old)					0.005564	76
Children 1-2 years old					0.002629	36
Children 3-5 years old					0.002480	34
Children 6-12 years old					0.001717	24
Youth 13-19 years old					0.001276	18
Adults 20-49 years old					0.001597	22
Adults 50+ years old					0.001660	23
Females 13-49 years old	0.225	0.006168	2.7		0.001587	22

[1] 95th percentile (Tier 1 analysis)

Table 5.2b. Summary of the Acute and Chronic Dietary Exposure and Risk (all commodities excluding turf; drinking water included).						
Population	aPAD (mg/kg/day)	Exposure (mg/kg/day)[1]	%aPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	no acute endpoint identified for these population subgroups			0.073	0.000252	3.4
All Infants (< 1 year old)					0.000735	10.1
Children 1-2 years old					0.000442	6.0
Children 3-5 years old					0.000432	5.9
Children 6-12 years old					0.000305	4.2
Youth 13-19 years old					0.000212	2.9
Adults 20-49 years old					0.000222	3.0
Adults 50+ years old					0.000213	2.9
Females 13-49 years old	0.225	0.001603	<1.0		0.000218	3.0

[1] 95th percentile (Tier 1 analysis)

Table 5.2c. Summary of the Cancer Dietary Exposure and Risk Resulting from all Registered/Proposed Uses Excluding Turf (drinking water and food sources).				
Scenario	Population[1]	Exposure (mg/kg/day)	Q_1^*	Cancer risk
all crops excluding turf	general U.S. population	0.000134	0.023	3×10^{-6}

[1] exposure for the general U.S. population; HED performs cancer analyses for only the general U.S. population

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Tetraconazole is not intended for use by homeowners, nor is it to be used on residential lawns. However, it is proposed for use on recreational turf such as golf courses, parks and other public areas. Therefore, HED assessed non-occupational post-application risk from recreational activity and playing golf on treated turf. Short-term and cancer aggregate risks were estimated.

Information for this section was adapted from several occupational and residential exposure assessments (Memo, M. Dow, D331997, 9/20/2006; Memo, M. Dow, D309312, 10/22/2004; Memo, M. Dow, D321615, 02/08/2006; Memo, M. Dow, D334610, 12/27/06.)

HED produced an assessment of residential risk to the triazole fungicides (Memo, J. Arthur, D322240, 12/09/05). The proposed uses of tetraconazole do not impact the triazole assessment.

6.1 Residential Handler Exposure

Based on the proposed use pattern, tetraconazole is not expected to be applied by homeowners. Application to golf courses, parks and other sites is considered to be an occupational handler event.

6.2 Residential Post-application Exposure

Since tetraconazole residues may be present on public recreational turf (and soil), an assessment of non-occupational post-application risk was conducted (the proposed agricultural uses are not expected to result in non-occupational exposure). Such individuals could include golfers on treated golf course turf or persons contacting treated turf through recreational use such as picnicking, use of treated parkland turf etc. HED assessed exposure and risk to children based on dermal and incidental oral (including hand-to-mouth, object-to-mouth and soil ingestion) exposure resulting from the proposed turf use. Exposure to adults was assessed based on dermal exposure only. Post-application inhalation exposure is expected to be negligible. HED used the standard procedure for assessing residential post-application exposure on day 0 of treatment for adults and children.

Hand-to-mouth, object-to-mouth, soil ingestion and dermal exposure pathways are assessed using the following equations. Exposure is compared to the short-term incidental oral and dermal NOAEL of 5.9 mg/kg/day using the standard risk convention MOE = NOAEL/exposure dose.

Hand-to-Mouth Exposure and Risk Calculations

PDRt for **hand-to-mouth** = TTRt * SA * EX * FQ * ET * CF1

where: PDRt = potential dose rate on day “t" (mg/day)
TTRt = turf transferable residue on day “t" (ug/cm^2 turf)
SA = surface area of the hands (cm^2/event); palmar surface area of 3 fingers = 20 cm^2
EX = extraction from the hand by saliva (50%)
FQ = frequency of hand-to-mouth activity (events/hr); 20 for short-term
ET = exposure time (hr/day); 2 hrs/day
CF1 = weight unit conversion factor to convert ug units in the TTR value to mg for the daily exposure (0.001 mg/ug)

and

TTRt = AR * F * CF2 * CF3

where: AR = application rate (lb ai/acre); 1.4 lb ai/acre
F = fraction of ai available on turf/grass (unitless); 5%
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the DFR or GR value (4.54E+8 ug/lb)
CF3 = area unit conversion to convert the surface area units (acre) in

the application rate to cm^2 for the TTR or GR value (2.47E-8 acre/cm^2)

TTR_t = 1.4 lb ai/A * 0.05 (%) *4.54^8 µg/lb * 2.47^{-8} A/cm^2 = 0.78 µg/cm^2

PDR_t = 0.78 µg/cm^2 * 20 cm^2/event * 0.50 (%) * 20 events/hr * 2 hr/day * 0.001 mg/µg = 0.312 mg/day ÷ 15 kg bw = 0.0208 mg ai/kg/day.

Therefore, children's hand-to-mouth MOE = 280.

Object-to-Mouth Exposure and Risk Calculations

PDRt for **object-to-mouth (turf)** = GRt * IgR * CF1

where: PDRt = potential dose rate on day "t" (mg/day)
GRt = grass (and plant matter) residue on day "t" (ug/cm^2)
IgR = mouthing rate of grass (cm^2/day); 25 cm^2/day
CF1 = weight unit conversion factor to convert ug units or residues on the grass to mg for the daily exposure (0.001 mg/ug)

and: GRt = AR * F * CF2 * CF3

where: AR = application rate (lb ai/acre); 1.4 lb ai/acre
F = fraction of ai available on turf/grass (unitless); 20%

CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the TTR or GR value (4.54E+8 ug/lb)
CF3 = area unit conversion to convert the surface area units (acre) in the application rate to cm^2 for the TTR or GR value (2.47E-8 acre/cm^2)

GR_t = 1.4 lb ai/A * 0.2 (%) * 4.54E* ug/lb * 2.47^{-8} acre/cm^2 = 3.14 µg/cm^2
and
3.14 µg/cm^2 * 25 cm^2/day * 0.001 mg/µg = 0.078 mg/day ÷ 15 kg bw = 0.0052 mg ai/kg/day.

Therefore, children's object-to-mouth MOE = 1,100.

Ingestion of Soil Exposure and Risk Calculations

PDRt for **incidental ingestion of soil** = SRt * IgR * CF1

where: PDRt = potential dose rate on day "t" (mg/day)
SRt = soil residue on day "t" (ug/g)
IgR = ingestion rate of soil (mg/day)
CF1 = weight unit conversion factor to convert the ug of residues on the soil to grams to provide units of mg/day (1E-6 g/ug)

and: SRt = AR * F * CF2 * CF3 * CF4

where: AR = application rate (lb ai/acre)

F = fraction of ai available in uppermost cm of soil (fraction/cm)
CF2 = weight unit conversion factor to convert the lbs ai in the application rate to ug for the soil residue value (4.54E+8 µg/lb)
CF3 = area unit conversion to convert the surface area units (acre) in the application rate to cm^2 for the SR value (2.47E-8 acre/cm^2)
CF4 = volume to weight unit conversion factor to convert the volume units (cm^3) to weight units for the SR value (0.67 cm^3/g soil)

SR_t = 1.4 lb ai/A * 1/cm* 4.54^8 µg/lb * 2.47^{-8} /cm^2 * 0.67 cm^3/g = 10.52 µg/g and

10.52 µg/mg * 100 mg/day * 0.000001 g/µg = 0.001052 mg/day ÷ 15 kg/day = 0.00007 mg ai/kg/day.

Therefore, children's soil ingestion MOE = 84,000.

Adult and Children's Dermal Post-application Exposure to Treated Turf

Recreational Activity on Turf

TTR_t = 1.4 lb ai/A * 0.05 (%) *4.54^8 µg/lb * 2.47^{-8} A/cm^2 = 0.78 µg/cm^2

Adults
0.78 µg/cm² * 14,500 cm²/hr * 0.001 mg/µg * 2 hr/day * 12% dermal absorption ÷ 60 kg = 0.045 mg/kg/day.

Therefore, adult's recreational MOE = 130.

Children
0.78 µg/m² * 5,200 cm²/hr * 0.001 mg/µg * 2 hr/day * 12% dermal absorption ÷ 15 kg = 0.065 mg/kg/day.

Therefore, children's recreational MOE = 91.

Golfing on Treated Turf
Exposure and risk from recreational activity on turf results in higher exposure than that for golfing. Golfing estimates are provided to understand risk if tetraconazole were restricted to golf courses only (and not unspecified turf).

Adult and Child Golfer post-application exposures may be estimated using the convention stated in ExpoSAC draft procedure regarding "Golfer Exposure Assessment For Adults and Children" (24 August 2000). The draft procedure states that adult and adolescent golfer dermal post-application exposure may be calculated as $DE_{(t)}$ (mg ai/kg/day) = ($TTR_{(t)}$ (µg/cm²)) * TC (cm²/hr) * hr/day/1000 µg/mg * BW (body weight (kg)) Where:
$DE_{(t)}$ = dermal exposure at time (t) attributable to golfing on previously treated turf (mg ai/kg/day).
$TTR_{(t)}$ = turf transferable residue at time $_t$ (µg/cm²)
TC = Transfer Coefficient (500 cm²/hr)
hr = exposure period (4 hours)
BW = body weight (kg) (60 kg for adult; adjusted (multiplied) by a factor of 1.7 for child golfers)

Therefore,

Adult Golfer
DE = 0.78 µg/cm² * 500 cm²/hr * 0.001 mg/µg * 4 hr/day * 12% dermal absorption ÷60 kg = 0.000312 mg/kg/day.
Therefore, the MOE for adult golfer = 1900.

Child Golfer
The adult dose level is adjusted by a factor of 1.7 to estimate child golfer exposure.
Therefore, 0.000312 mg/kg/day * 1.7 = 0.00053 mg/kg/day.

Therefore, the MOE for child golfer = 1100.

Conclusions
Based on the proposed turf use, HED estimates that non-occupational post-application risk results in MOEs of concern for children. The MOEs for children via dermal and oral pathways range from 91 to 1100 (HED's level of concern is an MOE of at least 100). Risk estimates for adults are not of concern (lowest MOE=130).

6.3 Other (Spray Drift)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for tetraconazole. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT7 computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

Acute Aggregate Risk
No acute residential/recreational exposures are expected. Since the acute dietary assessment included food and water only, the exposures in Table 5.2a represent aggregate exposures. The Tier 1 acute dietary analysis (food and water; drinking water estimate derived from the proposed turf application scenario) resulted in an exposure estimate for females 13-49 years old less than HED's level of concern (2.7% aPAD; see Table 5.2a). Since the dietary risk estimate from turf drinking water resulted in an unacceptable cancer risk alone (see below) and HED is recommending that the turf use not be established, the acute analysis was repeated with exclusion of the turf use (the drinking water estimate was derived from the pecan application scenario). The resulting risk estimate for females 13-49 years old does not exceed HED's level of concern (<1.0% aPAD; see Table 5.2b). An acute endpoint of concern was not identified for the general population including infants and children.

Short-term Aggregate Risk
Short-term aggregate risk is made up of dietary and non-dietary sources of exposure. As shown above in Section 6.2, if the turf use is granted, HED estimates that post-application risk will exceed HED's level of concern for children. This risk estimate does not include dietary sources of exposure. Therefore,

aggregate risk assessments were not performed since additional exposure through drinking water would increase the risk estimate.

Aggregate Cancer Risk
As stated above, in Section 5.2, dietary cancer risk including turf drinking water estimates exceeds HED's level of concern and HED recommends that the turf use not be registered. Dermal exposure from recreational turf uses would only increase the cancer risk. Therefore, aggregate cancer risk was not assessed.

8.0 Cumulative Risk Characterization/Assessment

Tetraconazole is a member of the triazole-containing class of pesticides, often referred to as the conazoles. EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. The conazole pesticides, as a whole, tend to exhibit carcinogenic, developmental, reproductive, and/or neurological effects in mammals. Additionally, all the members of this class of compounds are capable of forming, via environmental and metabolic activities, 1,2,4-triazole, triazolylalanine and/or triazolylacetic acid. These metabolites have also been shown to cause developmental, reproductive, and/or neurological effects. Structural similarities and sharing a common effect does not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate "by the same, or essentially the same sequence of major biochemical events. Hence, the underlying basis of toxicity is the same, or essentially the same for each chemical." (EPA, 2002) A number of potential events could contribute to the toxicity of conazoles (e.g., altered cholesterol levels, stress responses, altered DNA methylation). At this time, there is not sufficient evidence to determine whether conazoles share common mechanisms of toxicity. Without such understanding, there is no basis to make a common mechanism of toxicity finding for the diverse range of effects found. Investigations into the conazoles are currently being undertaken by the EPA's Office of Research and Development. When the results of this research are available, the Agency will make a determination of whether there is a common mechanism of toxicity and, therefore, a basis for assessing cumulative risk. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www.epa.gov/pesticides/cumulative.

To support existing tolerances and to establish new tolerances for conazole pesticides, including tetraconazole, EPA conducted human health risk assessments for exposure to 1,2 4-triazole, triazolylalanine, and triazolylacetic acid resulting from the use of all current and pending uses of triazole-containing pesticides (as of 9/1/05). The risk assessment is a highly conservative, screening-level evaluation in terms of hazards associated with the common metabolites (*e.g.*, use of maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (*i.e.*, high-end estimates of both dietary and non-dietary exposures). Acute and chronic aggregate risk estimates associated with these compounds are below the Agency's level of concern for all durations of exposure and for all population subgroups, including those of infants and children. The Agency's risk assessment for these common metabolites is available in the propiconazole reregistration docket at http://www.regulations.gov, Docket Identification (ID) Number EPA-HQ-OPP-2005-0497.

9.0 Occupational Exposure/Risk Pathway

Information for this section was adapted from several occupational and residential exposure assessments (Memo, M. Dow, D331997, 9/20/2006; Memo, M. Dow, D309312, 10/22/2004; Memo, M. Dow, D321615, 02/08/2006; Memo, M. Dow, D334610, 12/27/06.)

Uses are proposed on pecans, soybeans, sugar beets, peanuts and turf. Occupational handler and post-

application exposure may occur as a result of the proposed uses. Application methods and rates are described in Table 2.1. Most use sites carry a 14 day PHI. Re-treatment intervals range from 14-28 days. Soybeans and sugar beet may be treated twice a year while peanuts can be treated 4 times per year and pecans 8 times (see Table 2.1 for use pattern).

Short- (1-30 days) and intermediate-term (1-6 months) dermal and inhalation exposures were assessed.

9.1 Short-/Intermediate-Term Occupational Handler Risk

A variety of uses are proposed for tetraconazole. Formulations evaluated in this assessment (Domark® 230 ME and Eminent® 125SL) are liquid formulations which are mixed with water prior to spraying. All proposed uses were considered in this assessment. Those exposure scenarios expected to result in the highest occupational exposure were evaluated. Based upon the proposed agricultural uses, HED believes that the most highly-exposed occupational pesticide handlers (*i.e.,* mixers, loaders, applicators) are the following:

1) mixer/loader using open-pour loading of liquids for aerial spraying
2) applicator using open-cab ground-boom sprayer
3) applicator using open-cab airblast sprayer
4) applicator using high-pressure hand-wand sprayer
5) aerial applicator (pilot)

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline," that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves, as well as with a single layer of work clothing and the use of protective gloves or other PPE as might be necessary. The proposed product label involved in this assessment directs applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves made of any waterproof material such as nitrile, butyl, neoprene and/or barrier laminate.

