UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 31, 2007

MEMORANDUM

SUBJECT: Prothioconazole: Human Health Risk Assessment for Proposed Uses on Soybeans [Petition No: 6F7073, DP Barcode: 329704] and Sugar Beets [Petition No: 6F7134, DP Barcode: D335154] PC Code: 113961.

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Bayer CropScience submitted separate petitions (6F7073 for soybeans and 6F7134 sugar beets) for the establishment of permanent tolerances for residues of prothioconazole (2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione) and its desthio metabolite in/or the following commodities: soybean, seed; soybean, hay; soybean, forage; beet, sugar, tops; and beet sugar, roots.

The Registration Division (RD) of the Office of Pesticide Programs (OPP) has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, aggregate, and occupational exposure and risk assessments, as needed, to estimate the risk to human health that will result from the proposed use of prothioconazole in/on soybeans and sugar beets.

A summary of the findings and an assessment of human risk resulting from the registered and proposed uses of prothioconazole are provided in this document. The risk assessment was provided by Barry O'Keefe, the toxicology assessment by Myron Ottley, the residue chemistry data review by Steve Funk, the dietary assessment by Toiya Goodlow, and the occupational assessment by Sarah Winfield. The drinking water assessment was provided by Cheryl Sutton of the Environmental Fate and Effects Division (EFED).

Note: HED previously completed a Section 3 human health risk assessment for the use of prothioconazole on barley, canola, chickpea, dried shelled peas and beans crop subgroup, lentils, oilseed crop subgroup (rapeseed, Indian rapeseed, Indian mustard, field mustard, black mustard, flax, crambe, borage), peanut and wheat (spring, durum and winter) (Memo B. O'Keefe, et. al., 1/23/07, DP# 328967). As there are no new toxicity data associated with this action, the hazard characterization and endpoint selection, from the previous risk assessment are applied directly to this action.

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1.0 Executive Summary

Prothioconazole, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione, is a recently registered active ingredient developed by Bayer CropScience LP (i.e. the petitioner). Prothioconazole is a systemic demethylation inhibitor fungicide which belongs to the triazolinthione class of fungicides.

The petitioner states that prothioconazole has shown excellent protective, curative, and eradicative performance against plant diseases caused by ascomycetes, basidiomycetes, and deutromycetes fungi in many crops. The petitioner states that the principle mode of action of prothioconazole fungicide is the inhibition of demethylation at position 14 of lanosterol or 24-methylene dihydroano-sterol, both of which are precursors of sterols in fungi; i.e., it works through disruption of ergosterol biosynthesis (Ergosterol, a precursor to Vitamin D_2, is an important component of fungal cell walls).

The petitioner is currently proposing food/feed uses on soybean and sugar beet. Additionally, under PP#6F7073 (soybean) and PP#6F7134 (sugar beet), the petitioner requests the establishment of permanent tolerances for residues of the fungicide prothioconazole, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione and its desthio metabolite in/on the following raw agricultural commodities: soybean, seed; soybean, hay; soybean, forage; beet, sugar, roots; and beet, sugar, tops.

The end-use products (EPs) proposed for use on soybeans are Proline® 480 SC Fungicide (EPA File Symbol 264-IEL, 4 lb ai/gal) and Provost™ 433 SC Fungicide (EPA File Symbol 264-IAR, 1.2 lb ai/gal). It is noted that Proline® 480 SC Fungicide was recently registered in conjunction with PP#4F6830 and has been assigned EPA Reg. No. 264-825. The products are proposed for multiple broadcast postemergence foliar applications using ground or aerial equipment at maximum seasonal rates of 0.281 lb ai/A (Proline®) or 0.402 lb ai/A (Provost™). A 21-day preharvest interval (PHI) is proposed for both products.

The end-use products (EPs) proposed for use on sugar beets are Proline® 480 SC Fungicide and USF 0728 325 SC Fungicide (EPA File Symbol 264-XXX, 1.49 lb ai/gal). The products are proposed for multiple broadcast postemergence foliar applications using ground or aerial equipment at a maximum seasonal rate of 0.534 lb ai/A. The proposed PHIs are 7 days (Proline®) or 21 days (USF 0728 325 SC Fungicide).

There are no proposed or existing residential uses of prothioconazole.

Prothioconazole is a thio-triazole, and as such, HED notes that a separate risk assessment was conducted for the 1,2,4-triazole and its conjugates. Triazolylalanine (TA), triazolylhydroxoypropionic acid (THPA), and triazolylacetic acid (TAA), metabolites common to the triazole derivative class of fungicides, were also found to be metabolites of prothioconazole.

HED conducted an aggregate risk assessment for the metabolite/degradate 1,2,4-triazole (also referred to as free triazole) and its conjugates TA and TAA, including data review, hazard identification and endpoint selection, to support the extension of existing tolerances and the granting of new parent triazole derivative fungicide tolerances (DP# 322215, 2/7/06, M. Doherty *et al.*). TA and TAA residues are primarily associated with plant commodities whereas 1,2,4-T is associated with rats and livestock. In that assessment, it was concluded that there are no human health risk issues associated with 1,2,4-T or its metabolites that would preclude reregistration of the triazole-derivative fungicides registered at the time the risk assessment memo was issued or conditional registration of the triazole-derivative fungicide uses that have been proposed as of September 1, 2005. The risk assessment included uses of prothioconazole proposed in PP#4F6830; the last prothioconazole risk assessment. Additionally, in that aggregate triazoles risk assessment, HED concluded that new uses for triazole pesticides (such as the proposed prothioconazole uses addressed in this document) should be examined in terms of potential residues of 1,2,4-T and its conjugates, and that the risk assessment may require revision if new uses are for sites not already addressed by the current list of registered or proposed uses, if the formation of the metabolites exceeds the estimates used in the previous risk assessment, or if required toxicity data raise concerns not addressed by the current risk assessment.

Separate dietary risk assessments, based on conservative residue estimates, have been completed for 1,2,4-T and TA+TAA (combined) and are updated, as needed, for new triazole fungicide uses. The most recent dietary assessments for these compounds (W. Cutchin, DP Numbers 347252 and 347253, 12/19/07) include residue estimates for soybean and sugar beet commodities. Currently registered uses on soybean and sugar beet from the application of other triazole fungicides result in potentially greater residues of 1,2,4-T and TA+TAA (combined) on the resulting crop commodities than are attributable to these proposed uses of prothioconazole. Therefore, an updated assessment is not required to address dietary exposure to 1,2,4-T or to TA+TAA for these new prothioconazole petitions.

Toxicity/Hazard Assessment

The toxicology database for prothioconazole and its metabolites, submitted by Bayer CropScience, is extremely large, especially the number of complex toxicology studies. In addition to the full toxicology database for prothioconazole (also known as JAU6476), there is a second complete toxicology database for the major metabolite/degradate prothioconazole-desthio (also known as SXX0665), and additional studies on other minor metabolites/degradates. The toxicity database for prothioconazole (and its metabolites) is considered complete, and deemed adequate for endpoint selection for exposure risk assessment scenarios and for FQPA evaluation. Please refer to Appendix A for the toxicity profile tables. Please refer to the previous prothioconazole risk assessment document for further extensive details, including the executive summaries of the individual toxicology studies (B. O'Keefe, DP Barcode 328967, 1/23/07).

Acute Toxicity: Prothioconazole has low acute toxicity by oral, dermal, and inhalation routes. It is not a dermal sensitizer, or a skin or eye irritant. Prothioconazole-desthio also has low acute toxicity by oral, dermal, and inhalation routes. It is not a dermal sensitizer, or a skin irritant, but it is a slight eye irritant.

Subchronic Toxicity: The studies show that the target organs at the LOAEL include the liver, kidney, urinary bladder, thyroid and blood. Significant clinical chemistry findings were also made. NOAEL/LOAEL values across the family of chemicals (i.e., prothioconazole, and prothioconazole-desthio and prothioconazole sulfonic acid potassium salt metabolites) in the toxicity database indicate that prothioconazole-desthio is a most toxic chemical.

Chronic Toxicity: In addition to the target organs and effects observed in the subchronic studies (i.e., liver, kidney, urinary bladder, thyroid, hematology and clinical chemistry), chronic toxicity at the LOAEL also included body weight and food consumption changes, and toxicity to the lymphatic and GI systems. The relative potency of prothioconazole-desthio was greater than prothioconazole.

Carcinogenicity: Studies in the rat and mouse, using both prothioconazole and prothioconazole-desthio, showed no evidence of carcinogenicity. The data show that dosing was adequate, except in the rat cancer study using prothioconazole, where the dosing was considered too high.

Developmental Toxicity: The data indicated that prothioconazole and the three metabolites evaluated (i.e., prothioconazole-desthio, prothioconazole sulfonic acid potassium salt, and prothioconazole-deschloro) variously produce pre-natal developmental effects at levels equal to or below maternally toxic levels. Prothioconazole-desthio is the most toxic orally and dermally, with LOAELs significantly below that of the other chemicals. The rabbit is the more sensitive species. Lastly, prothioconazole-desthio is a developmental neurotoxicant, producing changes in brain morphometrics and increases in the occurrence of peripheral nerve lesions in the neonate. A NOAEL was not determined, since these observations were looked for only at the high dose level.

Reproductive Toxicity: Reproduction studies in the rat, conducted using prothioconazole and prothioconazole-desthio, suggested that these chemicals may not be primary reproductive toxicants. Reproductive and offspring toxicities were observed only in the presence of parental toxicity. Indeed, the parental LOAELs are lower. The data show that prothioconazole-desthio is more toxic by an order of magnitude. The nature of parental toxicity is similar to what was observed in the subchronic studies, such as body weight and food consumption changes, liver effects, etc. Reproductive effects included decreases in reproductive indices such as those that indicate pup survival and growth. Offspring toxicity was manifested by decreased pup weights and malformations such as cleft palate.

Neurotoxicity: Acute and subchronic neurotoxicity studies were conducted in the rat using prothioconazole. A developmental neurotoxicity study was conducted in the rat using prothioconazole-desthio. Prothioconazole-desthio was the more potent neurotoxicant.

*Dermal Toxicity***:** Acute dermal toxicity studies on prothioconazole and prothioconazole-desthio indicate that they are not irritants (Tox Category IV). One subchronic dermal rat study using prothioconazole failed to show any local or systemic toxicity. However, a dermal developmental toxicity study using prothioconazole-desthio showed local effects at a high dose in the rat.

*Comparative Toxicity***:** The available data show that the prothioconazole-desthio metabolite produces toxicity at the lowest dose levels in the areas of subchronic, developmental and reproductive toxicities compared with prothioconazole and the two additional metabolites that were tested.

FQPA: There are adequate data in the prothioconazole (including metabolites) database to characterize the potential for pre-natal or post-natal risks to infants and children: two-generation reproduction studies in rats; developmental studies in rats and rabbits; and a developmental neurotoxicity study in rats. The effects seen in these studies suggest that pups are more susceptible: pup effects were seen at levels below the LOAELs for maternal toxicity and, in general, were of comparable or greater severity compared to the effects observed in adults. In addition, since the developmental effects seen in the developmental neurotoxicity study (DNT) were investigated at the high dose level only, there is uncertainty concerning the LOAEL/NOAEL for developmental effects in this study. Thus, the FQPA factor is retained at 10X.

Dose Response & Endpoint Selection: In plants, the major metabolite/degradate of prothioconazole is prothioconazole-desthio, which is significantly more toxic than prothioconazole. Therefore, the residues of concern in plant commodities are both prothioconazole and its metabolite prothioconazole-desthio. Also, the residues of concern in edible ruminant tissues and milk are prothioconazole, and its desthio and 4-hydroxy metabolites and their conjugates.

Since exposure to prothioconazole-desthio in food and drinking water will be significant, and will in many cases exceed that of prothioconazole, the decision was made by HED, in conjunction with the Pesticide Management Regulatory Agency (PMRA) of Canada, to use the toxicity data on prothioconazole-desthio in the hazard and dose response characterization.

The prothioconazole risk assessment team selected the most sensitive and protective endpoints from the prothioconazole-desthio database to employ in the prothioconazole risk assessment. Appropriate endpoints were identified for the acute and chronic dietary exposure scenarios and appropriate occupational scenarios following dermal and inhalation exposures.

Acute Dietary Exposure: The endpoint from the developmental toxicity study in rabbits was selected for the acute dietary exposure scenario to females 13-49 years old, with a NOAEL of 2 mg/kg/day, and a developmental toxicity LOAEL of 10 mg/kg/day, based on multiple malformations including malformed vertebral body and ribs, and arthrogryposis. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X FQPA SF (safety factor) retained as a database uncertainty factor) was applied, resulting in an aRfD/aPAD of 0.002mg/kg/day. No dose and endpoint were set for the general population, including infants and children, because an appropriate study to use in this risk assessment was not identified.

Chronic Dietary Exposure: The endpoint from the chronic/oncogenicity study in rats was selected for the chronic dietary exposure scenario, with a NOAEL of 1.1 mg/kg/day, and a LOAEL of 8 mg/kg/day, based on liver histopathology in males and females [hepatocellular

vacuolation and fatty change (single cell, centrilobular, and periportal)]. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X FQPA SF (safety factor) retained as a database uncertainty factor) was applied, resulting in an cRfD/cPAD of 0.001mg/kg/day.

Short- and Intermediate-Term Dermal Occupational Exposure: The endpoint from the dermal developmental toxicity study in rats was selected for the dermal exposure scenarios, with a NOAEL of 30 mg/kg/day, and a LOAEL of 100 mg/kg/day, based on an increase incidence of supernumerary ribs (14^{th} rib). An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in a LOC margin of exposure (MOE) of 1000.

Short- and Intermediate-Term Inhalation Occupational Exposure: The endpoint from the developmental toxicity study in rabbits was selected for the inhalation exposure, with a NOAEL of 2.0 mg/kg/day, and a developmental toxicity LOAEL of 10 mg/kg/day, based on multiple malformations including malformed vertebral body and ribs, and arthrogryposis. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in a LOC margin of exposure (MOE) of 1000.

The available carcinogenicity and/or chronic studies in the mouse and rat show no increase in tumor incidence. Therefore, HED has concluded prothioconazole or its metabolites are not carcinogenic, and are classified "Not likely to be Carcinogenic to Humans" according to the 2005 Cancer Guidelines.