The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the data available for monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August, 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

Short- and intermediate-term dermal and inhalation handler risks were estimated. HED assumes 100% inhalation absorption and 12% dermal absorption. Short-term dermal and inhalation exposures were summed and compared to the short-term NOAEL of 5.9 mg/kg/day identified for short-term dermal and inhalation risk assessment. Intermediate-term dermal and inhalation exposures were summed and

compared to the NOAEL of 0.73 mg/kg/day identified for intermediate-term dermal and inhalation risk assessment. Exposure and risk estimates are presented in Table 9.1 below. **The risk estimate for applicators using high-pressure handwands to treat turf exceeds HED's level of concern (MOE=21). For the other uses, provided that mixer/loaders supporting aerial operations wear protective gloves, all estimated MOEs are >100, and the proposed uses do not exceed HED's level of concern for occupational pesticide handlers.**

Table 9.1. Estimated Short- and Intermediate-term Handler Exposure and Risk to Tetraconazole.						
Unit Exposure[1] mg/lb handled	Application Rate[2] lb ai/A	Units Treated[3] Per Day	Short-term Average Daily Dose[4] mg/kg/day	Short-term MOE[5]	Intermediate-term Average Daily Dose[4] mg/kg/day	Intermediate-term MOE[5]
Mixer/Loader -Liquid - Open Pour - Supporting Aerial Operations (Soybean)						
Dermal: No Glove 2.9 HC With Glove 0.023 HC Inhalation 0.0012 HC	0.1	1200 A	Dermal: No Glove 0.7 W Glove 0.0055 Inhalation 0.0024	No Glove 8 W Glove 746	Dermal: No Glove 0.6 W Glove 0.0047 Inhalation 0.0021	No Glove 1 W Glove 107
Applicator - Ground-boom - Open Cab (Sugar Beet)						
Dermal: No Glove 0.014 HC With Glove 0.014 MC Inhalation 0.00074 MC	0.1	200 A	Dermal: No Glove 0.00056 W Glove 0.00056 Inhalation 0.00025	No Glove 7,283 W Glove 7,283	Dermal: No Glove 0.00048 W Glove 0.00048 Inhalation 0.00021	No Glove 1,058 W Glove 1,058
Applicator – Airblast Sprayer-Open Cab (Pecans)						
Dermal: No Glove 0.36 HC With Glove 0.24 HC Inhalation 0.0045 HC	0.125	40 A	Dermal: No Glove 0.0036 W Glove 0.0024 Inhalation 0.000375	No Glove 1500 Gloves 2100	Dermal No Glove 0.0031 Glove 0.0021 Inhalation 0.00032	No Glove 210 Glove 300
Applicator-High-pressure Handwand (Turf)						
Dermal: No Glove 1.8 LC With Glove 0.64 LC Inhalation 0.079 HC	1.4 Or 90 gal/A	11 A Or 1000 gal/day	Dermal: No Glove 0.056 W Glove 0.02 Inhalation 0.02	No Glove 78 Gloves 150	Dermal: No Glove 0.048 W Glove 0.017 Inhalation 0.017	No Glove 11 Glove 21
Applicator - Fixed-wing Aircraft (Soybean)						
Dermal: No Glove 0. 0050 MC Inhalation 0.000068 MC	0.125	1200 A	Dermal: No Glove 0.0012 Inhalation 0.00014	No Glove 4,402	Dermal: No Glove 0.001 Inhalation 0.00012	No Glove 652

1. Unit Exposures are taken from "PHED Surrogate Exposure Guide," PHED Version 1.1, August, 1998.

Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Units = mg ai/lb ai handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence. Single layer of work clothing = long pants, long-sleeved shirt, shoes plus socks.
2. Application Rate. = Taken from proposed Eminent® 125SL Fungicide label.
3. Units Treated are taken from ExpoSAC SOP No. 9.1 "Standard Values for Daily Acres Treated in Agriculture" Revised 9/25/2001.
4. Average Daily Dose = Unit Exposure * Application Rate * Units Treated * Absorption Rate (12% dermal absorption) ÷ Body Weight (60 kg used for short-term estimates; 70 kg used for intermediate-term).
5. MOE = Margin of Exposure = NOAEL ÷ ADD. Short-term NOAEL = 5.9 mg ai/kg/day and intermediate-term NOAEL = 0.73 mg ai/kg/day.

9.2 Short-Term Occupational Post-application Risk

There is a potential for agricultural workers to have post-application exposure to pesticides during the course of typical agricultural activities. HED in conjunction with the ARTF has identified a number of post-application agricultural activities that may occur. HED has also identified TCs (cm^2/hr) relative to the various activities, which express the amount of foliar contact over time during each of the activities identified. The activity and crop with the highest TC associated with post-application activities is commercial turf/sod harvesting (6800 cm^2/hr); the registrant is a member of the ARTF and is allowed to use these data. A post-application risk assessment was provided for pecans, peanuts, sugar beets and turf for the sake of comparison between proposed uses.

Short-term (1-30 days) dermal risks were assessed. Inhalation risk is expected to be negligible. Intermediate-term risks were not assessed since HED does not expect workers to engage in post-application activities for more than 30 consecutive days.

The TCs used in this assessment are from an interim TC SOP developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on TCs. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound-specific DFR data, HED assumes 5% of the application rate is available as DFR on day zero after application [adapted from ExpoSAC SOP No. 3.1, August 7, 2000.

The highest TCs for each of the proposed uses are listed below. For each proposed use, one post-application risk assessment was performed, based on the highest TC.

Pecan: Hand harvesting and hand pruning: 2500 cm^2/hr

Peanut: Scouting and irrigation: 1500 cm^2/hr

Sugar beet: Scouting and irrigation: 1500 cm^2/hr

Turf: Sod harvesting: 6800 cm^2/hr; Golf course maintenance: 3400 cm^2/hr

Note: The sod harvest TC is taken from a study conducted by the ARTF and is therefore compensable if the registrant is not a current member of the ARTF. HED believes that the registrant is a member of the

ARTF; however, if not, or does not properly compensate the ARTF for use of the data, the TC may not be used for regulatory purposes. For purposes of compensation the MRID No. is 45432303.

Post-application risk for the soybean use was not assessed since, typically, soybeans are mechanically harvested (resulting in lower exposure than activities associated with the other proposed crops) and the application rate for soybeans is lower than other proposed uses (0.075 lb ai/acre). Therefore, it is expected that post-application risk from the soybean use will not exceed HED's level of concern.

The following convention may be used to estimate post-application exposure. All estimates are for "day zero" or the day of treatment.

Surrogate DFR = application rate * 5% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 when compound specific DFR data are not available.

Average Daily Dose (ADD) (mg ai/kg/day) = DFR µg/cm^2 * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/60 kg bw

MOE = NOAEL ÷ ADD; An MOE of 100 is adequate to protect agricultural workers.

Risk estimates are shown in Table 9.2 below. Calculations follow the table.

Table 9.2. Occupational Post-Application Risk Estimates for Tetraconazole.

Activity	Risk (MOE)	Days to Reach Target MOE (100)
Pecan: Hand Harvesting and Pruning	2100	N/A
Peanut: Scouting and Irrigation	4400	N/A
Sugar Beet: Scouting and Irrigation	4400	N/A
Turf: Sod Harvesting	69	4
Turf: Golf Course Maintenance	140	N/A

Since the estimated MOEs for pecan, peanut and sugar beet activities are greater than 100, post-application risk for these uses do not exceed HED's level of concern. However, the MOE for the turf use (sod harvest) exceeds HED's level of concern (MOE=69) on day zero.

HED assumes linearity between dose and response. When compound-specific DFR data are not available, HED assumes that residues decrease by 10% per day. Based on this assumption, an MOE of 100 for sod harvesting would not be achieved until DAT 4.

These estimates are conservative in that they are based upon the maximum rate of application and on TC's derived from ARTF monitoring studies. The DFR estimates and MOE may be refined if compound-specific data for these activities and these use sites are available.

Occupational Post-application Calculations:

Pecan
DFR = 0.125 lb ai/A * 0.05 * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.07 µg/cm² and
0.07 µg/cm² * 2,500 cm²/hr * 8 hr/day * 0.001 mg/µg * 0.12 (dermal absorption) * 1/60 kg = 0.0028 mg/kg/day.
MOE = NOAEL ÷ ADD; 5.9 mg/kg/day ÷ 0.0028 mg/kg/day = 2100.

Peanut
DFR = 0.1 lb/A * 0.05 * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.056 µg/cm² and
0.056 µg/cm² * 1,500 cm²/hr * 8 hr/day * 0.001 mg/µg * 0.12 (dermal absorption) * 1/60kg = 0.0013 mg/kg/day.
5.9 mg/kg/day ÷ 0.0013 mg/kg/day = 4400.

Sugar Beet
DFR = 0.1 lb/A * 0.05 * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.056 µg/cm² and
0.056 µg/cm² * 1,500 cm²/hr * 8 hr/day * 0.001 mg/µg * 0.12 (dermal absorption) * 1/60 kg = 0.0013 mg/kg/day.
5.9 mg/kg/day ÷ 0.0013 mg/kg/day = 4400.

Turf-Sod Harvest
DFR = 1.4 lb/A * 0.05 * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.78 µg/cm² and
0.78 µg/cm² * 6,800 cm²/hr * 8 hr/day * 0.001 mg/µg * 0.12 (dermal absorption) * 1/60 kg bw = 0.085 mg/kg/day.
5.9 mg/kg/day ÷ 0.085 mg/kg/day = 69.

Turf-Golf Course Maintenance
DFR = 1.4 lb/A * 0.05 * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 = 0.78 µg/cm² and
0.78 µg/cm² * 3,400 cm²/hr * 8 hr/day * 0.001 mg/µg * 0.12 (dermal absorption) * 1/60kg = 0.085 mg/kg/day.
5.9 mg/kg/day ÷ 0.085 mg/kg/day = 140.

9.3 Occupational Cancer Risk (Handler and Post-application)

Cancer risk is calculated by adjusting daily exposure to account for long-term exposure. This is performed by calculating a lifetime average daily dose (LADD). The LADD is derived by summing (when appropriate) the dermal and inhalation exposures to obtain an ADD, then multiplying the ADD by the assumed factors of:

$$\frac{\text{30 days exposure per year}}{\text{365 days per year}} * \frac{\text{35 years worked per lifetime}}{\text{70 years expected lifetime}} = 0.041$$

Cancer Risk is estimated by multiplying the Q_1^* (0.023 mg/kg/day) by the Lifetime Average Daily Dose (LADD). Estimates of cancer risk are based on short- and intermediate-term exposure estimates as shown above in Sections 9.1 and 9.2.

9.3.1 Occupational Handler Cancer Risk

The daily dermal and inhalation exposures for handlers are taken from Table 9.1. Intermediate-term

exposure estimates are conducted using a 70-kg body weight. In all exposure scenarios, workers are expected to wear protective gloves, except aerial applicators (pilots are not required to wear gloves). Workers are expected to work 30 days per year over a 70-year lifetime. Generally, HED uses average application rates for cancer risk assessment, but in the case of tetraconazole, information on the average application rate is not available. Cancer risk estimates for handlers are provided in Table 9.3.1 below.

Table 9.3.1. Estimated Cancer Risk for Occupational Handlers.

Intermediate-term Average Daily Dose[1] mg/kg/day	Factor to Convert to LADD[2]	Q_1^* (mg/kg/day)[3]	Estimated Cancer Risk[4]
Mixer/Loader-Liquid-Open Pour-Supporting Aerial Operations (Soybean)			
Dermal: 0.0047 Inhalation: 0.0021	0. 041	0.023	6.4×10^{-6}
Applicator-Ground-boom-Open Cab (Sugar Beets)			
Dermal: 0.00048 Inhalation: 0.00021	0.041	0.023	6.5×10^{-7}
Applicator-Airblast Sprayer-Open Cab (Pecans)			
Dermal: 0.0021 Inhalation: 0.00032	0.041	0.023	2.3×10^{-6}
Applicator-High-pressure Handwand (Turf)			
Dermal: 0.017 Inhalation: 0.017	0.041	0.023	3.2×10^{-5}
Applicator-Fixed-Wing Aircraft (Soybean)			
Dermal: No Glove 0.001 Inhalation 0.00012	0.041	0.023	1.1×10^{-6}

1. Exposure values taken from Table 9.1
2. $0.041 = \frac{\text{30 days exposure per year}}{\text{365 days per year}} * \frac{\text{35 years worked per lifetime}}{\text{70 years expected lifetime}}$
3. Q_1^* (0.023 mg/kg/day)
4. Cancer Risk = LADD * Q_1^*

The highest estimated cancer risk is for applicators using high-pressure handwand to treat turf. The estimated risk is **3.2×10^{-5}** for this use. The next highest cancer risk estimate is for mixer/loaders supporting aerial application, with a cancer risk estimate of **6.4×10^{-6}.** HED's level of concern for occupational cancer risk is 1×10^{-4} to 1×10^{-6}. Therefore, the proposed turf use exceeds HED's level of concern. Estimated cancer risks for all other proposed uses do not exceed HED's level of concern.

9.3.2 Occupational Post-application Cancer Risk

The daily dermal and inhalation exposures for handlers are taken from Section 9.2 (exposure values were adjusted slightly to account for a 70-kg body weight). Only dermal exposure was considered. Workers are expected to work 30 days per year over a 70-year lifetime. See Section 9.2 above for details about each of the exposure scenarios.

Table 9.3.2. Estimated Occupational Post-application Cancer Risk.

Average Daily Dose[1] mg/kg/day	Factor to Convert to LADD[2]	Q_1^* (mg/kg/day)[3]	Estimated Cancer Risk[4]
Pecan			
0.0024	0. 041	0.023	2.2×10^{-6}
Peanut			
0.0011	0.041	0.023	1.0×10^{-6}
Sugar Beet			
0.0011	0.041	0.023	1.0×10^{-6}
Turf-Sod Harvest			
0.073	0.041	0.023	6.9×10^{-5}
Turf-Golf Course Maintenance			
0.036	0.041	0.023	3.3×10^{-5}

1. Exposure values taken from Section 9.2 (adjusted to a 70 kg body weight).
2. 0.041 = 30 days exposure per year * 35 years worked per lifetime
   365 days per year 70 years expected lifetime

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3. Q_1^* (0.023 mg/kg/day)
4. Cancer Risk = LADD * Q_1^*

The highest estimated post-application cancer risk is for workers harvesting sod treated with tetraconazole (6.9×10^{-5}). The next highest cancer risk estimate is for workers doing golf course maintenance at 3.3×10^{-5}. HED's level of concern for occupational cancer risk is 1×10^{-4} to 1×10^{-6}. Therefore, the proposed turf use exceeds HED's level of concern. Estimated cancer risks for all other proposed uses do not exceed HED's level of concern.

9.3.3 Restricted-Entry Interval (REI)

Tetraconazole is classified in Acute Toxicity Category III for acute dermal toxicity and for primary eye irritation. It is classified in Acute Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is not a dermal sensitizer. Proposed labels indicate a 24-hour REI. The REI on labels is adequate to protect agricultural workers from post-application exposures to tetraconazole during the course of typical agricultural activities.