Drinking Water Exposure Assessment

The Environmental Fate and Effects Division (EFED) provided estimated drinking water concentrations (EDWCs) determined using the PRZM-EXAMS screening model. These EDWCs were incorporated directly into the dietary assessment. Water residues were incorporated in DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

EDWC point estimates were submitted for both lower and upper bounds to account for two major uncertainties in the drinking water modeling. First, some prothioconazole residues remained in the bound phase in EFED studies used to characterize persistence. To address this uncertainty, modeling was bounded based on inclusion and exclusion of unextracted residues in half-life calculations. Secondly, the two major water degradates of prothioconazole formed rapidly after application and have different mobility. To address this uncertainty, modeling was conducted using K_{OCs} (soil organic carbon-water partitioning coefficients) for prothioconazole-desthio and prothioconazole-S-methyl. The lower bound EDWCs represent the exclusion of unextracted residues and the use of the higher K_{oc} (i.e. less mobility). Conversely, the higher bound estimates represent the inclusion of unextracted residues and the use of the lower K_{oc} (i.e. less mobility). Any concern about the uncertainties of any bound residues or differences in K_{oc} values are adequately addressed by regulating and relying upon the upper bound EDWCs in the dietary risk assessment.

Estimated drinking water concentrations were further refined for peanuts and sugar beets. Regional default Percent Cropped Area factors (PCA) have been applied to estimated concentrations of these crops. DEEM analyses were performed using surface water EDWCs for both the upper and lower bound estimates for the peanut (previous registration) and sugar beet (proposed registration) crop scenarios, since these EDWC values were the highest reported for the respective acute (peanut, lower bound 13 ppb and upper bound 29 ppb) and chronic (sugar beet, lower bound 8.4 ppb and upper bound 13 ppb) exposure durations.

Residential Exposure/Risk Assessment

There are no proposed or existing residential uses of prothioconazole. Therefore, no residential exposure assessment is required.

Dietary/Aggregate Exposure/Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which used food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support the registration of new (soybean and sugar beet) and existing uses of prothioconazole.

Acute Dietary Exposure Results and Characterization: A moderately refined acute dietary exposure assessment was conducted for prothioconazole. Empirical processing factors (PFs) and livestock maximum residues were incorporated, and 100 percent crop treated (%CT) was assumed for the acute assessment. Average residue levels were also used, since all of the plant commodities included in this assessment are blended food forms. No acute endpoint was identified for the general U.S. population. Females, 13-49 years of age, was the only population subgroup included in the acute assessment. Dietary risk estimates were determined considering exposures from food alone and food plus water using EDWCs for surface water sources provided by EFED. EDWC values were submitted for both lower and upper bounds for the peanut application scenario, since this crop yielded the highest acute EDWC values. Ground water sources were not included, as the EDWCs for this water source are minimal in comparison to surface water.

The dietary exposure analyses result in acute dietary risk estimates that are below the Agency's level of concern (LOC) for food only, and for food and drinking water. At the 95th percentile, the food only exposure for females 13-49 years old utilized 8.4% of the acute population adjusted dose (aPAD). The exposure for food plus lower bound drinking water estimates represented 37% of the aPAD at the 95th percentile. The exposure for food and upper bound drinking water estimates utilized 76% of the aPAD at the 95th percentile.

Chronic Dietary Exposure Results and Characterization: A moderately refined chronic dietary exposure assessment was also performed. Empirical processing factors, average residues, and livestock maximum residues were incorporated into the chronic assessment; 100% crop treated was also assumed. Dietary risk estimates were determined considering exposures from food

alone and food plus upper or lower bound surface water EDWC point estimates based on the sugar beet application scenario, since this crop yielded the highest chronic EDWC values.

The dietary exposure analyses result in chronic dietary risk estimates that are below the Agency's LOC for food alone and food plus water. The highest exposure and risk estimates were for children 1-2 years old and all infants. The food only exposure represented 31% of the chronic population adjusted dose (cPAD) for children 1-2 years old. The highest exposure and risk estimates for food plus drinking water were for the all infants population subgroup. The exposure for food plus lower bound drinking water estimates utilized 65% of the cPAD; food plus upper bound drinking water estimates utilized 94% of the cPAD.

Occupational Exposure/Risk Assessment

There is potential for exposure from mixing, loading, and applying prothioconazole on proposed use sites, and from entering areas previously treated with prothioconazole. Short- and intermediate-term dermal and inhalation exposures are expected from handler activities, and short- and intermediate-term dermal exposures are expected from postapplication activities.

Handler Risk: Handler exposure scenarios considered representative of the potential exposures expected from the proposed prothioconazole use patterns on sugar beets and soybeans are as follows: mixing and loading (M/L) for aerial and groundboom equipment and application with aerial and groundboom equipment, as well as flagging for aerial applications**.** Total MOEs range from 860 to 3,800. Closed M/L for aerial application to sugar beets (at the maximum proposed rate) did not reach the LOC of an MOE of 1000 with engineering controls. However, closed M/L for aerial application for sugar beets at a reduced rate and soybean at the maximum rate did reach the LOC of an MOE of 1000 with engineering controls. M/L exposure scenarios for groundboom equipment reach MOEs of 1000 or greater with baseline clothing (long-sleeved shirt, long pants, shoes and socks) and the personal protective equipment (PPE) gloves. Both aerial and groundboom application (and flagging) exposure scenarios reach MOEs of 1000 with baseline clothing and no gloves.

Although the M/L for aerial application to sugar beets at the maximum proposed application rate does not result in an exposure estimate 1000X less than the quantitative hazard estimate (even with engineering controls) this estimate does involve potential overestimation of exposure. As mentioned above, prothioconazole exposure estimates are compared to prothioconazole-desthio endpoints, resulting in a highly protective risk assessment. Had risk from prothioconazole and prothioconazole-desthio been estimated in separate assessments, lower prothioconazole-desthio exposure estimates would have yielded a greater margin of exposure. Therefore, an MOE of 860 at the maximum proposed label rate may not indicate a risk of concern.

Postapplication Risk: Postapplication dermal MOEs reach 1000 or greater on the day of application for postapplication activities such as scouting in low crops with minimal plant growth, as well as hand weeding; however, for activities such as scouting in crops with fuller foliage plants, and irrigating crops, up to 2 days following application are required to reach MOEs of 1000. Therefore, the labels, which indicate restricted-entry intervals (REIs) of 12 and 24 hours, need to be amended to indicate an REI of 2 days in order to be protective of the LOC.

Additionally, two formulations, PROVOST™ 433 SC Fungicide (for use on peanuts and soybeans) and USF 0728 325 SC Fungicide (for use on sugar beets) include other active ingredients (i.e., namely, tebuconazole and trifloxystrobin) – the Registration Division (RD) must ensure that the REI is also protective of these additional active ingredients. Other label amendments are discussed below under recommendations.

Recommendations for Tolerances

HED has completed a human health risk assessment for the proposed new uses on soybeans and sugar beets of the active ingredient prothioconazole. Provided that revised Sections B and F as specified in Section 9.0 of this document are submitted, the residue chemistry, toxicological, and occupational databases support the establishment of a *conditional registration* and the following permanent tolerances for residues of prothioconazole as follows:

Tolerances for combined residues of prothioconazole and its desthio metabolite:

Soybean, forage	4.5	ppm
Soybean, seed	0.15	ppm
Soybean, hay	17	ppm
Beet, sugar, roots	0.25	ppm

The registration should be made conditional upon receipt of additional data specified in Section 9.0.

860.1200 Directions for Use

- A revised Section B is required to specify a preharvest interval of 7 days for soybean forage and hay.

860.1550 Proposed Tolerances

- The petitioner is required to submit a revised Section F to incorporate the CAS name of prothioconazole-desthio in the tolerance expression and to specify that residues of the metabolite are calculated as parent. In addition, the revised Section F should reflect the recommended tolerances and commodity definitions presented in Table 4.1.9.

Recommendations for Labels

- **PREVIOUS:** State on the label that sunflower and safflower are excluded from the oilseed crop group

- USF 0728 325 SC Fungicide, on page 4 of the proposed label, remove the language describing use directions for chemigation. The label states "apply USF 0728 325 SC through irrigation equipment only to crops for which chemigation is specified on this label." There is one crop on the label (sugar beets), and chemigation is not specified in the use directions (whereas aerial and ground application methods are specified).

- USF 0728 325 SC Fungicide should specify a 30-day plant-back interval for crops not on the label.

- USF 0728 325 SC Fungicide, for sugar beets, the retreatment intervals are contradictory, i.e., in the restrictions section it lists 14- to 30-day spray intervals for foliar and soilborne diseases; but within the soilborne disease section it lists a 10- to 14-day spray schedule. Since EFED relied on a 14- to 30-day interval for the drinking water numbers for sugar beets, HED suggests that the label should not specify 10- to 14-day intervals.

- Change the REI to 48 hours on all labels.

- Remove all references to rice on the Proline 480 SC label.

- Indicate on the labels, that hand-harvesting is prohibited.

Environmental Justice Considerations

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

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

Review of Human Research

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

2.0 Ingredient Profile

A summary of prothioconazole end-use products proposed for use on the crops discussed in this document is listed in Table 2.1.

Table 2.1. Prothioconazole End-Use Products.

Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
PROLINE® 480 SC Fungicide	264-IEL	41% 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione	Soluble concentrate (SC)	Barley, oilseed (except sunflower and safflower) crop group, dried shelled pea and bean (except soybean) subgroup, peanut, soybean, sugar beet, and wheat.	Broad spectrum systemic fungicide for the control of Ascomycetes, Basidiomycetes, and Deuteromycetes diseases	Applications may be made alone or as a tank mix with other fungicides, insecticides, or herbicides. To optimize disease control, the lowest labeled rate of spray surfactant should be tank-mixed with PROLINE ® 480 SC Fungicide. Application through any type of irrigation system is prohibited. For crops not listed on this label, do not plant back within 30 days of last application. REI – 24 hours

Table 2.1. Prothioconazole End-Use Products.						
Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
PROVOST^{TM} 433 SC Fungicide	264-IAR	12.9% (also contains 25.8% **tebuconazole**)	SC	Peanuts and soybeans		Provides control or suppression of many important diseases. When reference is made to disease suppression, suppression can mean either erratic control from good to fair or consistent control at a level below that obtained with the best commercial disease control products. For crops not listed on this label, do not plant back within 30 days of last application. REI – 24 hours
USF 0728 325 SC Fungicide	264-XXX	16.0% (also contains 13.7% trifloxystrobin **trifloxystrobin**)	SC	Sugar beets	Broad spectrum fungicide, that provides control or suppression of several important diseases of sugar beets (*e.g.*, Cercospora Leaf Spot, Powdery Mildew, Rhizoctonia Stem Canker, Crown Rot).	Provides control or suppression of many important diseases. When reference is made to disease suppression, suppression can mean either erratic control from good to fair or consistent control at a level below that obtained with the best commercial disease control products. Contains both Group 11 and Group 3 fungicides. To limit the potential for development of disease resistance: alternate each application with at least one application of a fungicide from a different fungicide group. REI – 12 Hours

2.1 Summary of Registered/Proposed Uses

Prothioconazole is a systemic, broad spectrum fungicide in the triazole chemical class developed by Bayer CropScience. Prothioconazole is a demethylation-inhibitor (DMI-type) fungicide which works through disruption of ergosterol biosynthesis (ergosterol, a precursor to Vitamin D_2, is an important component of fungal cell walls). Prothioconazole fungicide is for the control of ascomycetes, basidiomycetes, and deuteromycetes diseases. Applications may be made alone or as a tank mix with other fungicides, insecticides, or herbicides. To optimize disease control, the lowest labeled rate of spray surfactant should be tank-mixed with prothioconazole formulations. Application through any type of irrigation system is prohibited. For crops not listed on the proposed labels, do not plantback within 30 days of last application.

Prothioconazole, formulated as PROLINE ® 480 SC Fungicide, is currently registered for food/feed uses on: barley, canola, chickpea, dried shelled peas and beans crop subgroup, lentils, oilseed crop subgroup (rapeseed, Indian rapeseed, Indian mustard, field mustard, black mustard,

flax, crambe, borage), peanut and wheat (spring, durum and winter); and is proposed for use on soybeans and sugar beets. Additionally, two new prothioconazole formulations, PROVOST™ 433 SC Fungicide (for use on peanuts and soybeans) and USF 0728 325 SC Fungicide (for use on sugar beets) are being proposed for registration. The directions for use of prothioconazole on proposed and existing crop sites are summarized in Tables 2.2 and 2.3, respectively.

Table 2.2. Summary of Directions for Proposed Uses of Prothioconazole.

Application Timing, Type and Equipment	Trade Name	Max. Single rate (lb ai/A)	Max. number of Appl. per Season	Max. Seasonal Application Rate (lb ai/A)	PHI (Days)	Use Directions and Limitations
Soybean						
Postemergence; Broadcast foliar; Ground and aerial	Proline® 480 SC Fungicide	0.078-0.094	3	0.281	21	A 10- to 21-day retreatment interval is specified, and use of a spray surfactant is recommended. Apply in a minimum of 5 and 15 gal/A using aerial and ground equipment, respectively.
	Provost™ 433 SC Fungicide	0.028	3	0.402	21	
Sugar Beet						
Postemergence; Broadcast foliar or Banded; Ground and aerial	Proline® 480 SC Fungicide	0.134-0.178	3	0.534	7	For foliar disease: apply at the first sign of disease, and use higher use rate and shorter intervals when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties. For soil-borne disease control: apply either broadcast or in a 7-inch band at the 4-leaf to row closure growth stage. In general, a 14- to 30-day retreatment interval is specified depending on the region. However, a 10 to 14 day retreatment interval is specified for soilborne diseases on the USF 0728 label only. Use of a spray surfactant is recommended. Apply in a minimum of 5 and 10 gal/A using aerial and ground equipment, respectively.
	USF 0728 325 SC Fungicide	0.093-0.128	3	0.530	21	

Table 2.3. Summary of Directions for Existing Uses of Prothioconazole						
Appl. Type, and Equip.	Appl. Rate (lb ai/A) [fl oz/A]	Max. No. Appl. per Season	Retreatment Interval (days)	Max. Seasonal Appl. Rate (lb ai/A) [fl oz/A]	PHI (days)	Use Directions and Limitations
Barley (for Fusarium Head Blight)						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 - 5.7]	2	7 to 14	0.29 [9.4]	32	Apply as a preventative foliar spray within the time period when 70 to 100% of the barley heads on the main stem are fully emerged when weather conditions are favorable for disease development and up to 3 to 5 days after full head emergence. Spray equipment must be set up to provide good coverage to barley heads (using ground application equipment, use forward and backward mounted nozzles or nozzles with a two-directional spray).
Barley (for Leaf and Stem Diseases)						
Broadcast foliar spray; Ground or aerial	0.088 – 0.13 [2.8 - 4.3]	2	7 to 14	0.27 [8.6]	32	Apply as a preventative foliar spray when the earliest disease symptoms appear on the leaves or stems.
Canola						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 - 5.7]	2	5 to 7	0.36 [11.4]	36	Apply when the canola crop is in the 20 to 50% bloom stage (approximately 4-8 days after the canola crop begins to flower, not after 50% bloom stage). Best protection will be achieved when the fungicide is applied prior to petals beginning to fall, and will allow for the maximum number of petals to be protected. The lower application rate is recommended for most canola crops, the higher rate is recommended for fields with a history of heavy disease pressure or for dense crop stands. Good spray coverage of the plants is essential.
Chickpea						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 - 5.7]	3	10 to 14	0.53 [17.1]	7	Apply at first sign of disease. Use higher use rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Dried Shelled Peas and Beans Subgroup (Grain, Sweet, White and White Sweet lupins; Field, Kidney, Dry lima, Pinto and Tepary beans; Adzuki bean, Black-eyed pea, Catjang, Cowpea, Crowder pea, Moth bean, Mung bean, Rice bean, Southern pea and Urd bean; Dry broad bean; Guar; Lablab bean; Pea [including Field pea] and Pigeon pea)						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 – 5.7]	3	5 to 14	0.53 [17.1]	7	Apply at the first sign of disease. Use higher use rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Lentils						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 – 5.7]	3	10 to 14	0.53 [17.1]	7	Apply at early flower or at the first sign of disease. Use higher use rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Oilseed Crop Subgroup (Rapeseed, Indian rapeseed, Indian mustard, Field mustard, Black mustard, Flax, Crambe and Borage)						