10.0 Data Needs and Label Requirements

10.1 Toxicology

10.2 Residue Chemistry

●Revised labels excluding all turf uses
●Revised Section F
●Revised Section B: **(1)** pecan: revised label should be submitted which indicates a PHI of 30 days, spray volumes of >100 GPA for ground applications and >10 GPA for aerial applications, and removes references concerning the addition of a surfactant to the spray solution; **(2)** peanut: Revised label should be submitted which prohibits the feeding of peanut hay to livestock and removes references concerning the addition of a surfactant to the spray solution; **(3)** sugar beet: Revised label should be submitted which removes references concerning the addition of a surfactant to the spray solution; and **(4)** soybean:

Revised Section B which is consistent with the use directions provided in the email dated 20-June-2006 from Mel Graben (Isagro USA) to Lisa Jones (EPA/OPP/RD), Based on advice from the ChemSAC (minutes of 7-Jun-2006) and the magnitude of the residue studies, the following revisions should be included on the label: (a) since the magnitude of the residue studies employed a final application at the R5 crop growth stage, replace the proposed restriction, "Do not apply Domark at or after growth stage R6 (full seed)" with, "Do not apply after soybean growth stage R5 (beginning seed)"; (b) since the magnitude of the residue studies did not include an adjuvant in the spray solutions, information concerning the addition of a adjuvant to the spray solution should be removed from the label; and (c) include the following restriction, "Do not use on vegetable soybean varieties grown for their immature pods."
●Storage Stability Data: HED requests that the petitioner submit additional data determining the storage stability of T in soybean seed, AGF, meal, and hulls (487 days).
●Field Trial Data: HED requests that the petitioner reanalyze the soybean field trial and processing samples using a method capable of quantitatively determining residues of tetraconazole *per se* (storage stability data are also required).

10.3 Occupational/Residential

None.

Appendix A: Hazard Assessment

The requirements (CFR §158.340) for food use for tetraconazole are in Table 1

Table 1. 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[a]
870.3200 ..... 21-Day Dermal	Yes	Yes
870.3250 ..... 90-Day Dermal	No	No
870.3465 ..... 90-Day Inhalation	No	No
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[b]
870.4100b ..... Chronic Toxicity (nonrodent)	Yes	Yes
870.4200a ..... Oncogenicity (rat)	Yes	Yes[b]
870.4200b ..... Oncogenicity (mouse)	Yes	Yes
870.4300 ..... Chronic/Oncogenicity	Yes	Yes[b]
870.5100 ..... Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300 ..... Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	Yes	Yes
870.5395 ..... Mutagenicity—Other Genotoxic Effects	Yes	Yes
870.6100a ..... Acute Delayed Neurotoxicity (hen)	No	–
870.6100b ..... 90-Day Neurotoxicity (hen)	No	–
870.6200a ..... Acute Neurotoxicity Screening Battery (rat)	No	–
870.6200b ..... 90 Day Neurotoxicity Screening Battery (rat)	No	–
870.6300 ..... Developmental. Neurotoxicity	No	--
870.7485 ..... General Metabolism	Yes	Yes
870.7600 ..... Dermal Penetration	No	–
870.7200 Companion Animal Safety	No	–

[a] The dog chronic oral toxicity study (870.4100) satisfies the data requirements for 870.3150

[b] The combined chronic toxicity/oncogenicity study in the rat satisfies the requirements for guidelines 870.4100a, 870.4200a, and 870.4300

All Studies:

Subchronic Toxicity

870.3100 4-Week Oral Toxicity - Rat

EXECUTIVE SUMMARY: In a subchronic toxicity range-finding study (MRID 44751304), M14360 Technical (Tetraconazole 92.0% ai, Batch number FCF/T/59) was administered by gavage (as a suspension of 1% methylcellulose) to 5 male and female Crl:CD BR rats per dose level at levels of 0, 70, 200, or 500 mg/kg/day.

Since this study is an early range-finding study performed only to determine adequate dose levels used in other studies, only a summary of this study is provided in order to confirm the adequacy of the dose selection rationale used in later studies.

Due to the severity of clinical signs observed at the 500 mg/kg/day dose level and in 3 of 5 females at the 200 mg/kg/day dose levels, these animals were sacrificed after only 1 or 2 doses during week 1. The 500 mg/kg/day dose level was aborted. One of the remaining females at the 200 mg/kg/day dose level was sacrificed during week 3. Clinical signs at 500 mg/kg/day included "state of collapse", labored breathing, salivation after dosing, urogenital staining, unsteady gait, lethargy, red peri-orbital staining, cold to the touch, "wet mouth, forepaws and ventral surface", and muscular spasms. Macroscopic findings included congestion of the adrenals, gastric distension in 3/5 males and females at 500 mg/kg/day and congestion of the forestomach in 3/5 males at 500 mg/kg/day.

Less severe signs were noted in females at the 200 mg/kg/day dose level. The investigators also noted lack of grooming, slow and infrequent respiration, and salivation. At 70 mg/kg/day clinical signs included salivation persisting one hour after dosing in both males and females, brown peri-oral staining (in one female), hair loss in 4 of 5 females and "dirty tails" in all 5 females.

A decrease in bodyweight gain was noted in 70 and 200 mg/kg/day males. No effect was noted in females at either remaining dose level. However, food consumption was comparable to controls. Decreased WBC and lymphocyte counts were noted in 200 mg/kg/day males. A lower total white cell count was also noted for 3 of 5 males at the 70 mg/kg/day dose level. A decrease in plasma glucose was noted in both sexes at the 200 and 70 mg/kg/day dose levels. Increases in albumin and globulin fractions were noted in 200 and 70 mg/kg/day males, BUN and calcium levels increased in 200 mg/kg/day males, and slight increases in sodium and phosphorus levels were observed in 200 mg/kg/day females.

A dose related increase in liver weight was noted in both sexes at 200 and 70 mg/kg/day. At termination, enlarged livers and pale incisors were observed in all 200 mg/kg/day rats and enlarged liver was seen in one male at 70 mg/kg/day. In addition, an increase in kidney weights was apparent in males at 200 and 70 mg/kg/day dose levels. Also, at 70 mg/kg/day, a statistically significant increase in the mean weight of ovaries was noted. No abnormalities were observed in kidneys after gross examination.

In conclusion, clearly the 500 and 200 mg/kg/day dose levels resulted in severe toxicity. Based on this 4-week gavage study, doses exceeding 70 mg/kg/day would not be supported in longer term studies.

This subchronic study is acceptable/nonguideline for range-finding purposes.

870.3100 4-Week Oral Toxicity - Rat

EXECUTIVE SUMMARY: In this rat study (MRID # 44751305), tetraconazole technical(92% ai) was administered in the diet to groups of ten male and ten female Charles River Sprague Dawley rats/sex/dose in the diet at dosages of 0, 40, 160, 640, 2500 or 10000 ppm (males: 0, 4.4, 17.5, 68.4, 229 mg/kg/day; females 0, 3.8, 16.1, 62.3, 217 mg/kg/day) daily for 4 weeks.

All rats at the high dose showed severe symptoms of inappetence, body weight loss, reduced fecal output, emaciation and hunched posture. These were sacrificed after 5 days of treatment. Their livers were pale and showed irregular areas of necrosis and inflammation.

At the 2500 ppm dosage, all rats exhibited emaciation and hunched posture from week 1 which lasted in some of them the duration of the treatment. At the lower doses there were no clinical signs or deaths.

Food intake was reduced in rats receiving 640 ppm (90% in males and 73% of controls in females) and 2500 ppm (39% in males and 46% of controls in females) during week one. Reduced food consumption persisted in females for the study duration at 640 and 2500 ppm and in males at the 2500 ppm level.

Body weight gains were also depressed in a dose-related manner at the 640 and 2500 ppm levels in males and females. In males it was more prominent in the first week and showed recovery subsequently. After 4 weeks of treatment body weight gains were 92% and 47% of controls for the males at the 640 and 2500 ppm, respectively. For the females it was 69% and 35% of the controls, respectively.

Hematological parameters were comparable in all treatment groups. Biochemical findings were reported in the 160, 640 and 2500 ppm. These included decreased sugar, increased total protein due to increased globulin fractions, increased potassium and phosphorus, decreased cholesterol in males and increased cholesterol in females. Biologically-relevant changes were decreased glucose at 640 and 2500 ppm in males and 2500 ppm in females and decreased cholesterol in males at 2500 ppm and increased cholesterol in females at 2500 ppm.

Significantly increased liver weights were observed in males from 40 ppm through the 2500 ppm level and in females in the 640 and 2500 ppm groups. Increased kidney weights relative to body weight were seen in all treatment groups of male rats and in the 160-, 640- and 2500-ppm groups in females. Increased testes weight was seen in the 640 and 2500 ppm males and decreased uterine weight in the 2500 ppm females.

Enlarged livers were seen in a dose related manner in males (0%, 10%, 20%, 50%, 100%) and females (0%, 0%, 0%, 30%, 100) at the 0, 40, 160, 640, and 2500 ppm, respectively. Pale liver was seen in all rats at the 2500 ppm with accentuated liver markings. Small uteri were noted in females at 2500 ppm. There were no morphological abnormalities in kidneys or testes.

A dose related incidence of minimal centrilobular and/or mid-zonal hepatocyte enlargement in rats at the 160, 540 and 2500 ppm was observed. Also, minimal to moderate fine vacuolation of centrilobular and midzonal hepatocytes was noted in both sexes at 2500 ppm.

Based on the hepatotoxic findings (increased liver weight, enlarged livers, enlarged centrilobular hepatocytes) the LOAEL in rats following administration of tetraconazole in the diet for 4 weeks was 40 ppm for males (4.4 mg/kg/day) and 160 ppm for females (15.3 mg/kg/day). A NOAEL was not established for males, but for females it is 40 ppm (3.8 mg/kg/day).

This range finding toxicity study is classified as acceptable/non-guideline.

870.3100 4-Week Oral Toxicity - Rat

EXECUTIVE SUMMARY: In this rat study (MRID # 44751306), Tetraconazole technical(92% ai) was administered in the diet to groups of ten male Charles River Sprague Dawley rats/dose in the diet at 0, 2, 5, 15 or 40 ppm (0, 0.21, 0.52, 1.57, 4.19 mg/kg/day) daily for 4 weeks. The purpose of the study was exploratory to enable selection of dose levels for longer term studies. The high dose of 40 ppm was selected based on no clear evidence of a no effect level in a previous study (MRID # 44751305).

All rats survived the treatment and there were no clinical reaction signs to the test material in any of the groups. Inclusion of tetraconazole in the diet did not have an effect on the body weight gain in rats, their food and water consumption, or food efficiency.

Plasma glutamate dehydrogenase (GDH) activity was slightly higher in week 4 for animals receiving the 15 ppm (167% of control, $p<0.05$) and 40 ppm (233%,$p<0.01$) tetraconazole. Plasma glutamic-oxaloacetic transaminase (GOT) activity was higher in week 4 for animals receiving the 40 ppm (117%, $p<0.05$). These increases were dismissed as being toxicologically important since all the values were considered to be within the ranges for the age and strain of the rat.

There were no treatment related effects on organ weights, macroscopic or microscopic effects. Livers appeared normal.

In this range finding study toxic effects were not observed at any of the levels tested. A NOAEL in male rats following administration of tetraconazole in the diet for 4 weeks was 40 ppm (4.19 mg/kg/day).

This range finding toxicity study is classified as acceptable/non-guideline.

870.3100 90-Day Oral Toxicity - Rat

Executive Summary: In this subchronic rat study (MRID # 44335504), tetraconazole technical (M-14360)(93.1% ai) was administered in the diet to groups of ten male and ten female Charles River Sprague Dawley rats/sex/dose in the diet at dosages of 0, 10, 60 or 360 ppm (males: 0, 0.7, 4.1, 23.9 mg/kg/day; females 0, 0.9, 5.5, 28.7 mg/kg/day) daily for 90 days.

No clinical signs or deaths were reported in any of the groups. Food consumption was not affected by the treatment as measured by the cumulative group mean food intake. Male rats at the high dose group significantly ($p<0.05$) gained more weight than controls (116.7% of control group weight gains) while females at the high dose group had significantly lower mean body weight gains (83% of the control group weight gains). The other treated groups had mean body weight gains comparable to the controls. There were no treatment-related changes in urinary or hematology parameters. There were alterations of no toxicological significance in some clinical chemistry parameters. These included a slight decrease in the albumin fraction with an increase in the globulin fraction amongst all treated males; significantly decreased alkaline phophatase and increased potassium values in the 360 ppm females; dosage-related increases in calcium in all treated males; significantly increased cholesterol values in rats receiving 360 ppm; and reduced plasma transaminases in rats (males and females) receiving 60 or 360 ppm diets particularly amongst females which also exhibited reduced glutamic dehydrogenase values. These clinical chemistry determinations were within 95% of the historical values for this strain of rats.

Treatment related increases in liver weights relative to body weight were seen in the 60 ppm (females only) and in 360 ppm treated males and females. Kidney weights relative to body weight were also significantly increased in the 360 ppm females rats. Macroscopic post mortem examination revealed two

males at 360 ppm with enlarged livers and two males at 360 ppm and a single female at 10 ppm with swollen liver. Histological examinations revealed minimal centrilobular hepatocyte enlargement in all rats receiving 360 ppm and 5/10 males and a single female receiving 60 ppm.

Based on increased body weight gain in males, decreased body weight gain in females, increased absolute and relative liver weights in males and females, enlarged and swollen livers in males, enlarged centrilobular hepatocytes in all males and females, the LOAEL in rats following administration of tetraconazole in the diet for 90 days was 360 ppm (23.9/28.7 mg/kg/day in M/F). The (NOAEL) in rats was 60 ppm (4.1/5.5 mg/kg/day in M/F).

This subchronic toxicity study is classified as acceptable and satisfies the guideline requirement for a subchronic oral study (870-3100) in rats.

870.3100 90-Day Oral Toxicity - Mice

Executive Summary: In a subchronic toxicity study (MRID 44778701) M14360 (tech., 94.6% ai) was administered to 10 Crl:CD-1 (ICR) BR mice/sex/dose in the diet at dose levels of 0, 5, 25, 125 or 625 ppm (equivalent to average daily doses of 0, 1, 4, 16 or 85 mg/kg/day, males and 0, 1, 4, 20 or 103 mg/kg/day, females). This study was conducted as a range-finding study for the mouse carcinogenicity study and only the following parameters were evaluated: body weight; food consumption; water consumption (week 12); serum BUN, SGPT and SGOT; organ weights of liver, brain, kidney and testes; complete gross examination; and microscopic evaluation of liver and kidney.

At 125 ppm, increased serum SGPT (+165% above controls) and SGOT (+56%), decreased serum BUN (-19%), slightly increased mean/absolute liver weights (15%/15%) and microscopic liver lesions (4/10 single cell necrosis, 1/10 each necrosis and single cell degeneration vs. 0 in controls) were observed in females (most of these findings showed a dose-related increase at 625 ppm). Two of ten males had single liver cell degeneration and only a slight (+39%; not significant) increase in SGPT. At 625 ppm, increased serum SGPT (+103%), decreased BUN (-15%) and increased absolute/relative liver weights (+77%/+75%), along with single cell necrosis and areas of necrosis (each 2/10), were also observed in males. In addition, midzonal hepatocyte hypertrophy and vacuolization in females (4/10 and 3/10, respectively) and liver cell degeneration in 1/10 females were also observed. Although the incidence of centrilobular hepatocyte hypertrophy was increased in both sexes at 25 ppm and higher, it was not considered toxicologically significant at that dose level, based on minimal severity and lack of other liver effects. Females appeared to be more sensitive at 125 ppm while significant changes in liver parameters and histopathology occurred in males at 625 ppm only. The systemic toxicity LOAEL (based on the limited parameters evaluated) is 125 ppm (16 mg/kg/day), based on liver toxicity in females. The NOAEL is 25 ppm (4 mg/kg/day).

This subchronic toxicity study is classified Acceptable-Nonguideline. It does not satisfy the guideline requirement for a subchronic oral study in the rodent (82-2a) because numerous parameters were not evaluated (see Study Deficiencies section of Discussion). However, the study was intended to determine dose levels for the mouse carcinogenicity study and not to satisfy guideline requirements. Furthermore, an acceptable subchronic rat study is available. A new study is not required.