Table 2.3. Summary of Directions for Existing Uses of Prothioconazole						
Appl. Type, and Equip.	Appl. Rate (lb ai/A) [fl oz/A]	Max. No. Appl. per Season	Retreatment Interval (days)	Max. Seasonal Appl. Rate (lb ai/A) [fl oz/A]	PHI (days)	Use Directions and Limitations
Broadcast foliar spray; Ground or aerial	0.134 -0.178 [4.3 – 5.7]	2	5 to 7	0.356 [11.4]	36	Apply when the crop is 20 to 50% bloom stage (not after the 50% bloom stage). Utilize higher rate for fields with history of heavy disease pressure or for dense crop stands. Good spray coverage is essential.
Peanut						
Broadcast foliar spray; Ground or aerial	0.16 -0.18 [5.0 – 5.7, PROLINE] 0.038-0.10 [4.0 – 10.7, PROVOST]	4	14 to 21	0.71 [22.8, PROLINE] 0.40 [42.8, PROVOST]	14	Soil Borne disease: Utilize the high use rate. Make four consecutive applications at 14 day intervals. In a typical 7 spray application, the formulation should be applied for sprays 3, 4, 5 and 6. For control of soil-borne diseases when using a Leaf Spot Advisory Program schedule, begin in July and continue at 14 day intervals. The formulation must be carried by rainfall or irrigation into the root zone, drought conditions will decrease effectiveness against the root and pod rots. Foliar disease: Apply the specified rate in a preventive spray schedule. Apply up to 4 sprays using a 14 day interval. Use higher rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Wheat (spring, durum and winter) (for Fusarium Head Blight)						
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 – 5.7]	2	7 to 14	0.29 [9.37]	30	Apply within the time period from when at least 75% of the wheat heads on the main stem are fully emerged to when 50% of the heads on the main stem are in flower. Optimal timing of application may be at or around 15% flower. Spray equipment must be set up to provide good coverage to wheat heads (using ground application equipment, use forward and backward mounted nozzles or nozzles with a two-directional spray). PROLINE may be applied up to the point where wheat heads are in the full flower growth stage.
Wheat (spring, durum and winter) (for Leaf and Stem Diseases)						
Broadcast foliar spray; Ground or aerial	0.13 -0.16 [4.3 - 5.0]	2	7 to 14	0.29 [9.37]	30	Apply as a preventative foliar spray or when the earliest disease symptoms appear on the leaves or stems. Wheat fields should be observed closely for early disease symptoms, particularly when susceptible varieties are planted and/or under prolonged conditions favorable for disease development. PROLINE may be applied up to the point where wheat heads are in the full flower growth stage.

2.2 Structure and Nomenclature

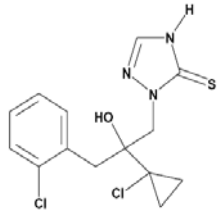
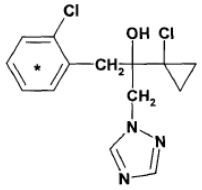
Table 2.4. Prothioconazole Nomenclature.	
Chemical structure of prothioconazole	
Empirical Formula	$C_{14}H_{15}Cl_2N_3OS$
Common name	Prothioconazole
Company experimental name	JAU 6476
IUPAC name	2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione
CAS name	2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione
CAS registry number	178928-70-6
End-use product/EP	PROLINE ® 480 SC Fungicide
Chemical Class	Triazolinthione
Known Impurities of Concern	None

Table 2.5. Prothioconazole-Desthio Nomenclature	
Chemical Structure	
Company experimental name	JAU 6476-desthio (SXX 0665)

2.3 Physical and Chemical Properties

Table 2.6. Physicochemical Properties of the Technical-Grade Prothioconazole.		
Parameter	Value	Reference
Molecular Weight	344.26 g/mol	
Melting point	139.1 - 144.5 °C	MRID 46246003
Density (g/ml at 20^0C)	1.36 (pure active ingredient)	MRID 46246003
	1.17 at 20 °C (end use product)	MRID 46246003
Water solubility (g/L)	5.0 pH 4 buffer at 20 °C 0.3 pH 8 buffer at 20 °C 2.0 pH 9 Buffer at 20 °C	MRID 46246003

Table 2.6. Physicochemical Properties of the Technical-Grade Prothioconazole.		
Parameter	Value	Reference
Solvent solubility at 20 °C (g/L)	g/L at room temp acetone >250 acetonitrile 10-100 dichloromethane 100-250 dimethylsulfoxide 100-250 ethyl acetate <250 n-heptane <0.1 1-octanol 10-100 polyethylene glycol >250 2-propanol 10-100 xylene 1-10	MRID 46246003
Vapor pressure (Pa at 20 or 25 °C)	$<4 \times 10^{-7}$	MRID 46246003
Dissociation constant, pK_a	6.9	MRID 46246003
Octanol/water partition coefficient, $Log(K_{OW})$	at 20 °C unbuffered: Kow = 11300; log K_{ow} = 4.05 pH 4: K_{ow} = 14600; log = 4.16 pH 7: K_{ow} = 6600; log = 3.82 pH 9: K_{ow} = 100; log = 2.00	MRID 46246003
UV/visible absorption spectrum	Peak maxima at 275 nm. No absorption at >300 nm.	MRID 46246003

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The toxicology database for prothioconazole and its metabolites, which was previously submitted by Bayer CropScience, is extremely large, especially the number of complex toxicology studies. In addition to the full toxicology database for prothioconazole (also known as JAU6476), there is a second complete toxicology database for the major metabolite/degradate prothioconazole-desthio (also known as SXX0665), and additional studies on other minor metabolites/degradates. The toxicity database for prothioconazole (and its metabolites) is considered complete, and deemed adequate for endpoint selection for exposure risk assessment scenarios and for FQPA evaluation. Please refer to Appendix A for the toxicity profile tables. Please refer to the previous prothioconazole risk assessment document for further extensive details, including the executive summaries of the individual toxicology studies (B. O'Keefe, DP Barcode 328967, 1/23/07).

3.1.2 Toxicological Effects

NOAEL and LOAEL: The NOAEL (No Observed Adverse Effect Level) is the dose level, in a given study, at which no adverse effects were noted. Similarly, the LOAEL (Lowest Observed Adverse Effect Level) is the dose level at which effects of toxicological significance were observed. NOAELs/LOAELs derived from the toxicity database are well characterized [with the exception of certain endpoints in the developmental neurotoxicity study] and are used as endpoints for appropriate risk assessments.

Acute Toxicity: Prothioconazole has low acute toxicity by oral, dermal, and inhalation routes. It is not a dermal sensitizer, or a skin or eye irritant. Prothioconazole-desthio also has low acute toxicity by oral, dermal, and inhalation routes. It is not a dermal sensitizer, or a skin irritant, but it is a slight eye irritant.

Subchronic Toxicity: The studies show that the target organs at the LOAEL include the liver, kidney, urinary bladder, thyroid and blood. Significant clinical chemistry findings were also made. NOAEL/LOAEL values across the family of chemicals (i.e., prothioconazole, and prothioconazole-desthio and prothioconazole sulfonic acid potassium salt metabolites) in the toxicity database indicate that prothioconazole-desthio is a more toxic chemical.

Chronic Toxicity: In addition to the target organs and effects observed in the subchronic studies (i.e., liver, kidney, urinary bladder, thyroid, hematology and clinical chemistry), chronic toxicity at the LOAEL also included body weight and food consumption changes, and toxicity to the lymphatic and GI systems. The relative potency of prothioconazole-desthio was greater than prothioconazole.

Carcinogenicity: Studies in the rat and mouse, using both prothioconazole and prothioconazole-desthio, showed no evidence of carcinogenicity. The data show that dosing was adequate, except in the rat cancer study using prothioconazole, where the dosing was considered too high.

Developmental Toxicity: The data indicated that prothioconazole and the three metabolites evaluated (i.e., prothioconazole-desthio, prothioconazole sulfonic acid potassium salt, and prothioconazole-deschloro) can be primary developmental toxicants, producing effects including malformations in the conceptus at levels equal to or below maternally toxic levels in some studies, particularly those studies conducted using prothioconazole-desthio. Prothioconazole-desthio is the most toxic orally and dermally, with LOAELs significantly below that of the other chemicals. The rabbit is the more sensitive species, qualitatively. Lastly, prothioconazole-desthio is a developmental neurotoxicant, producing malformations and such neurotoxic effects as changes in brain morphometrics and increases in the occurrence of peripheral nerve lesions in the neonate. A NOAEL was not determined for the neurotoxicity, since these observations were looked for only at the high dose level.

Reproductive Toxicity: Reproduction studies in the rat, conducted using prothioconazole and prothioconazole-desthio, suggested that these chemicals may not be primary reproductive toxicants. Reproductive and offspring toxicities were observed only in the presence of parental toxicity. Indeed, the parental LOAELs are lower. The data show that prothioconazole-desthio is more toxic by an order of magnitude. The nature of parental toxicity is similar to what was observed in the subchronic studies, such as body weight and food consumption changes, liver effects, etc. Reproductive effects included decreases in reproductive indices such as those that indicate pup survival and growth. Offspring toxicity was manifested by decreased pup weights and malformations such as cleft palate.

Neurotoxicity: Acute and subchronic neurotoxicity studies were conducted in the rat using prothioconazole. A developmental neurotoxicity study was conducted in the rat using prothioconazole-desthio. Prothioconazole-desthio was the more potent neurotoxicant.

Dermal Toxicity: Acute dermal toxicity studies on prothioconazole and prothioconazole-desthio indicate that they are not irritants (Tox Category IV). One subchronic dermal rat study using prothioconazole failed to show any local or systemic toxicity. However, a dermal developmental toxicity study using prothioconazole-desthio showed systemic toxicity as evidenced by an increase in supernumerary ribs at maternally non-toxic doses.

Comparative Toxicity: The available data show that the prothioconazole-desthio metabolite produces toxicity at the lowest dose levels in the areas of subchronic, developmental and reproductive toxicities compared with prothioconazole and the two additional metabolites that were tested.

Endocrine Disruption: The submitted data on the toxicity of prothioconazole and its desthio, deschloro, and sulfonic acid K salt metabolites do not suggest a concern for endocrine disruption at this time.

3.1.3 Dose-response

In plants, the major metabolite/degradate of prothioconazole is prothioconazole-desthio, which is significantly more toxic than prothioconazole. Therefore, the residues of concern in plant commodities are both prothioconazole and its metabolite prothioconazole-desthio. Also, the residues of concern in edible ruminant tissues and milk are prothioconazole, and its desthio and 4-hydroxy metabolites and their conjugates.

Since exposure to prothioconazole-desthio in food and drinking water will be significant, and will in many cases exceed that of prothioconazole, the decision was made by HED, in conjunction with PMRA, to use the toxicity data on prothioconazole-desthio in the hazard and dose response characterization.

The prothioconazole risk assessment team selected the most sensitive and protective endpoints from the prothioconazole-desthio database to employ in the prothioconazole risk assessment. Appropriate endpoints were identified for the acute and chronic dietary exposure scenarios and

appropriate occupational scenarios following dermal and inhalation exposures. Residential exposure scenarios are not anticipated.

In determining endpoints for acute dietary risk assessments, the toxic effects in three studies were considered, as follows:

Study	NOAEL mg/kg/day	LOAEL mg/kg/day	Toxic Effects	Comment
Developmental Toxicity – Rat MRID 46246321, 43246322	3	10	increased incidence of supernumerary ribs and incomplete/delayed ossifications.	Possibly appropriate for Acute Dietary, Females 13 – 50 years. Quantitative susceptibility demonstrated in that the maternal NOAEL/LOAEL are 30/100 mg/kg/day
Developmental Toxicity – Rabbit MRID 46246327	2	10	malformed vertebral body and ribs, arthrogryposis, and multiple malformations	Appropriate for Acute Dietary, Females 13 – 50 years Quantitative susceptibility demonstrated in that the maternal NOAEL/LOAEL are 10/50 mg/kg/day
Developmental Neurotoxicity – Rat MRID 46246418	3.6	15.1	deviated snout, malocclusion	Appropriate for Acute Dietary, Females 13 – 50 years
	15.1	43.3	Dystocia	Maternal effects. Possibly appropriate for Acute Dietary, General Population
	not reported	not reported	brain morphometric changes and increased incidence of peripheral nerve lesions	Appropriate for Acute Dietary, General Population since effects seen in neonate, indicating the potential for effects to occur in children and adults following a single postnatal dose.

The endpoints from the developmental neurotoxicity (DNT) study are considered because they show effects that could occur in both adults and offspring, following single or multiple exposures. However, because morphometric changes and peripheral nerve lesions were reported only at the high doses level in the DNT study, a NOAEL and LOAEL could not be established for these endpoints. The lack of this information limits the utilization of this study for endpoint selection. Therefore, the resulting database uncertainties form the basis for retaining the FQPA factor throughout the risk assessment.

The endpoints from the rat and rabbit developmental studies are considered because developmental endpoints are identified. Since the endpoints occur at levels below the maternal NOAEL, susceptibility in the offspring is demonstrated.

The weight of evidence evaluation of these toxic effects and the doses selected for risk assessment were discussed in detail in Section 3.5 of the previous prothioconazole risk assessment document (B. O'Keefe, DP Barcode 328967, 1/23/07).

3.1.4 FQPA

There are adequate data in the prothioconazole (including metabolites) database to characterize the potential for pre-natal or post-natal risks to infants and children: two-generation reproduction studies in rats; developmental studies in rats and rabbits; and a developmental neurotoxicity study in rats. The effects seen in these studies suggest that pups are more susceptible: pup

effects were seen at levels below the LOAELs for maternal toxicity and, in general, were of comparable or greater severity compared to the effects observed in adults. In addition, since the developmental effects seen in the developmental neurotoxicity (DNT) study were investigated at the high dose level only, there is uncertainty concerning the LOAEL/NOAEL for developmental effects in this study. Thus, the FQPA factor is retained at 10X (see Section 3.3 of the previous prothioconazole risk assessment document (B. O'Keefe, DP Barcode 328967, 1/23/07) for details).