870.3150 90-Day Oral Toxicity - Dog

None. Satisfied by chronic study (MRID 44305303)

870.3200 21/28-Day Dermal Toxicity – Rabbit

Executive Summary: In a repeated dose dermal toxicity study (MRID 44751307), M 14360 125 SL formulation (12.04% w/w tetraconazole) was applied to the clipped skin of six young adult New Zealand White rabbits/sex/dose at dose levels of 0, 250, 1,000, or 2,000 mg/kg/day (0, 30.1, 120.4, or 240.8 mg ai/kg/day) for 6 hours/day, 7 days each week, for 3 weeks. The treated area was covered with a porous gauze patch to maintain the test material in contact with the skin and the patch was secured in place with Johnson and Johnson hypoallergenic tape.

Dermal irritation was observed in rabbits in all treatment groups. No edema was observed for any of the Group 2 animals during the study. In Group 2, slight erythema was observed on day 5 in one male and well-defined erythema was observed in 5 males on day 8 which persisted through out the study. One female in Group 2 developed slight erythema on day 13 and 4 females developed well-defined erythema whose persistence varied throughout the study. One male in Group 3 developed slight edema on day 8 which persisted only for one day. All treated males and females in Group 3 developed well-defined erythema beginning day 5 which progressed to well-defined erythema and persisted throughout the study. Two males and one female in Group 4 developed slight edema and one male developed well-defined edema which disappeared towards the end of the study. All treated animals in group 4 developed slight to well-defined erythema beginning day 2 which progressed to well-defined erythema throughout the rest of the study. Minimal acanthosis was seen in sections of treated and untreated skin from some rabbits in Groups 2, 3 and 4. Subepidermal neutrophil infiltration was observed in the treated and untreated skins from both control and treated animals. Microscopic examination of the kidneys and the livers from the male and female rabbits treated with the highest dose did not reveal any treatment-related microscopic alterations.

For all treatment groups, there were no biologically significant, treatment-related differences in food consumption, hematological or clinical blood chemistry parameters, organ weights, or macroscopic or microscopic organ (other than treated skin) morphology between rabbits in the treated and the control groups. No significant systemic toxicity was observed as a result of treatment at any dose level. The LOAEL for dermal toxicity (irritation) was 250 mg/kg/day (30.1 mg a.i/kg/day), based on the occurrence of erythema in the treated skin of several rabbits in this treatment group. A NOAEL for skin irritation was not determined. The NOAEL for systemic toxicity is 2,000 mg/kg/day (240.8 mg ai/kg/day). A systemic toxicity LOAEL was not determined.

This repeated dose dermal toxicity study is classified acceptable/guideline (§82-2) and satisfies the guideline requirements for a repeated dose dermal toxicity study in rabbits.

870.3465 90-Day Inhalation – Rat

Not required

Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

Executive Summary: In a developmental toxicity study (MRID 44335505) M 14360 (94.6% ai) was administered to 120 pregnant BR VAF/Plus rats, at dose levels of 0, 5, 22.5, 100 mg/kg/day by oral gavage from days 2 through 15 of gestation. Treatment-related effects noted at100 mg/kg/day consisted of decreased body weight gain (22%), and food consumption (≥ 23%,increased water intake (9-15%) and increased liver and kidney weights. There was a dose-related increase in the incidence of salivation in the main study and in the range-finding study, however, this effect was considered primarily due to bolus

dosing and not treatment-related. No macroscopic changes were noted at post-mortem examination. Exposure to 5 mg/kg/day did not result in any significant maternal toxicity.

Therefore, the maternal toxicity LOAEL is 100 mg/kg/day based on decreased body weight gain (22%), and food consumption (≥ 23%,increased water intake (9-15%) and increased liver and kidney weights. The maternal toxicity NOAEL is 22.5 mg/kg/day.

Developmental toxicity was noted at 100 mg/kg/day and consisted of increased incidence of small fetuses, and supernumerary ribs. Increased incidences of hydroureter and hydronephrosis seen at 100 mg/kg/day exceeded the high end value of the historical control range.

Therefore, the LOAEL and NOAEL for developmental toxicity were 100 and 22.5 mg/kg/day, respectively.

The developmental toxicity study in the rat is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3a) in rats.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Executive Summary: In a developmental toxicity study (MRID 44335506), M 14360 (94.6% ai) was administered to 16 New Zealand White rabbits/dose by gavage at dose levels of 0, 7.5, 15, and 30 mg/kg/day from days 6 through 18 of gestation.

Compound-related maternal toxicity was limited to depressed body weight gain during the dosing period from days 6-18 of gestation. No treatment-related effects occurred in mortality, clinical signs, food consumption, or cesarean parameters. The maternal LOAEL is 30 mg/kg/day, based on decreased body weight gain. The maternal NOAEL is 15 mg/kg/day.

No treatment-related effects in developmental parameters were noted. The developmental LOAEL is greater than 30 mg/kg/day. The developmental NOAEL is 30 mg/kg/day.

The developmental toxicity study in the rabbit is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

Executive Summary: In a two-generation reproduction study (MRID 44305306), M 14360 (94.6%) was administered to 28 Crl:CD® (SD) BR VAF/Plus rats/sex/dose (P adults) and 24 Crl:CD® (SD) BR VAF/Plus rats/sex/dose (F_1 adults) in the diet at dose levels of 0, 10, 70, and 490 ppm (0, 0.7, 4.9, and 35.5 mg/kg/day for males or 0, 0.8, 5.9, and 40.6 mg/kg/day for females). The study design included a standard reproduction protocol with litters standardized to four animals per sex on Day 4 post-partum and with two matings of the P generation.

Parental toxicity included increased mortality of adult females in the P and F_1 generations at 490 ppm, decreased body weight gain and food consumption at premating for P females and both F_1 sexes at 490 ppm, increased absolute and relative liver weights of both P and F_1 sexes at 490 (except absolute liver weights in F_1 males), increased relative kidney weights in P females and both F_1 sexes at 490 ppm, compound-related mortality of one P female at 70 ppm, increased relative liver weights of F_1 females at

70 ppm, and increased incidence of centrilobular hepatocyte enlargement in both P and F_1 sexes at 490 ppm. No concomitant liver pathology was noted in the F_1 females at 70 ppm.

Offspring toxicity included decreased litter weight and mean pup weight of F_1A, F_1B, and F_2 litters at 490 ppm and increased relative liver weights of both sexes in all litters at 490 ppm. Increased relative liver weights of F_1B and F_2 female pups at 70 ppm were noted, but since no histopathology was performed on the weanling pups, verification of these changes as adverse could not be achieved.

Mating performance and fertility did not appear to be affected in either generation at any treatment level. The increased incidences of peri-parturient mortality associated with dystocias at 490 ppm in P and F_1 females and increased gestation of intervals at 70 and 490 ppm in P females was affected due to maternal toxicity rather than compound toxicity.

The LOAEL for parental toxicity was 490 ppm (35.5 mg/kg/day in males and 40.6 mg/kg/day in females) based on decreased body weight gain and food consumption during pre-mating, increased relative liver and kidney weights, hepatocellular hypertrophy, and gastric irritation in males and females. The NOAEL was 70 ppm (4.9 mg/kg/day in males and 5.9 mg/kg/day in females

The LOAEL for offspring toxicity was 490 ppm (35.5 mg/kg/day in males and 40.6 mg/kg/day in females) based on decreased litter weight and mean pup weight in litters of all generations before weaning and increased relative liver weights at weaning in both sexes of all litters. The NOAEL was 70 ppm (5.9 mg/kg/day).

The LOAEL for reproductive toxicity was not established. The NOAEL was 490 ppm (35.5 mg/kg/day in males and 40.6 mg/kg/day in females).

The reproductive study in the rat is classified as acceptable/guideline and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

Chronic Toxicity

870.4300 Chronic Toxicity – Rat

Executive Summary: In a carcinogenicity toxicity study (MRID 44305304), tetraconazole (94.6% ai) was administered to Crl:CD (SD) rats 50/sex/dose in the diet at dose levels of 0 (control) 10, 80 ,640 and 1280 ppm for males and 0 (control), 10, 80 and 640 ppm for females. This corresponds to 0, 0.6, 4.4, and 39.4 mg/kg/day for females and 0.0, 0.4, 3.4, 27.7 and 59 mg/kg/day for males. The study was 2 years in length and the animals were exposed to the test article throughout the duration of the study. An additional 20 rats/sex/dose were sacrificed and examined at 12 months.

There were no compound-related effects on mortality. Group mean body weights at terminal sacrifice were decreased 7% and 24% in 640 and 1280 ppm males respectively and were decreased 24% in 640 ppm females. Group mean food consumption for the entire study was decreased 5.1% and 15.2% in 640 and 1280 ppm males and 13.9% in 640 ppm females. At their respective high dose, both male and female serum glucose levels were reduced from 13.6% to 26% in males and 5.5 to 18.4% in females, depending on the time point. Packed cell volume, red blood cell counts and hemoglobin levels were reduced in both sexes at their respective high doses and also in males at 640 ppm. These were, at some time points statistically significant (SS) though the percentage wise decreases were never extreme (about 6% for PCV, 10% for Hb and 3% for RBC). Both the serum glucose and hematology alterations are likely to be attributable to the decreased food consumption and body weights seen in both sexes at these doses and are

thus, secondary to compound exposure. Significant increases in serum phosphorus were seen in 640 and 1280 ppm males, but no signficant alterations in phosphorus levels were seen in females of any dose. The only clinical signs likely related to compound exposure were: long upper incisors seen in 17 and 44 male rats at 640 and 1280 ppm, respectively (compared to incidences of 1, 0, and 1 at doses of 0, 10 and 80 ppm, respectively); pale lower incisors seen in 38 and 47 male rats at 640 and 1280 ppm, respectively (compared to 1, 3, and 3 males at doses of 0, 10 and 80 ppm, respectively); and pale lower incisors in the 640 ppm females (1, 0, 0 and 7 at doses of 0, 10, 80 and 640 ppm, respectively). Absolute adrenal weights were decreased, compared to controls, 18 and 33.6% in the 640 and 1280 ppm males, respectively, but only 3.4% in the 640 ppm females. Adrenal weights, relative to body weights, were decreased 12.8 and 25.65 in 640 and 1280 ppm males and 175 in 640 ppm females. Absolute pituitary weights were decreased compared to controls, 34.2 and 46.8% in 640 and 1280 ppm males but only 9.4% in 640 ppm females. Pituitary weights, relative to body weights, were decreased 13.4% and 23% at 640 and 1280 ppm in males but were not greatly altered in females. The decreases in relative adrenal and pituitary weights in males were SS, but none of the decreases seen in females was. Both sexes did show an increase in relative liver weights at 640 and 1280 ppm from the males and 640 ppm for the females. These increases were SS. Necropsy findings reiterated the incisor findings seen as clinical observations in both sexes. Males, but not females, showed at the 1280 ppm dose (and to a much lesser extent the 640 ppm dose) necropsy findings of white cranium, thickened cranium and thickened parietal bones. No control animals displayed these signs but from 3 to 6 and from 25 to 34 640 and 1280 ppm males did. Liver findings at necropsy consisted of pale subcapsular areas in both sexes (6, 7, 8, 24 and 29 in control through 1280 ppm male groups and 5, 9, 11, and 17 in control through 640 ppm female groups) as well as accentuated lobular markings in the males only (2, 4, 2, 14, 25 in control through 1280 ppm groups). Histopathology findings supported the liver findings at necropsy for both sexes. Hepatic findings at histopathology were indicative of cellular proliferation and hypertrophy. Some findings, such as centrilobular hypertrophy, (incidences were 0, 0, 17, 34, and 44 in control through 1280 ppm males and 0, 0 17 and 39 in control through 640 ppm females) were increased in the 80 ppm groups. Most hepatic findings, however, were confined mostly to the 640 and 1280 ppm males and 640 ppm females. Fine vacuolation of hepatocytes and inflammatory cell foci in males were not seen at all in controls but were seen in anywhere from 18 to 62% of the 640 and 1280 ppm males. The skull bone findings at necropsy were supported by the histopathology findings which found an increased incidence of osseous hypertrophy of the parietal bones (8 and 43 incidences at 640 and 1280 compared to zero in controls) and osseous hypertrophy of the cranium (8 and 45 at 640 and 1280 compared to zero in controls). Additionally, in males only, an increased incidence of cystic follicular atrophy in the thyroid was seen (6 in 1280 ppm and zero in all other groups).

The findings in the liver at doses less than1280 ppm (cellular proliferation/hypertrophy) are indicative of an adaptive response rather than a toxicologic response. Only at the 1280 ppm dose, where increases in inflammatory foci are seen, can the liver responses be called toxicologically significant. The alterations in the skeletal system at 640 ppm in males can be considered toxicologically relevant.

The LOAEL is 640 ppm (27.7/39.4 mg/kg/day in male/female) based on histopathology of the bone (osseous hypertrophy of the cranium/parietal bone), pale and thickened incisors, and decreased absolute and relative adrenal and pituitary weights in males; decreased body weight (at terminal sacrifice) in females. The NOAEL is 80 ppm (3.4/4.4 mg/kg/day in male/female).

Under the conditions of this study, there was no evidence of a treatment-related increase in tumor incidence when compared to controls. Therefore, tetraconazole is not a carcinogen in this study. Dosing is considered adequate to assess the carcinogenic potential of tetraconazole, based on histopathology of the bone (osseous hypertrophy of the cranium/parietal bone), pale and thickened incisors, and decreased absolute and relative adrenal and pituitary weights in males at 640 ppm and decreased body weight (at

terminal sacrifice) in females at 640 ppm and in males at 1280 ppm.

This carcinogenicity study in the rat is Acceptable-Guideline, and does satisfy the guideline requirement for a carcinogenicity study (83-2b) in the rat. Although this study was submitted to fulfill the Subdivision F guideline requirement for a carcinogenicity study (83-2b), it also satisfies the requirement for a combined chronic toxicity/carcinogenicity study (83-5) in the rat.

870.4100b Chronic Toxicity - Dog

Executive Summary: In a chronic toxicity study (MRID No. 44305303), tetraconazole as M 14360 (94.6%) was administered to groups of four male and four female Beagle dogs/dose in *the diet,* at dose levels of 0, 22.5, 90, or 360 ppm (equivalent to achieved intakes of 0, 0.73, 2.95 or 12.97 for males or 0, 0.82, 3.33 or 14.50 mg/kg/day for females) for 52 weeks.

Exposure to M 14360 had no effect on feed consumption, hematological parameters or urinalysis. Treatment-related effects at the high dose included slight but nonsignificant body weight reductions in both sexes from study week 3 to termination; significantly increased alkaline phosphatase, γ-glutamyltransferase, alanine aminotransferase and ornithine carbamoyl transferase in both sexes from study week 13 to 52, increased absolute and relative liver and kidney weights for both sexes, and histopathological changes in both organs. In the mid-dose group, effects were manifested as increased absolute and relative kidney weights for males correlated with histopathological findings in the males (apparent hypertrophy in cortical tubules of the kidneys-1 male). No adverse effects were seen at the low dose.

Based on these considerations, the NOAEL is 22.5 ppm (equivalent to achieved intakes of 0.73 mg/kg/day for males or 0.82 mg/kg/day for females) and the LOAEL is 90 ppm (equivalent to achieved intakes of 2.95 mg/kg/day for males or 3.33 mg/kg/day for females), based on increased absolute and relative kidney weights and histopathological changes in the male kidney.

This chronic toxicity study in the dog is acceptable, and does satisfy the guideline requirement for a chronic oral study (83-1b) in the dog.

Carcinogenicity

870.4200a Carcinogenicity Study - Rat

See Chronic Toxicity

870.4200b Carcinogenicity (feeding) - Mouse

Executive Summary: In a carcinogenicity study (MRID 44305305) M14360 (95.05% ai) was administered to 50 Crl:CD-1 (ICR) mice/sex/dose in their diet at dose levels of 0, 10, 90, 800, 1250 ppm (for males: 0, 1.4, 12, 118, 217 mg/kg/day; for females: 0, 1.6, 14.8, 140, 224 mg/kg/day) for 80 weeks.