3.2 Hazard Identification and Toxicity Endpoint Selection

3.2.1. Summary of Dose Response and Endpoint Selection

The prothioconazole risk assessment team selected the most sensitive and protective endpoints from the prothioconazole-desthio database to employ in the prothioconazole risk assessment. Appropriate endpoints were identified for the acute and chronic dietary exposure scenarios and appropriate occupational scenarios following dermal and inhalation exposures.

Acute Dietary Exposure: The endpoint from the developmental toxicity study in rabbits was selected for the acute dietary exposure scenario to females 13-49 years old, with a NOAEL of 2 mg/kg/day, and a developmental toxicity LOAEL of 10 mg/kg/day, based on multiple malformations including malformed vertebral body and ribs, and arthrogryposis. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in an aRfD/aPAD of 0.002mg/kg/day. No dose and endpoint were set for the general population, including infants and children, because an appropriate study to use in this risk assessment was not identified.

Chronic Dietary Exposure: The endpoint from the chronic/oncogenicity study in rats was selected for the chronic dietary exposure scenario, with a NOAEL of 1.1 mg/kg/day, and a LOAEL of 8 mg/kg/day, based on liver histopathology in males and females [hepatocellular vacuolation and fatty change (single cell, centrilobular, and periportal)]. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in an cRfD/cPAD of 0.001mg/kg/day.

Short- and Intermediate-Term Dermal Occupational Exposure: The endpoint from the dermal developmental toxicity study in rats was selected for the dermal exposure scenarios, with a NOAEL of 30 mg/kg/day, and a LOAEL of 100 mg/kg/day, based on an increased incidence of supernumerary ribs (14^{th} rib). An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in a LOC margin of exposure (MOE) of 1000.

Short- and Intermediate-Term Inhalation Occupational Exposure: The endpoint from the developmental toxicity study in rabbits was selected for the inhalation exposure, with a NOAEL of 2.0 mg/kg/day, and a developmental toxicity LOAEL of 10 mg/kg/day, based on multiple malformations including malformed vertebral body and ribs, and arthrogryposis. An uncertainty factor (UF) of 1000X (10X for interspecies extrapolation, 10X for intraspecies variations, 10X for database uncertainty) was applied, resulting in a LOC margin of exposure (MOE) of 1000.

3.2.2 Level of Concern for Margin of Exposure

A summary of the level of concern margins of exposure (MOEs) for risk assessment purposes are presented below:

Table 3.2.2 Summary of Levels of Concern for Risk Assessment.

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	1000	1000	None
Inhalation	1000	1000	None
Residential Exposure			
Dermal or Inhalation	None	None	None

Occupational exposure: **DERMAL** and **INHALATION**: Based on the conventional uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation), plus a 10X database uncertainty factor for lack of a NOAEL for brain morphometry and peripheral nerve lesions in the oral developmental neurotoxicity study.

Residential exposure: None expected.

3.2.3 Recommendation for Aggregate Exposure Risk Assessments

For this assessment all dietary exposures, i.e., food and drinking water, are aggregated. For the proposed and existing crops, the estimated concentrations of prothioconazole and its' degradates in drinking water, provided by EFED, were incorporated directly into the acute and chronic dietary assessments.

For exposures to mixers, loaders, and applicators, risk estimates for short- and intermediate-term exposures from both inhalation and dermal routes are added together, because the hazard/endpoint is the same. Because the MOEs for dermal and inhalation exposures are calculated using different NOAELs, a total MOE approach [$1/((1/MOE_{dermal}) + (1/MOE_{inhalation}))$] is be used to combine dermal and inhalation risks.

3.2.4 Classification of Carcinogenic Potential

The available studies in the mouse and rat show no increase in tumor incidence. Therefore, HED has concluded prothioconazole or its metabolites are not carcinogenic, and are classified "Not likely to be Carcinogenic to Humans" according to the 2005 Cancer Guidelines.

3.2.5 Summary Tables of Toxicological Doses and Endpoints for Prothioconazole for Use in Human Risk Assessments

Table 3.2.5.1 Summary of Toxicological Doses and Endpoints for Prothioconazole desthio for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13 – 49)	NOAEL = 2.0 mg/kg/day	UF_A=10x UF_H=10x FQPA SF=10x (UF_{DB})	Acute RfD = 0.002 mg/kg/day aPAD = 0.002 mg/kg/day	**Developmental Toxicity study in rabbits** LOAEL = 10 mg/kg/day, based on structural alterations including malformed vertebral body and ribs, arthrogryposis, and multiple malformations.
Acute Dietary (General Population, including infants and	None	None	None	**An appropriate study was not identified**
Chronic Dietary (All Populations)	NOAEL=1.1 mg/kg/day	UF_A=10x UF_H=10x FQPA SF=10x (UF_{DB})	Chronic RfD = 0.001 mg/kg/day cPAD = 0.001 mg/kg/day	**Chronic/Oncogenicity study in rats** LOAEL = 8.0 mg/kg/day based on liver histopathology (hepatocellular vacuolation and fatty change (single cell, centrilobular, and periportal)).
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months)	N/A	N/A	N/A	Incidental oral exposure endpoint not identified because residential exposure is not anticipated.
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	N/A	N/A	N/A	Dermal endpoints are not applicable because residential exposure is not anticipated.
Inhalation Short- and Intermediate-term (1-30 days and 1-6 months)	N/A	N/A	N/A	Inhalation endpoints are not applicable because residential exposure is not anticipated
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

For acute and chronic dietary (food and water) risk assessments, the 10x FQPA SF has been retained in the form of a UF_{db} (10x) for the lack of NOAEL and a LOAEL from the developmental neurotoxicity study, regarding some neurotoxic endpoint (peripheral nerve lesions and brain morphometrics).

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

sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 3.2.5.2 Summary of Toxicological Doses and Endpoints for Prothioconazole desthio for Use in Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL=30 mg/kg/day	UF_A=10x UF_H=10x UF_{DB} = 10x	Occupational LOC for MOE = 1000	**Dermal developmental study in rats** LOAEL = 100 mg/kg/day based on an increased incidence of supernumerary rib (14th rib).
Inhalation Short- and Intermediate-term (1-30 days and 1-6 months)	NOAEL=2.0 mg/kg/day Inhalation absorption are assumed to be 100%	UF_A=10x UF_H=10x UF_{DB} = 10x	Occupational LOC for MOE = 1000	**Developmental Toxicity study in rabbits** LOAEL = 10 mg/kg/day, based on structural alterations including malformed vertebral body and ribs, arthrogryposis, and multiple malformations.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

The LOC for occupational exposure to prothioconazole desthio is based on the conventional uncertainty factor of 100x (UF_A = 10x and UF_H = 10x) and an additional UF_{DB} (10x) for the lack of NOAEL and a LOAEL from the developmental neurotoxicity study, regarding some neurotoxic endpoint (peripheral nerve lesions and brain morphometrics).

3.3 Endocrine disruption

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

4.0 Dietary Exposure/Risk Characterization

The potential for dietary exposure to prothioconazole and its metabolites and/or degradates includes consumption of food and drinking water. Acute and chronic dietary (food plus drinking water) exposure analyses were conducted.