Significantly increased mortality was observed at the highest dose (72% for males and 34% for females) compared to the control (24% for males and 16% for females). Increased incidence of swollen, hard, or dark abdomens was noted in mice (both sexes) receiving 1250 ppm of the test material. Although absolute mean body weights were comparable among groups, decreased body weight gains were observed at 800 ppm (73% of the control in both sexes)and at 1250 ppm (73% and 80% of the control for males and females, respectively)at the end of the study.

Gross pathology revealed slight to severe changes in the liver which correlated with the dose given. At 90 ppm, the liver appeared pale with accentuated lobular markings. At higher concentrations (800-1250 ppm), masses were found with raised, pale, or dark subcapsular areas. Masses were also found in the kidneys of male animals receiving 1250 ppm M14360. Dose-related increase of liver weights were noted in mice of both sexes given ≥90 ppm of the test material. Kidney weights were also found to increase slightly (9-11% above controls) in males receiving ≥90 ppm.

Histopathological findings revealed liver toxicity including hepatocyte vacuolation, fat deposition, granulomatous inflammation, pigmented macrophages, generalized hepatocyte enlargement, and bile duct hyperplasia in mice receiving 1250 and 800 ppm of the test material. In addition, at the high dose of 1250 ppm, non-neoplastic changes were noted in the brain, lungs, kidneys, testes, epididymides, and ovaries. Of particular interest is the sizeable increase in the absence of corpora lutea in the ovaries and in the absence of sperm in the epididymides at 800 and 1250 ppm and the effects on the testes (reduced spermatogenesis, tubular atrophy, and interstitial cell hyperplasia) at 1250 ppm. Thickening of compact bone of the cranium, in the ribs, collar bone (females only), and femur (females only) at 800 and 1250 ppm also appears to be treatment related.

Neoplastic findings were noted in the liver where a statistically significant increased incidence of combined benign and malignant liver cell tumors was observed at 1250 ppm (84% for males and 64% for females) and 800 ppm (48% for males and 22% for females) compared to the control (20% for males and 0% for females). The tumor incidence in animals receiving ≤90 ppm was found to be similar to that of controls. Historical control data show that the incidence of hepatocellular adenomas ranged from 7.7% to 24% in males and 0% to 1.9% in females and the incidence of hepatocellular carcinomas ranged from 0% to 14% in males and was 0% in females.

The systemic toxicity LOAEL is 90 ppm (12 and 14.8 mg/kg/day for males and females, respectively), based on increased liver weight and hepatocyte vacuolation in both sexes and increased kidney weights in males. The NOAEL is 10 ppm (1.4 and 1.6 mg/kg/day for males and females, respectively).

There was evidence of increased incidence of combined benign and malignant liver tumors in mice of both sexes treated with M14360 at 800 ppm (48% for males and 22% for females) and 1250 ppm (84% for males and 64% for females) compared to the control (20% for males and 0% for females). The doses were found to be adequate to test its carcinogenic potential based on the reduction of body weight gain and increased mortality at the highest dose.

This study is classified Acceptable/ Guideline and satisfies the guideline requirement for a carcinogenicity study (83-2; OPPTS 870.4100) in mice.

Mutagenicity

870.5265-Gene Mutation: Reverse gene mutation assay in bacteria

In independently in vitro mammalian cell gene mutation assays (MRID No. 44335508), L5178Y mouse lymphoma cells were exposed to Tetraconazole as M 14360 (94.6%) at eight concentrations ranging from 5 to 125 µg/mL with or without S9 activation (Trial 1) or 10 to 100 µg/mL +/-S9 (Trial 2). The S9 was derived from Aroclor 1254-induced Sprauge Dawley rat livers, and the test material was delivered to the test system in dimethylsulfoxide.

Cytotoxicity was observed in all trials at ≥ 100 µg/mL +/-S9. Findings with the positive controls

confirmed the sensitivity of the test system to detect mutagenesis. There was, however, no indication that M 14360 induced a mutagenic response, either in the presence of absence of S9 activation.

The study is classified as Acceptable and satisfies the requirements for an in vitro mammalian forward gene mutation study (84-2).

870.5300-Gene Mutation: Forward gene mutation assay in mammalian cells

In independently in vitro mammalian cell gene mutation assays (MRID No. 44335508), L5178Y mouse lymphoma cells were exposed to tetraconazole as M 14360 (94.6%) at eight concentrations ranging from 5 to 125 µg/mL with or without S9 activation (Trial 1) or 10 to 100 µg/mL +/-S9 (Trial 2). The S9 was derived from Aroclor 1254-induced Sprauge Dawley rat livers, and the test material was delivered to the test system in dimethylsulfoxide.

Cytotoxicity was observed in all trials at ≥ 100 µg/mL +/-S9. Findings with the positive controls confirmed the sensitivity of the test system to detect mutagenesis. There was, however, no indication that M 14360 induced a mutagenic response, either in the presence of absence of S9 activation.

The study is classified as Acceptable and satisfies the requirements for an in vitro mammalian forward gene mutation study (84-2).

870.5375-Cytogenetics: *in vitro* mammalian cytogenetic assay

In independently conducted in vitro chromosome aberration assays (MRID No. 44335507), Chinese hamster ovary (CHO) cells were exposed for 6 hours to Tetraconazole as M 14360 (94.0±0.5%) at doses ranging from 0.5-250 µg/mL in both the absence and presence of S9 activation. Cells were harvested 24 hours after initiation of treatment and metaphases were analyzed from cells dosed with 15.6, 31.3 or 62.5 µg/mL -S9 or 3.9, 7.8 or 15.6 µg/mL +S9. CHO cells were also continuously exposed to 0.5-250 µg/mL -S9 for 24 or 5-60 µg/mL -S9 for 48 hours and metaphases were analyzed from cultures treated with 7.8, 15.6 or 31.3 µg/mL (24-hour treatment) or 5, 10 or 15 µg/mL (48-hour treatment). The S9 was derived from Aroclor 1254-induced Sprague Dawley rat livers, and the test material was delivered to the test system in dimethylsulfoxide.

Cytotoxicity was observed at ≥31.3 µg/mL -S9 (6-hr. treatment and 24-hr. cell harvest or 24 hrs. of continuous treatment before sampling); ≥15 µg/mL -S9 (48 hrs of continuous treatment before sampling) and at ≥15.6 µg/mL +S9 (6-hr. treatment and a 24-hr. cell harvest). The positive controls induced the expected high yield of cells with structural and/or numerical chromosome aberrations. There was, however, no evidence that M 41360 induced a clastogenic response at any nonactivated or S9-activated dose. Similarly, there was no evidence that M 41360 had an adverse effect on the number of chromosomes (*i.e.,* polyploidy).

The study is classified as Acceptable and satisfies the guideline requirement for an in vitro mammalian cell cytogenetic assay (84-2).

870.5395- Other Effects: *in vivo* mammalian cytogenetic assay

In an in vivo mouse micronucleus assay (MRID No. 44335509), groups of five male and five female CD-1 mice received single oral gavage administrations of 185, 370 or 740 mg/kg Tetraconazole as M 14360 (94.6%). Bone marrow cells were collected 24, 48 or 72 hours after compound administration and were examined for micronucleated polychromatic erythrocytes (MPEs). The test material was delivered to the

test animals in aqueous 1% methylcellulose.

One male and four females in the high-dose group succumbed to treatment prior to the scheduled sacrifice; other toxic signs at this concentration included piloerection, hunched posture, lethargy, decreased respiration and pallor of extremities. The test material was not cytotoxic to the target tissue. The positive control induced the expected high yield of MPEs. There was, however, no evidence that M 14360 was clastogenic or aneugenic at any dose or harvest time.

The study is classified as Acceptable and satisfies the guideline requirement for a mouse micronucleus assay (84-2).

870.5550- Other Genotoxic Effects: UDS synthesis in mammalian cell culture

In independently performed unscheduled DNA synthesis (UDS) assays (MRID No. 44335510), cultured HeLa cells were exposed to 12 concentrations of M 14360 (94.6%) ranging from 0.25-512 μg/mL in both the absence and the presence of S9 activation in both trials. The S9 fraction was derived from Aroclor 1254-induced male Sprague Dawley rat livers and the test material was delivered to the test system in dimethylsulfoxide.

Cytotoxicity was evident in all trials at ≥64 μg/mL +/-S9. The positive controls induced significant and dose-related increases in UDS. There was, however, no evidence that M 14360 induced a genotoxic effect under any test condition in either assay.

The study is classified as Acceptable and satisfies the guideline requirement for an unscheduled DNA synthesis assay (84-2).

4.9 Metabolism

870.7485 Metabolism - Rat

Executive Summary: These two reports on the excretion and distribution of ^{14}C-Tetraconazole are part of a series of studies submitted by the registrant on the metabolism and pharmacokinetics of this material to satisfy OPPTS 870.7485 (OPP 85-1) guidelines. Single oral doses of ^{14}C-Tetraconazole phenyl labeled (MRID 44268114) or triazole ring labeled (MRID 44268116) were administered in a 1% methyl cellulose/physiological saline suspension to two male and two female Sprague-Dawley rats at dose levels of 5 or 60 mg/kg for each label. One animal of each sex in each study received the vehicle only. The treated animals were placed individually in glass metabolism cages where urine, feces and expired air were collected for 168 hours. At the end of this period animals were sacrificed to determine radioactivity in blood, tissues, organs, carcass and cage washes.

Average total recovered radioactivity ranged from 99% to 114% for the phenyl label and 96% to 109% for the triazole label of the administered dose (AD). Most of the radioactivity was recovered in the urine, particularly the triazole label. At the 5 mg/kg dose 77% and 79% of the AD of the phenyl label and 95% and 81% of the triazole label were recovered in the urine of males and females, respectively. At the 60 mg/kg label these values were 79 and 70% for the phenyl label and 87% and 79% for the triazole label in males and females, respectively. In the triazole study, males excreted the radio label into the urine more and faster than in the females. Compared to the phenyl label, more of the triazole label was excreted at both doses in the urine.

Radioactivity in the tissues was minimal and accounted for less than 1% in the phenyl label. For the

triazole label 0.9% and 1.4% of the AD (low dose, males and females, respectively) 1.9% and 0.7% (high dose , males and females, respectively) od the AD was recovered in the tissues. Radioactivity was mostly in the carcass. No radioactivity was detected in the heart, spleen, gonads, brain or adrenals of either sex of both treatments or in the lungs of males of the phenyl treatment or in the kidneys of the males of the triazole treatment. Radioactivity recovered in the cage washes at the termination of the study were less than 1% of the AD.

The balance of the radioactivity was recovered in the feces. More radioactivity was excreted for the phenyl label (21-32%) than in the triazole label (12-16% of the AD). Male rats generally excreted the radiolabel into the feces faster than in the females for both labels.

Based on the recovery data of both labels the study authors postulated that metabolism of tetraconazole in the rat may involve cleavage of the molecule between the phenyl and the triazole ring. The data also suggests that tetraconazole is not accumulated in rat tissues following a single oral dose.

This part of the metabolism study in the rat investigating the excretion and distribution of ^{14}C-tetraconazole following a single oral dose is classified Acceptable. However, this study by itself does not satisfy the guideline requirement for a metabolism study (85-1) pending an acceptable classification of remaining studies.

870.7485 Metabolism - Rat

Executive Summary: This report is part of a series of studies submitted by the registrant on the metabolism and pharmacokinetics of ^{14}C-Tetraconazole to satisfy OPPTS 870.7485 (OPP 85-1) guidelines. Groups of rats (5/sex/dose level/exposure period) were given single oral dose of nonradiolabeld M 14360 at 5 or 60 mg/kg for 14 days followed by single oral dose of [^{14}C] triazole ring labeled M 41360(MRID 44268119) in a 0.75% (w/v) methyl cellulose/HPLC water suspension. The treated animals were placed individually in Nalgene^{R} metabolism cages where urine and feces were collected for the study duration of the radiolabel treatment. Animals were sacrificed at various intervals to determine radioactivity in blood, tissues, organs, carcass and cage washes.

The test material was readily absorbed and distributed in the body as the early sacrifice date (8 hours after dosing) of the animals showed. The recovery of the radiolabel was quantitative (100.9 ± 4.0% of the administered dose was recovered). Urine was the major route of excretion accounting for nearly 87% of the AD after 7 days of exposure. Most of the urinary radioactivity was excreted during the first 48 hours. Fecal elimination of the radioactivity was the next major route accounting for 12-16% of the AD after 7 days of exposure. The test material was depurated from the body within 7 days and very little residual radioactivity was detected in the tissues representing less than 1% of the AD. Very minor sex differences were seen. Both males and females slightly eliminated in the feces more of the AD at the lower dose than at the higher dose level. The authors compared the results of this multiple doing regiment to a single dosing reported in MRID # 44268117(reviewed in a separate DER). Female rats receiving multiple doses of either dose level excreted approximately twice the radioactivity in urine of the rats that received the single dose during short exposures of 28 hours or less. It was suggested by the authors that the administration of multiple doses of M 14360 may stimulate the induction of enzymes that convert M 14360 to metabolites that are water soluble and readily excreted in the urine.

There were no deficiencies in the conduct of the study. Calculation errors in the original report (MRID 44268119) showed high levels of radioactive residues in the bone, fat and muscle tissues. An amendment (MRID 45206901) correcting these errors showed that the radioactivity in these tissues was less than 0.2% of the AD. This part of the metabolism study in the rat investigating the excretion and distribution

of ^{14}C-triazole —14360 following repeated oral administration is classified Acceptable. However, this study by itself does not satisfy the guideline requirement for a metabolism study(OPPT 870.7485; §85-1) pending an acceptable classification of remaining studies.

870.7485 Metabolism - Rat

Executive Summary: In a series of rat metabolism studies [MRIDs 44305307, 44305308, 45068401 (pilot study), and 45068402 (pilot study)], [^{14}C-phenyl]tetraconazole (96.9% radiochemical purity; Lot # 140) and [^{14}C-triazole]tetraconazole (99% radiochemical purity; Lot # 768-35-E) with unlabeled tetraconazole (97.6% ai; Lot # 18873/37 or 99.3% ai; Lot # 14644/38) were administered to Sprague Dawley rats [3/sex/dose (pilot); 5/sex/dose] as a single oral (gavage) dose at 5 or 60 mg/kg.

Dosed radioactivity was quantitatively recovered in urine, feces, and tissues in the mass balance studies, with 92.0-100.7% being recovered within 72 hours of dosing. Absorption of [^{14}C]tetraconazole from the G.I. tract of rats was evident in both low- and high-dose animals based on the high level of urinary excretion, with ranged from 50.7-71.0% by 48 hours post-dose in all groups.

Only minor differences were noted in the pattern of excretion between the sexes, labels, and dose levels. In the low-dose [^{14}C-phenyl] animals, the highest levels of overall excretion were delayed and then plateaued somewhat in the females when compared to males (males, 12 hours; females, 24-48 hours). In all high-dose [^{14}C]tetraconazole animals, the highest levels of overall excretion were delayed in the females when compared to males (males, 24 hours; females, 48 hours).

For both labels, increasing the dose level delayed excretion slightly, but had no effect on overall excretion. In the [^{14}C-triazole] animals, urinary excretion was higher (1.1-1.4x), while fecal excretion was lower (0.3-0.6x) when compared to the [^{14}C-phenyl] animals. Male and female rats excreted greater amounts of radioactivity in the urine (51.9-75.9% dose) than in the feces (11.8-36.0% dose) within 72 hours post-dose. No sex-related differences were observed at either dose level or label. Radioactivity remaining in the carcass/tissues accounted for 2.8-5.8% of the dose.

For both labels, ^{14}C-residues in tissues of females were generally higher, except the GI tract, when compared to the same tissue in males of the same dose group, with the largest differences occurring in the gonads, adrenals, and carcass. Although actual ^{14}C-residue concentrations in tissues differed between dose groups and labels, the relative distribution of radioactivity between tissues were the same within each dose group and label. ^{14}C-Residues were highest in the GI tract, liver, and adrenals, and lowest in females in carcass and blood and in males in gonads and blood. For both labels, increasing the dose level from 5 to 60 mg/kg (12x) increased the concentration of radioactivity in tissues by 10.0 -12.6x on average for males and 12.9 - 16.7x on average for females, with the greatest increases occurring in the GI tract and liver in females and carcass in both sexes.

Differences were noted in the maximum blood concentrations between sexes, dose groups, and labels as follows: in the [^{14}C-phenyl] animals, T_{max} occurred at approximately 1 hour post-dose in the low-dose males and females, 4 hours post-dose in high-dose males, and 18 hours post-dose in high-dose females; in the [^{14}C-triazole] animals, T_{max} occurred at approximately 8 hours post-dose in the low-dose males, 18 hours post-dose in the low-dose females, 16 hours post-dose in high-dose males, and 28 hours post-dose in high-dose females. In both dose groups of both labels, maximum concentrations of radioactivity in blood were slightly higher (1.4-1.7x) in the males. No significant differences were noted in the half-life of the test substance between sexes, dose levels, or labels. In the [^{14}C-phenyl] animals, males had lower median AUC values (0.73-0.77x, $p \leq 0.05$) when compared to females at both dose levels and median AUCs for the high-dose rats were higher (18-19x, $p \leq 0.05$) than median AUCs for the low-dose rats,

reflecting the 12x increase in dose. Regarding T_{max}, the high-dose group had a later (3.3-4.1x, $p \leq 0.0625$) average peak time than the low-dose animals of both sexes. In the high-dose group, females had a later (4.8x, $p \leq 0.0625$) average peak time than males; this difference was also observed in the low-dose females (3.9x) when compared to males, although the difference did not attain statistical significance. In the [^{14}C-triazole] animals, males had higher median AUC values (1.1-1.3x, $p \leq 0.05$) when compared to females at both dose levels and median AUCs for the high-dose rats were higher (13-16x, $p \leq 0.05$) than median AUCs for the low-dose rats, reflecting the 12x increase in dose. Regarding T_{max}, the high-dose group had a later (1.6-2.0x, $p \leq 0.05$) average peak time than the low-dose animals of both sexes. At both dose levels, females had later (1.8-2.3x, $p \leq 0.05$) average peak times than males.

When comparing between labels, half-lives were shorter (0.63-0.76x) in the [^{14}C-triazole] animals when compared to the [^{14}C-phenyl] animals. T_{max} was delayed (1.5-6.7x) in the [^{14}C-triazole] animals with respect to the [^{14}C-phenyl] animals. AUC values were higher (1.7-3.6x) in the [^{14}C-triazole] animals when compared to the [^{14}C-phenyl] animals. Increasing the dose level had no effect on the $t_{½}$ between sexes or labels.

These rat metabolism studies are classified acceptable/guideline and, in conjunction with other submitted metabolism studies, satisfy the guideline requirement for metabolism studies (§85-1).

870.7485 Metabolism - Rat

Executive Summary: These three reports are part of a series of studies submitted by the registrant on the metabolism and pharmacokinetics of ^{14}C-Tetraconazole (M-14360) to satisfy OPPTS 870.7485 (OPP 85-1) guidelines. Single oral doses of [^{14}C] triazole ring labeled M-14360 (MRID 44268117) were administered in a 0.75% (w/v) methylcellulose/HPLC water suspension to ten Sprague-Dawley rats of each sex at dose levels of 5 or 60 mg/kg/10 mL. The treated animals were placed individually in Nalgene^{R} metabolism cages. Urine and feces were collected from five rats/sex/dose for 168 hours at which time these animals were killed and their tissues and organs were harvested. The remaining five animals/sex/group were killed at peak blood levels of radioactivity occurring at 8-28 hours of post dosing and their tissues and organs were harvested. Radioactivity was measured in urine, feces, blood, tissues, organs, carcasses and cage washes from all animals.

Urine samples from the first 48 hour collections were pooled and processed for HPLC analysis and for metabolite determination. Similarly feces samples from first 48 hour collections were pooled and processed for HPLC analysis and for metabolite determination. Similarly, urine and fecal samples obtained from rats administered repeated oral doses of [^{14}C] triazole ring labeled M-14360(MRID 44268119: reviewed in a separate DER) were processed for metabolite isolation and identification. The primary identification of metabolites was performed by an HPLC system for profiling. The isolated metabolites were further identified by HPLC, derivitization and GC/MS analysis. Triazole and M-14360 acid were isolated from urine samples and identified by GC/MS comparison with standards. M-14360 alcohol and M-14360 were isolated and identified by GC/MS comparison with standards in a companion ^{14}C-Phenyl M-14360 metabolism study (MRID 44268115: reviewed in a separate DER).

Average total recovered radioactivity for either high or low single oral dose in males or females ranged from 95% to 102% of the administered dose (AD). Most of the radioactivity (75%) was recovered in the urine after 7 days. Recovered radioactivity in the feces ranged from 15% (high dose) to 18% (low dose) of the AD. In the urine and fecal samples, triazole was the major metabolite for both dose levels and sexes. M-14360 acid along with minor metabolites of M-14360 alcohol and its glucuoronide conjugate (M3) were also isolated from the urine. In the feces minor amounts of the parent material, M-14360, the acid and alcohol were also isolated.

Radioactivity in the tissues was minimal after 7 days and accounted for less than 1.5% of the AD. However earlier sacrifices showed that the radioactive dose was absorbed and distributed throughout the various body organs and tissues. Heart, spleen, gonads, brain, kidneys, lungs or adrenals of either sex of both treatments had the lowest radioactive residues at any sacrifice time. The data indicate that M-14360 or its metabolites are not accumulated in rat tissues following a single oral dose.

The metabolic cleavage of M-14360 to yield triazole appears to be the major step in M-14360 metabolism. The study authors postulate that this step is glutathione mediated. A metabolic pathway was proposed where the initial step is the formation of an aldehyde intermediate of M-14360 following dealkylation of the fluoro-alkyl group of the molecule.

Following a single oral low or high dose, male rats produced in the urine more triazole than females (65-67% of the AD vs 48% in females), while urine from females had more of M-14360 acid (7-13% vs 3.5-4% for males), M-3 (2-4% vs 0.0-0.6% for males), and M-14360 alcohol (1.4-2.4% vs 0.0% for males). The same pattern, though not as pronounced, was also seen in the multiple dosing study.

There were also dose and sex differences in the quantitative and qualitative nature of the metabolites in the feces from single and repeated dose animals. In the multiple dosing, triazole (3.2-3.9% of the AD for males and females at the low dose vs 6.5-6.8% for the high dose), M-14360 acid, M-14360 alcohol, M-14360, M6 and others were reported while in the single dosing only triazole (5.6 - 10.4% of the administered low and high doses in both sexes), M-14360 acid and M-14360 were reported.

95-98% of the urinary and fecal metabolites were identified.

This part of the metabolism study in the rat investigating the excretion and distribution of ^{14}C-triazole — 14360 following a single oral dose and metabolite identification is classified Acceptable. However, this study by itself does not satisfy the guideline requirement for a metabolism study (85-1) pending an acceptable classification of remaining studies.

Special Studies

Liver Enzyme Induction - Rat

Executive Summary: In a subchronic toxicity study (MRID 44751310, Tetraconazole 95.2% ai, Batch number FCF/T/122-95) was administered to 6 male and female Crl:CD BR rats per dose level at levels of 0, 10, 80, 640 ppm in the diet. The positive control was Phenobarbital (Na) salt, 75 mg/kg/day.

Data generated in this study indicate that Tetraconazole administration for 4 weeks results in liver enzyme induction at dose levels of 80 and 640 ppm. Induction at the 640 ppm dose level was similar to that induced by phenobarbital at 75 mg/kg/day.

This subchronic toxicity study in rats is an acceptable non-guideline study in rats.

Liver Enzymes Induction - Mice

Executive Summary: In a subchronic toxicity study (MRID 44751309), Tetraconazole 96.3% ai, Batch number FCF/T/113-94) was administered to 18 male and female Crl:CD-1 (ICR)BR mice per dose level at levels of 0, 20, 800, 1250 ppm in the diet. The positive control was Phenobarbital (Na) salt, 75 mg/kg/day.

Data generated in this study indicate that Tetraconazole administration for 4 weeks results in liver enzyme induction.

Statistically significant increases were apparent in females at the 20 ppm dose level based on increases in microsomal protein, cytochrome P450, and ethylmorphine N-demethylase. At all dose levels in males and females, 7-pentoxyresorufin O-dependentylase values were statistically elevated. At 800 and 1250 ppm, statistically significant findings were typically noted. However, dose-response increases were not apparent in these findings at the 1250 ppm level as compared to the lower 800 ppm level.

This subchronic toxicity study in rats is an acceptable non-guideline study in mice.

Appendix B: Metabolism Assessment

B.1. Nature of the Residue in Plants

Soybean (46706301.der.doc): Soybean plants were treated with two foliar applications of [triazole-^{14}C]-tetraconazole at 0.09 lb ai/acre. The first application was made 57 days after planting (R3 growth stage (beginning pod) and the second application was made 15 days later (R5 growth stage; beginning seed). Mature pod samples were harvested 46 days after the last application and seeds were separated from the pods. Only mature seed samples were analyzed. Table B.1.1 is a summary of the TRRs and identified/characterized residues.

Sugar Beets (D278236, W. Donovan, 22-Oct-2001; D282558, W. Donovan, 17-May-2002): The [triazole-^{14}C]-tetraconazole study employed 3 foliar applications at 0.089 lbs ai/acre (RTI = 21 days); the [phenyl-^{14}C]-tetraconazole study employed 3 foliar applications at 0.089 lb ai/acre or 0.447 lb ai/acre (RTI = 28 days). Mature sugar beet root and leaf samples were harvested 0 and 35 days after the final application (triazole labeled study) or 23 days after the final application (phenyl labeled study). Tables B.1.2 and B.1.3 are summaries of the TRRs and identified residues for these samples.

Wheat (D259205, W. Donovan, 18-May-2000; D267481, W. Donovan, 12-Oct-2000): The petitioner submitted data from three wheat metabolism studies. **In one study**, wheat was treated with a single foliar spray application of [triazole-^{14}C]-tetraconazole at 0.132 lb ai/acre (treated 29 days after planting). Whole wheat plants were harvested 0, 1, 2, 5, 9, 15, 27, 41, 55, and 77 days after application; mature wheat samples were collected 75 days after application and separated into wheat straw, husk, and kernel. The TRRs in whole plants harvested 0-77 days following application ranged from 0.30 ppm to 2.26 ppm. TRRs were generally higher at earlier harvest intervals and declined as the PHI increased. Chromatographic analyses of organic extracts from all harvest intervals identified tetraconazole as the only residue component in whole wheat plants; however, quantitative values (% TRR and ppm) of the residue were not reported for various extracts and fractions. TRRs in wheat kernel and husk were 0.04 ppm and were not analyzed further. **In a second study**, spring wheat was treated with two foliar applications of [triazole-^{14}C]- or [phenyl-^{14}C]-tetraconazole at 0.111 lb ai/acre. The first application was made at appearance of the second node and the second application was made 23 days later after the wheat head was fully emerged. Whole wheat plants were collected immediately after the first application, immediately prior to the second application, immediately after the second application, and at maturity (41 days after the second application). The mature wheat samples were separated into head and stem. All of the samples were analyzed for TRRs and were extracted for residue identification/characterization; however, quantitative data concerning the identified residues were only provided for wheat grain and straw. Table B.1.4 is a summary of the TRRs and identified residues for these samples. **In a third study**, wheat was treated with three foliar applications of [triazole-^{14}C]- or [phenyl-^{14}C]-tetraconazole at 0.11 lb ai/acre. A RTI of 8 days was employed and straw and grain samples were harvested at maturity 44 days after the third application (only the wheat straw samples were analyzed). Table B.1.5 is a summary of the TRRs and identified residues.

Grape (D259205, W. Donovan, 18-May-2000; D278236, W. Donovan, 22-Oct-2001): Both the [triazole-^{14}C]- and [phenyl-^{14}C]-tetraconazole grape metabolism studies employed 4 foliar applications at 0.0246 lbs ai/acre. The first application was made 2 weeks after flowering, the second and third applications were made at 14-day intervals, and the fourth application was made at the beginning of ripening. Mature grape samples were harvested 60 days after the last application. Subsamples were processed into wine using simulated commercial procedures. Tables B.1.6 and B.1.7 are summaries of the TRRs and identified residues.

Table B.1.1. Summary of the [triazole-^{14}C]-Tetraconazole Soybean Metabolism Study (TRRs expressed in tetraconazole equivalents).		
	Mature Soybean Seed; PHI = 46 days; TRR = 0.4518 ppm	
	% TRR	ppm
Tetraconazole	5.95	0.0269
TA	14.05	0.0635
Glucose conjugate of TA	75.19	0.3397
Total identified	**95.17**	**0.4300**
Unextractable (PES)	7.50	0.0339

Table B.1.2. Summary of the [triazole-^{14}C]-Tetraconazole Sugar Beet Metabolism Study (TRRs expressed in tetraconazole equivalents).								
	Root; 0-Day PHI (TRR = 0.008 ppm)		Root; 35-Day PHI TRR = 0.007 ppm)		Leaves; 0-Day PHI (TRR = 3.107 ppm)		Leaves; 35-Day PHI (TRR = 1.336 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tetraconazole	residue identification was not performed				82.14	2.550	48.43	0.652
T					2.42	0.071	5.57	0.074
TAA					1.34	0.042	5.55	0.073
Triazolyl hydroxypropionic acid					2.42	0.077	7.06	0.094
M14360-acid					1.38	0.043	4.78	0.063
M14360-DFA					2.79	0.090	9.73	0.128
M14360-alcohol					0.93	0.029	1.11	0.015
Total identified[1]					**93.42**	**2.902**	**82.23**	**1.099**
Characterized								
Unknown, Metabolite 7	residue identification was not performed				0.43	0.014	0.88	0.011
Polar unknowns					0.57	0.017	1.26	0.017
Unknowns (acid hydrolysate)					0.91	0.030	3.91	0.054
Acetone/methanol reflux					1.47	0.044	2.59	0.035
Cellulose					0.91	0.029	1.85	0.025
Lignin					0.02	0.001	0.08	0.002
Total characterized/identified					**97.73**	**3.037**	**92.8**	**1.243**
Nonextractable					1.55	0.049	4.18	0.054

[1] Tetraconazole and its metabolites were tentatively identified by TLC and/or confirmed by GC/MS

Table B.1.3. Summary of the [phenyl-^{14}C]-Tetraconazole Sugar Beet Metabolism Study (TRRs expressed in tetraconazole equivalents).				
	3 x 0.089 lb ai/acre		3 x 0.447 lb ai/acre	
	Root; 23-Day PHI (TRR = 0.007	Leaves; 23-Day PHI TRR = 5.034	Root; 23-Day PHI (TRR = 0.042 ppm)	Leaves; 23-Day PHI (TRR = 26.910 ppm)

	ppm)		ppm)					
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tetraconazole	residue identification was not performed		70.86	3.567	70.9	0.0298	residue identification was not performed	
M14360(C-1)-alcohol			0.10	0.005	--	--		
M14360-alcohol			0.42	0.021	--	--		
M14360-acid			0.26	0.013	5.5	0.0023		
M14360-DFA			3.58	0.180	6.4	0.0027		
M14360-alcohol-conjugate			--	--	6.7	0.0028		
M14360-alcohol-O-glucoside			3.71	0.187	--	--		
M14360-alcohol-O-diglucoside			1.61	0.081	--	--		
M14360-alcohol-O-malonydiglucoside			10.21	0.514	--	--		
M14360-hydroxydetriazolyl-O-malonydiglucoside			3.48	0.175	--	--		
Total identified[1]			**94.23**	**4.743**	**89.50**	**0.0376**		
Nonextractable			--		5.9	0.0028		

[1] Tetraconazole and its metabolites were tentatively identified by TLC and/or confirmed by GC/MS

Table B.1.4. Summary of the [triazole-^{14}C]- and [phenyl-^{14}C]-Tetraconazole Wheat Metabolism Study (2 x 0.111 lb ai/acre; PHI = 41 days; TRRs expressed in tetraconazole equivalents).								
	[triazole-^{14}C]-tetraconazole				[phenyl-^{14}C]-tetraconazole			
	grain; PHI = 41		straw; PHI = 41		grain; PHI = 41		straw; PHI = 41	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tetraconazole	6.29	0.042	49.23	3.602	52.17	0.048	49.54	2.828
TA	50.07	0.331	--	--	--	--	--	--
TAA	24.90	0.165	--	--	--	--	--	--
M14360-alcohol	--	--	0.60	0.044	--	--	0.58	0.033
M14360-acid	--	--	1.83	0.134	--	--	1.63	0.093
M3+4 (not identified)	--	--	2.4	0.176	--	--	2.62	0.150
M8+9+10+11+11+16+17+18	--	--	8.76	0.640	--	--	11.83	0.676
M12+13+14+15[2]	--	--	20.40	1.494	--	--	18.24	1.040
Unidentified	3.91[1]	0.026[1]	--	--	23.91[1]	0.021[1]	--	--
Total Identified	**81.26**	**0.538**	**51.66**	**3.78**	**52.17**	**0.048**	**51.75**	**2.954**
Bound	3.22	0.021	16.78	1.228	19.57	0.018	15.56	0.888

[1] at least 6 compounds

[2] Metabolites 12, 13, 14, and 15 were present as conjugates. As hydrolysis with □-glucosidase was unsuccessful, apparently no conjugates with □-glucose were present. HCl hydrolysis reduced the amount of polar compounds. The free molecules correspond to M14360-alcohol, M14360(C-1)-alcohol and M14360-ketone.

Table B.1.5. Summary of the [triazole-^{14}C]- and [phenyl-^{14}C]-Tetraconazole Wheat Metabolism Study (3 x 0.111 lb ai/acre; PHI = 37 days; TRRs expressed in tetraconazole equivalents).				
	[triazole-^{14}C]-tetraconazole; straw; PHI = 37 days; TRR = 12.453 ppm		[phenyl-^{14}C]-tetraconazole; straw; PHI = 37 days; TRR = 11.475	
	% TRR	ppm	% TRR	ppm
Tetraconazole	63.03	7.849	69.55	7.981
M14360-DCP-3-OH	1.00	0.124	1.18	0.135
M14360-DCP-5-OH	0.82	0.102	0.96	0.110
M14360-alcohol	0.45	0.056	0.44	0.050
M14360-DFA	0.27	0.033	0.20	0.023
M14360-acid	0.19	0.024	0.21	0.024
M14360-CP(C-1)-alcohol	2.59	0.322	2.38	0.273
M14360-ketone	0.35	0.043	0.28	0.032
M14360(C-1)-alcohol	2.12	0.015	0.14	0.016
Total identified	**70.82**	**8.568**	**75.34**	**8.644**
Bound	21.03	2.619	19.08	2.189
Cellulose	5.03	0.626	6.19	0.710
Lignin	3.61	0.450	3.58	0.410

Table B.1.6. Summary of the [triazole-^{14}C]-Tetraconazole Grape Metabolism Study.						
	Grape; 60-day PHI (TRR = 0.166)		Wine (TRR = 0.038 ppm)		Wine Sediment (TRR = 0.743 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tetraconazole[1]	53.15	0.088	40.27	0.015	46.94	0.349
Total identified	**53.15**	**0.088**	**40.27**	**0.015**	**46.94**	**0.349**
Metabolite G1[2]	3.29	0.006	8.06	0.003	0.50	0.004
Metabolite G2[2]	1.04	0.002	8.05	0.003	1.11	0.008
Metabolite G3[2]	1.86	0.003	4.58	0.001	0.91	0.007
Metabolite G4[2]	3.15	0.005	10.45	0.004	0.81	0.006
Metabolite G5[2]	0.86	0.001	7.53	0.003	0.98	0.007
Aqueous	4.97	0.008	21.06	0.008	0.71	0.005
n-Hexane (reflux)	0.64	0.001	--	--	0.75	0.006
Methanol (reflux)	2.66	0.004	--	--	5.21	0.039
Aqueous (reflux)	1.53	0.003	--	--	1.10	0.008
Cellulose	4.75	0.008	--	--	5.73	0.042
Lignin	8.79	0.015	--	--	11.27	0.084
Total characterized/identified	**86.69**	**0.144**	**100.0**	**0.037**	**76.02**	**0.565**
Nonextractable	13.29	0.022	not reported	not reported	23.99	0.179

[1] Tetraconazole was identified by TLC.

[2] G1-G5 were characterized as polar metabolites; petitioner indicated that the triazole and phenyl rings are not separated

Table B.1.7. Summary of the [phenyl-^{14}C]-Tetraconazole Grape Metabolism Study.						
	Grape; 60-day PHI (TRR =0.217)		Wine (TRR = 0.034 ppm)		Wine Sediment (TRR = 0.921 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Tetraconazole[1]	54.95	0.120	55.42	0.019	50.23	0.463
Total identified	**54.95**	**0.120**	**55.42**	**0.019**	**50.23**	**0.463**
Metabolite G1[2]	2.49	0.005	5.89	0.002	0.48	0.004
Metabolite G2[2]	1.18	0.003	5.34	0.002	0.72	0.008
Metabolite G3[2]	1.44	0.003	5.34	0.002	0.48	0.004
Metabolite G4[2]	3.57	0.008	9.78	0.003	1.12	0.010
Metabolite G5[2]	0.93	0.002	14.71	0.005	0.81	0.008
Aqueous	0.83	0.002	3.54	0.001	0.15	0.002
n-Hexane (reflux)	0.87	0.002	--	--	1.14	0.011
Methanol (reflux)	2.36	0.005	--	--	4.63	0.043
Aqueous (reflux)	0.92	0.002	--	--	0.63	0.006
Cellulose	6.11	0.013	--	--	9.11	0.085
Lignin	11.34	0.024	--	--	14.25	0.131
Total characterized/identified	**86.99**	**0.189**	**100.02**	**0.034**	**83.75**	**0.775**

Nonextractable	13.01	0.029	not reported	not reported	16.20	0.148

[1] Tetraconazole was identified by TLC.

[2] G1-G5 were characterized as polar metabolites; petitioner indicated that the triazole and phenyl rings are not separated

B.2. Nature of the Residue in Livestock

Goat (D263068, W. Donovan, 29-Feb-2000; D254411, W. Donovan, 18-May-2000; D279986, W. Donovan, 17-May-2002): Following oral administration of [phenyl-^{14}C]-tetraconazole or [triazole-^{14}C]-tetraconazole to lactating goats for 5 consecutive days at a dietary burden of 0.45 ppm, respective TRRs were 0.036-0.118 ppm and 0.12-0.59 ppm in milk (plateau by day three for both labels), 3.440 ppm and 3.21 ppm in liver, 0.872 and 0.82 ppm in kidney, 0.069 and 0.34 ppm in leg muscle, 0.068 and 0.33 ppm in rump muscle, 0.791 and 0.65 ppm in subcutaneous fat, 0.814 and 0.84 ppm in omental fat, and 0.807 and 0.75 ppm in perirenal fat. Residues were higher in triazole-label milk and muscle samples; otherwise, TRRs were similar between the two labels. Tables B.2.1 and B.2.2 are summaries of the identified/characterized residues.

Hen (D278236, W. Donovan, 22-Oct-2001): Following oral administration of [phenyl-^{14}C]-tetraconazole or [triazole-^{14}C]-tetraconazole to hens for 3 consecutive days at a dietary burden of ~10 ppm, respective TRRs were 0.048-1.882 ppm and 0.092-2.253 in egg yolk (plateau was not reached for either label), 0.268-1.191 ppm and 0.306-1.297 in egg yolk (plateau was not reached for either label), 3.560 ppm and 3.518 ppm in liver, 0.532 ppm and 0.599 ppm in muscle, and 11.293 and 11.612 in fat. In general, residues were slightly higher in triazole labeled egg white and yolk; in the tissue samples, residue levels were similar between the two labels. Tables B.2.3 and B.2.4 are summaries of the identified/characterized residues.

B.3. Rotational Crop Studies

The petitioner submitted a confined rotational crop study conducted with [phenyl-^{14}C]-tetraconazole and [triazole-^{14}C]-tetraconazole (D263068, W. Donovan, 29-Feb-2000; D254411, W. Donovan, 18-May-2000; D267481, W. Donovan, 12-Oct-2000; D278236, W. Donovan, 22-Oct-2001; D282558, W. Donovan, 12-May-2002). Soil was treated with either [phenyl-^{14}C]-tetraconazole or [triazole-^{14}C]-tetraconazole at 0.45 lb ai/acre and planted with carrot, lettuce, and wheat at PBIs of 30, 120, and 365 days (≥4.5x/≥1.1x the proposed maximum single/seasonal application rate for rotated crops). Table B.3.1 is a summary of the TRRs and Tables B.3.2 and B.3.3 are summaries of the identified/characterized residues following planting into soil treated with triazole- or phenyl-labeled tetraconazole.

Table B.3.1. TRRs in Confined Rotational Crop Samples (TRRs expressed in tetraconazole equivalents).

	0.45 lb ai/acre phenyl labeled tetraconazole[1]			0.45 lb ai/acre triazole labeled tetraconazole			triazle label TRR ÷ phenyl TRRs		
	30-day PBI	120-day PBI	365-day PBI	30-day PBI	120-day PBI	365-day PBI	30-day PBI	120-day PBI	365-day PBI
carrot root	0.031	0.022	0.036	0.206	0.427	0.393	6.7	19	11
carrot top	0.033	0.051	0.117	0.557	0.599	0.834	17	12	7
lettuce	0.025	0.043	0.018	0.295	0.435	0.836	12	10	46
wheat grain	0.026	0.025	0.005	0.188	0.417	0.512	7	17	102
wheat forage	0.152	0.089	0.024	0.902	2.617	1.497	6	29	62
wheat straw	1.389	0.855	0.269	1.494	1.460	0.821	1	2	3

Table B.2.1 Summary of the [phenyl-^{14}C]-Tetraconazole Goat Metabolism Study (TRRs expressed in tetraconazole equivalents).																
	milk, Day 5 PM (TRR = 0.118 ppm)		omental fat (TRR = 0.814 ppm)		perirenal fat (TRR = 0.807 ppm)		subcutaneous fat (TRR = 0.791 ppm)		kidney (TRR = 0.872 ppm)		liver (TRR 3.440 ppm)		foreleg muscle (TRR = 0.069 ppm)		rump muscle (TRR = 0.068 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
tetraconazole	78.8	0.093	96.2	0.783	95.3	0.769	85.6	0.677	52.5	0.458	85.1	2.929	79.7	0.055	75.0	0.051
M14360-DFA	5.1	0.006	--	--	--	--	--	--	--	--	--	--	--	--	--	--
M14360-ketone	--	--	1.7	0.014	1.7	0.014	4.3	0.034	4.2	0.037	4.5	0.156	2.9	0.002	4.4	0.003
M14360-alcohol	--	--	--	--	--	--	--	--	--	--	<0.1	0.001	--	--	--	--
unknowns	11.0	0.013	--	--	--	--	1.1	0.009	5.8	0.051	--	--	--	--	<1.5	<0.001
unknown	3.4	0.004	1.6	0.013	1.4	0.011	7.1	0.056	4.6	0.040	1.4	0.047	--	--	<1.5	<0.001
protease hydrolysate	--	--	NR	NR	0.5	0.004	0.8	0.006	11.0	0.096	1.2	0.041	--	--	--	--
total identified	**83.9**	**0.099**	**97.9**	**0.797**	**97.0**	**0.783**	**89.9**	**0.711**	**56.7**	**0.495**	**<89.7**	**3.086**	**82.6**	**0.057**	**79.4**	**0.054**
total identified/characterized	98.3	0.116	99.5	0.810	98.9	0.798	98.9	0.782	81.8	0.714	<92.9	3.195	82.6	0.057	<82.4	<0.056
nonextractable	1.4	0.002	0.5	0.004	1.0	0.010	1.2	0.009	18.3	0.160	7.1	0.244	13.5	0.009	12.7	0.009

Table B.2.2 Summary of the [triazole-^{14}C]-Tetraconazole Goat Metabolism Study (TRRs expressed in tetraconazole equivalents) .																
	milk, Day 5 (TRR = 0.53 ppm)		omental fat (TRR = 0.84 ppm)		perirenal fat (TRR = 0.75 ppm)		subcutaneous fat (TRR = 0.65 ppm)		kidney (TRR = 0.82 ppm)		liver (TRR 3.21 ppm)		foreleg muscle (TRR = 0.34 ppm)		rump muscle (TRR = 0.33 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
tetraconazole	13.2	0.07	81.0	0.68	73.3	0.55	66.2	0.43	42.7	0.35	82.2	2.64	11.8	0.04	9.1	0.03
T	79.2	0.42	13.1	0.11	18.6	0.14	27.7	0.18	48.8	0.40	7.8	0.25	76.5	0.26	81.8	0.27
unknowns	<1.9	<0.01	--	--	--	--	--	--	--	--	--	--	--	--	--	--
polar material	--	--	1.2	0.01	9.3	0.07	--	--	--	--	--	--	0.5	0.01	3.0	0.01
protease hydrolysate	--	--	1.49	0.01	--	--	1.21	0.01	--	--	2.36	0.08	--	--	--	--
total identified	**92.4**	**0.49**	**94.1**	**0.79**	**91.9**	**0.69**	**93.9**	**0.61**	**91.5**	**0.75**	**90.0**	**2.89**	**88.3**	**0.30**	**90.9**	**0.30**
total identified/characterized	<94.3	<0.50	96.79	0.81	101.2	0.76	95.11	0.62	91.5	0.75	92.36	2.97	88.8	0.31	93.9	0.31

nonextractable	2.03	0.01	0.57	<0.01	2.41	0.02	0.48	<0.01	1.53	0.01	3.16	0.10	1.57	0.01	1.59	0.01

Table B.2.3 Summary of the [triazole-^{14}C]-Tetraconazole Hen Metabolism Study (TRRs expressed in tetraconazole equivalents).										
	liver (TRR = 3.518 ppm)		muscle (TRR = 0.599 ppm)		fat (TRR = 11.612 ppm)		egg yolk (TRR = 2.253 ppm)		egg white (TRR = 1.297 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
tetraconazole	91.36	3.214	88.73	0.531	95.00	11.031	88.67	1.998	91.51	1.187
M14360-DCP-3OH	1.19	0.042	0.95	0.006	--	--	--	--	--	--
M14360-DFA	0.61	0.021	0.61	0.004	--	--	0.92	0.021	--	--
T	1.44	0.051	5.03	0.030	--	--	2.48	0.056	3.25	0.042
unknown (water soluble)	0.51[1]	0.018[1]	--	--	--	--	1.97[2]	0.044[2]	--	--
protease hydrolysate	0.80	0.028	not applicable		not applicable		1.20	0.027	not applicable	
total identified	**94.60**	**3.328**	**95.32**	**0.571**	**95.00**	**11.031**	**92.07**	**2.075**	**94.76**	**1.229**
nonextractable	1.28	0.045	2.84	0.017	0.01	0.001	1.38	0.031	0.39	0.005

[1] at least 5 compounds
[2] at least 4 compounds

Table B.2.4 Summary of the [phenyl-^{14}C]-Tetraconazole Hen Metabolism Study (TRRs expressed in tetraconazole equivalents).										
	liver (TRR = 3.560 ppm)		muscle (TRR = 0.532 ppm)		fat (TRR = 11.293 ppm)		egg yolk (TRR = 1.882 ppm)		egg white (TRR = 1.191 ppm)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
tetraconazole	96.58	3.438	100.74	0.536	104.98	11.855	96.56	1.817	104.28	1.242
M14360-DCP-3OH	1.33	0.047	0.62	0.003	--	--	--	--	--	--
M14360-DFA	0.60	0.021	0.69	0.004	--	--	1.85	0.035	--	--
unknown (water soluble)	0.53	0.019	--	--	--	--	2.28	0.043	--	--
protease hydrolysate	1.12	0.040	not applicable		not applicable		1.91	0.036	not applicable	
total identified	**98.51**	**3.506**	**102.05**	**0.243**	**104.98**	**11.855**	**98.41**	**1.852**	**104.28**	**1.242**
nonextractable	3.12	0.111	1.32	0.007	0.03	0.003	3.13	0.059	0.42	0.005

[1] at least 5 compounds
[2] at least 4 compounds

Table B.3.2. Characterization/identification of TRRs in rotational crop commodities planted in soil treated with [triazole-^{14}C]-tetraconazole at 0.446 lb ai/acre (TRRs expressed in tetraconazole equivalents)

	30-DAT Carrot		120-DAT Carrot		365-DAT Carrot		30-DAT Carrot		120-DAT Carrot		365-DAT Carrot tops	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	8.74	0.018	9.84	0.042	3.82	0.015	3.59	0.020	4.34	0.026	3.24	0.027
TA	66.99	0.138	55.27	0.236	65.65	0.258	2.69	0.015	11.52	0.069	12.23	0.102
THP	17.48	0.036	24.35	0.104	19.59	0.077	69.48	0.387	59.76	0.358	63.07	0.526
TAA	--	--	--	--	--	--	--	--	--	--	--	--
Total identified	**93.21**	**0.192**	**89.46**	**0.382**	**89.06**	**0.350**	**75.76**	**0.422**	**75.62**	**0.453**	**78.54**	**0.655**
Metabolite RC-1	1.94	0.004	4.21	0.018	0.26	0.001	2.88	0.016	4.01	0.024	4.20	0.035
Metabolite RC-2	9.22	0.019	8.20	0.035	9.41	0.037	6.64	0.037	5.68	0.034	6.11	0.051
Metabolite RC-4	--	--	--	--	--	--	7.00	0.039	5.51	0.033	5.75	0.048
Metabolite RC-7	--	--	--	--	--	--	--	--	--	--	--	--
Metabolite RC-8	--	--	--	--	--	--	1.08	0.006	1.33	0.008	0.84	0.007
Metabolite RC-9	--	--	--	--	--	--	0.36	0.002	0.50	0.003	0.24	0.002
Total characterized/ identified	**104.37**	**0.215**	**101.87**	**0.435**	**98.73**	**0.388**	**93.72**	**0.522**	**92.65**	**0.555**	**95.68**	**0.798**
Nonextractable	<LOD	<LOD	<LOD	<LOD	1.02	0.004	5.39	0.030	6.34	0.038	4.56	0.038
	30-DAT Lettuce		120-DAT Lettuce		365-DAT Lettuce		30-DAT Wheat		120-DAT Wheat		365-DAT Wheat	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	3.39	0.010	3.68	0.016	1.92	0.016	8.51	0.016	6.71	0.028	2.15	0.011
TA	14.91	0.044	18.85	0.082	5.38	0.045	39.89	0.075	40.05	0.167	42.97	0.220
THP	59.32	0.175	47.36	0.206	79.90	0.668	18.62	0.035	24.94	0.104	25.98	0.133
TAA	--	--	--	--	--	--	14.89	0.028	10.55	0.044	12.11	0.062
Total identified	**77.62**	**0.229**	**69.89**	**0.304**	**87.20**	**0.729**	**81.91**	**0.154**	**82.25**	**0.343**	**83.21**	**0.426**
Metabolite RC-1	1.02	0.003	4.83	0.021	1.20	0.010	1.59	0.003	1.20	0.005	0.58	0.003
Metabolite RC-2	5.76	0.017	8.73	0.038	2.87	0.024	4.79	0.009	5.04	0.021	6.64	0.034
Metabolite RC-4	9.15	0.027	8.50	0.037	4.19	0.035	--	--	--	--	--	--
Metabolite RC-7	--	--	--	--	0.60	0.005	2.13	0.004	0.72	0.003	0.20	0.001
Metabolite RC-8	1.02	0.003	1.15	0.005	0.48	0.004	2.13	0.004	0.48	0.002	0.58	0.003
Metabolite RC-9	0.34	0.001	0.46	0.002	0.12	0.001	0.53	0.001	0.48	0.002	0.39	0.002
Total characterized/ identified	**94.91**	**0.280**	**93.56**	**0.407**	**96.66**	**0.808**	**93.08**	**0.175**	**90.17**	**0.376**	**91.60**	**0.469**
Nonextractable	4.75	0.014	5.52	0.024	3.59	0.030	7.45	0.014	9.35	0.039	8.20	0.042
	30-DAT Wheat		120-DAT Wheat		365-DAT Wheat		30-DAT Wheat		120-DAT Wheat		365-DAT Wheat	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	2.77	0.025	1.30	0.034	0.54	0.008	9.97	0.149	11.31	0.165	7.43	0.061
TA	55.10	0.497	41.07	1.075	54.04	0.809	27.85	0.416	10.41	0.152	18.63	0.153
THP	--	--	--	--	--	--	37.75	0.564	34.79	0.508	28.75	0.236
TAA	30.82	0.278	56.67	1.483	33.80	0.506	1.67	0.025	15.00	0.219	13.03	0.107
Total identified	**88.69**	**0.800**	**99.04**	**2.592**	**88.38**	**1.323**	**77.24**	**1.154**	**71.51**	**1.044**	**67.84**	**0.557**
Metabolite RC-1	--	--	--	--	--	--	0.40	0.006	3.36	0.049	5.36	0.044
Metabolite RC-2	--	--	--	--	2.07	0.031	--	--	2.81	0.041	4.75	0.039
Metabolite RC-4	--	--	--	--	--	--	0.27	0.004	2.88	0.042	5.85	0.048
Metabolite RC-7	2.22	0.020	1.07	0.028	1.20	0.018	2.95	0.044	3.01	0.044	2.92	0.024
Metabolite RC-8	0.44	0.004	0.23	0.006	0.20	0.003	3.15	0.076	3.01	0.044	2.68	0.022

Metabolite RC-9	--	--	--	--	--	--	1.00	0.047	0.75	0.011	0.49	0.004
Total characterized/ identified	**91.35**	**0.824**	**100.34**	**2.626**	**91.85**	**1.375**	**85.01**	**1.270**	**87.33**	**1.275**	**89.89**	**0.738**
Nonextractable	6.32	0.057	2.37	0.062	5.48	0.082	15.26	0.228	14.11	0.206	11.45	0.094

Table B.3.3. Characterization/identification of TRRs in rotational crop commodities planted in soil treated with [phenyl-^{14}C]-tetraconazole at 0.45 lb ai/acre (TRRs expressed in tetraconazole equivalents)

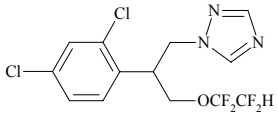
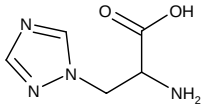
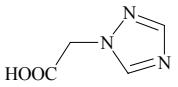
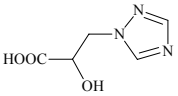
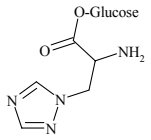
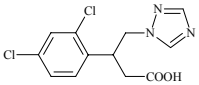
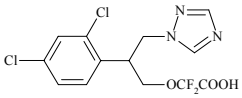
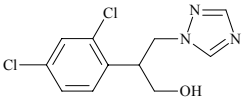
	30-DAT Carrot root		120-DAT Carrot		365-DAT Carrot,		30-DAT Carrot,		120-DAT Carrot,		365-DAT Carrot, tops	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	80.7	0.025	72.7	0.016	72.2	0.026	57.6	0.019	45.1	0.023	50.4	0.059
M14360-DFA	–	–	–	–	2.8	0.001	3.0	0.001	3.9	0.002	3.4	0.004
M14360-acid	–	–	–	–	2.8	0.001	9.1	0.003	11.8	0.006	14.5	0.017
M14360(C-1)alcohol-coniug	–	–	–	–	–	–	3.0	0.001	3.9	0.002	1.7	0.002
M14360-ketone	–	–	–	–	–	–	–	–	–	–	1.7	0.002
Water soluble	6.5	0.002	9.1	0.002	8.3	0.003	21.2	0.007	25.5	0.013	--	--
Bound	19.4	0.006	18.2	0.004	11.1	0.004	–	–	–	–	12.0	0.014
Cellulose	10	0.003	10.9	0.002	2.8	0.001	–	–	–	–	4.4	0.005
Lignin	3.9	0.001	--	--	--	--	–	–	–	–	2.0	0.002
Total Identified	**80.7**	**0.025**	**72.7**	**0.013**	**77.8**	**0.028**	**72.7**	**0.024**	**64.7**	**0.033**	**71.7**	**0.084**
Total characterized/ identified	**106**	**0.033**	**100**	**0.022**	**100**	**0.036**	**100**	**0.033**	**96.1**	**0.049**	**96.6**	**0.113**
	30-DAT Lettuce		120-DAT Lettuce		365-DAT Lettuce		30-DAT Wheat		120-DAT Wheat		365-DAT Wheat	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	40.0	0.010	46.5	0.020	66.7	0.012	77.6	0.118	50.6	0.045	66.7	0.016
M14360-ketone-coniug	8.0	0.002	7.0	0.003	5.6	0.001	–	–	2.3	0.002	–	–
M14360-DFA	–	–	–	–	–	–	4.0	0.006	6.7	0.006	–	–
M14360-acid	–	–	–	–	2.8	0.001	0.7	0.001	6.7	0.006	–	–
M14360(C-1)alcohol-coniug	16.0	0.004	23.3	0.010	22.2	0.004	1.3	0.002	4.5	0.004	–	–
M14360-alcohol-coniug	–	–	–	–	–	–	0.7	0.001	2.3	0.002	–	–
Water soluble	28.0	0.007	18.6	0.008	5.6	0.001	4.0	0.006	6.7	0.006	20.8	0.005
Bound	–	–	–	–	–	–	10.5	0.016	15.7	0.014	16.7	0.004
Cellulose	–	–	–	–	–	–	3.8	0.006	6.1	0.005	8.3	0.002
Lignin	–	–	–	–	–	–	1.8	0.003	2.7	0.002	2.9	0.001
Total Identified	**64**	**0.013**	**76.8**	**0.033**	**97.3**	**0.018**	**84.3**	**0.128**	**73.1**	**0.065**	**66.7**	**0.016**
Total characterized/ identified	**96.0**	**0.024**	**97.7**	**0.042**	**100**	**0.018**	**101**	**0.154**	**102**	**0.091**	**104**	**0.025**
	30-DAT Wheat		120-DAT Wheat		365-DAT Wheat		30-DAT Wheat		120-DAT Wheat		365-DAT Wheat	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	% TRR	ppm	%TRR	ppm	%TRR	ppm
Tetraconazole	48.0	0.667	43.5	0.372	46.8	0.126	15.4	0.004	16.0	0.004	80.0	0.004
M14360-ketone + coniug	5.9	0.082	5.7	0.049	–	–	–	–	–	–	–	–
M14360-DFA	11.0	0.153	9.9	0.085	7.1	0.019	–	–	–	–	–	–
M14360-acid	4.6	0.064	8.9	0.076	6.7	0.018	23.1	0.006	20.0	0.005	–	–
M14360(C-1)alcohol-coniug	6.3	0.088	3.3	0.028	11.5	0.031	–	–	–	–	–	–
M14360-alcohol-coniug	3.2	0.045	3.7	0.032	1.9	0.005	–	–	–	–	–	–
Water soluble*	3.2	0.045	6.8	0.058	8.2	0.022	42	0.011	40	0.010	–	–

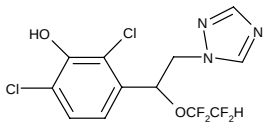
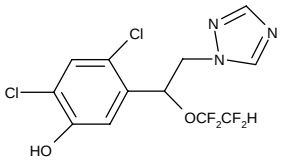
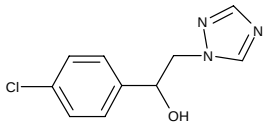
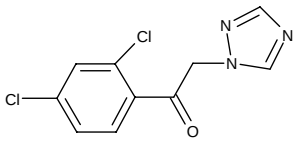
Bound	15.1	0.210	15.8	0.135	16.0	0.043	23.1	0.006	24.0	0.006	–	–
Cellulose	5.8	0.080	7.0	0.060	7.4	0.020	3.8	0.006	6.1	0.005	–	–
Lignin	2.9	0.040	3.5	0.030	3.5	0.010	1.8	0.003	2.7	0.002	–	–
Total Identified	**79**	**1.099**	**75**	**0.642**	**74**	**0.199**	**38.5**	**0.01**	**36.0**	**0.009**	**80.0**	**0.004**
Total characterized/ identified	**97.5**	**1.354**	**97.7**	**0.835**	**98.1**	**0.263**	**104**	**0.027**	**100**	**0.025**	**80.0**	**0.004**

B.4 Residue Analytical Methods

The petitioner previously submitted GC/ECD methods for the determination of residues of tetraconazole *per se* in plant and livestock commodities. HED has determined that these methods are adequate for tolerance enforcement (D280006, W. Donovan, 10-Jan-2002). Briefly, the methods involve extraction. with acetone or hexane:acetone, solvent partition and column clean-up, and GC/ECD analysis. The GC/ECD methods were successfully validated by the ACB in sugar beet top, sugar beet root, banana, peanut, milk, and liver (D264936 and D264683, P. Schermerhorn, 18-Dec-2001). The ACB-determined LOQ in sugar beet top was 0.1 ppm and in sugar beet root, banana, peanut, milk, and liver was 0.01 ppm. The GC/ECD method was also successfully radiovalidated in wheat grain, wheat straw, milk, and muscle (D278236, W. Donovan, 22-Oct-2001; D267481, W. Donovan, 12-Oct-2000). Adequate confirmatory methods using GC with mass spectrometry (GC/MS) were also submitted by Sipcam Agro USA (D278236, W. Donovan, 22-Oct-2001). HED concludes that these methods are sufficient to enforce the recommended tolerances.

Attachment 1. Chemical Structures

Common Name; Chemical Name	**Structure**
Tetraconazole *CAS:* 1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy) propyl]-1*H*-1,2,4-triazole	
Triazole (T) 1,2,4-triazole	
Triazolyl alanine (TA) 3-(1*H*-1,2,4-triazol-1-yl)alanine	
Triazolyl acetic acid (TAA) (1*H*-1,2,4-triazol-1-yl)acetic acid	
Triazolyl hydroxypropionic acid (THP) (2-hydroxy-3-[1*H*-1,2,4-triazol-1-y]propionic acid	
Glucose conjugated of Triazole Alanine (gluc-TA)	
M14360-acid 2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)- propionic acid	
M14360-difluoroacetic acid (M14360-DFA) 5-(2,4-dichlorophenyl)-2,2-difluoro-6-(1*H*-1,2,4- triazol-1-yl)-oxahexanoic acid	
M14360-alcohol 2-(2,4-dichlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1- propanol	

Common Name; Chemical Name	**Structure**
M14360-DCP-3-OH	
M14360-DCP-5-OH	
M14360-CP(C-1)-alcohol	
M14360-ketone **identical to the propiconazole metabolite CGA-91304**	
M14360(C-1)-alcohol **identical to the propiconazole metabolite CGA-91305**