4.1 Pesticide Metabolism and Environmental Degradation

References:

Prothioconazole. Petition for Establishment of Tolerances for Use on Barley, Oilseed (Except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (Except Soybean) Crop Subgroup, Peanut, Rice, and Wheat. Summary of Analytical Chemistry and Residue Data. PP#4F6830. DP303508, S. Funk, 08/21/06.

Prothioconazole. Petitions for Establishment of Tolerances for Use on Sugar Beet (PP#6F7134) and Soybean (PP#6F7073). Summary of Analytical Chemistry and Residue Data. DP331663, S. Funk, 12/19/07.

4.1.1 Metabolism in Primary Crops

No plant metabolism studies were submitted with the subject petitions. The petitioner has previously submitted metabolism studies with prothioconazole (labeled in the triazole and phenyl rings) reflecting foliar uses on wheat, peanut, and sugar beet, and seed treatment (phenyl-ring label only) of wheat. Detailed discussions of these plant metabolism studies are presented in the residue chemistry summary document DP# 303508, 8/21/06, S. Funk (PP#4F6830). The data indicate that the metabolism of prothioconazole is similar in dissimilar crops. Prothioconazole was not found to be a major component of the residue in plant commodities, at 1.0-7.4% TRR in wheat matrices, peanut hay, and sugar beet tops; prothioconazole was not identified in peanut nutmeat or sugar beet root. Prothioconazole-desthio was a major component of the residue, at 9.3-35% TRR in wheat matrices, 24-28% TRR in peanut hay, 6.2% TRR in peanut nutmeat, and 19-58% TRR in sugar beet tops and root. In triazole-label studies, triazolylalanine accounted for 71% TRR in wheat grain, 4.1-25% TRR in wheat forage, hay, and straw, 50% TRR in peanut nutmeat, 29% TRR in sugar beet root, and <2% TRR in peanut hay and sugar beet tops. Triazolylacetic acid accounted for 19% TRR in wheat grain, <5% TRR in wheat forage, hay, and straw, and peanut nutmeat and hay, and was not identified in sugar beet root or tops. Free triazole was not identified in any plant matrix.

*Conclusion*s: The nature of the residue in plants is adequately understood. The residues of concern for tolerance enforcement and for risk assessment in plant commodities are defined as the sum of prothioconazole and its metabolite prothioconazole-desthio, calculated as prothioconazole.

4.1.2 Metabolism in Rotational Crops

Bayer CropScience previously submitted two confined rotational crop studies to support the proposed uses, one conducted using [phenyl-^{14}C]-prothioconazole (MRID 46246225) and one conducted using [triazole-^{14}C]-prothioconazole (MRID 46246226). Additionally, a limited field rotational crop study (MRID 46246227) on the representative crops mustard greens (leafy vegetable), turnip (root vegetable), and wheat (cereal grain) was previously submitted. Detailed discussions of the results of these studies were presented in the previous residue chemistry summary document (*DP# 303508; S. Funk, 08/21/06)* and in the previous risk assessment document *(DP# 328967; B. O'Keefe, 01/23/07).*.

Conclusions: The metabolism in rotational crops was found to be qualitatively similar to that in the primary crops peanut, sugar beet and wheat, as the same major metabolites were detected. The presence of minor unknown polar compounds indicated that composition of metabolites in rotational crops was influenced by the metabolism of prothioconazole in soil. In addition, it appeared that conjugation was more prevalent in rotational crop metabolism than in primary crop metabolism. The confined study did show the potential for accumulation of residue in rotated crops.

4.1.3 Metabolism in Livestock

No animal metabolism studies were submitted with the subject petitions. The petitioner has previously submitted metabolism studies with prothioconazole (labeled in the triazole and phenyl rings) with goats and hens. With the exception of some qualitative and quantitative differences observed between goats and hens, the metabolism of prothioconazole was very similar in all livestock. Prothioconazole was found to be a major residue in liver, kidney (goat only) and fat, at 11-31% TRR and was identified in muscle at 2.5-13% TRR; prothioconazole was found at lower levels in milk and egg (<4% TRR). Prothioconazole-desthio was a major metabolite in fat and egg, at 15-29% TRR, but was found at lower levels in other tissues and milk (<8% TRR). 4-Hydroxy prothioconazole was found at ~11% TRR in goat liver and at <8.5% TRR in other goat matrices and in hen liver and muscle. Two co-eluting metabolites, JAU6476-O- or S-glucuronide and JAU6476-3-hydroxy-desthio, were found to be major metabolites, at ~34% TRR in goat kidney and 4.4%-24% TRR in goat milk and tissues, and hen matrices. In triazole-label studies, 1,2,4-triazole accounted for a significant portion of radioactivity in egg (11% TRR) and hen muscle (19% TRR); 1,2,4-triazole was found at lower levels in hen liver and fat (<2% TRR) but was not detected in goat matrices. Thiocyanate was found to account for a major portion of radioactivity in milk and goat kidney, muscle, and fat, at 9.0-41% TRR; thiocyanate was found at lower levels in goat liver (~2% TRR) and hen matrices (<10% TRR). JAU6476-triazolyl-ethanol was a major metabolite in egg (16% TRR) and hen muscle (28% TRR), was found at lower levels in hen liver and fat (<4% TRR), and was not detected in goat matrices. Additional metabolites found at significant levels were JAU6476-S-methyl, at 20-28% TRR in hen fat (found at <7% TRR in other hen matrices and <1% TRR in goat liver), and JAU6476-hydroxy-glucuronide, at 11% TRR in goat fat (<7% TRR in other goat matrices and in hen liver).

Conclusions. The nature of the residue in animal commodities is adequately understood. For the purpose of tolerance enforcement, the residues of concern are the sum of prothioconazole, the prothioconazole-desthio metabolite, and conjugates that can be converted to either of these two compounds by acid hydrolysis, calculated as prothioconazole. For purposes of risk assessment, the residues of concern consist of prothioconazole, the prothioconazole-desthio metabolite, the 4-hydroxy prothioconazole metabolite, and conjugates that can be converted to any of these three compounds by acid hydrolysis.

4.1.4 Analytical Methodology

Residue Chemistry Memo DP# 318440, 7/30/07, P. Schermerhorn (TMV Report)
Residue Chemistry Memo DP#s 303508 & 314517, 8/21/06, S. Funk (PP#4F6830)

Adequate analytical methods exist for the determination of the residue as defined for both tolerance enforcement and for determination of the residues of concern for risk assessment for both plant and livestock commodities. Two methods (LC/MS/MS Method RPA JA/03/01 for plants and LC/MS/MS Method Bayer Report No. 200537 for animals) which use liquid chromatography with tandem mass spectrometry using electrospray ionization in both the positive and negative modes have successfully passed tolerance method validation at ACB/BEAD. However, ACB recommended that revisions of these methods should be submitted to include at least two multiple reaction monitoring (MRM) transitions to preclude the need for a confirmatory method. In addition, we reiterate the data gap cited in the initial prothioconazole petition (PP#4F6830) that the proposed data collection and enforcement methods for livestock commodities must be validated for poultry commodities.

The data-collection method used for the analysis of samples collected from the soybean and sugar beet field and processing studies is adequate. Samples were analyzed for total prothioconazole-derived residues (prothioconazole and its metabolite prothioconazole-desthio) using LC-MS/MS method (RPA JA/03/01) which is similar to the enforcement method. The validated LOQ for total prothioconazole-derived residues was 0.05 ppm for soybean and sugar beet matrices, and 1 ppm for soybean aspirated grain fractions. Samples were also analyzed for residues of 1,2,4-triazole and triazole conjugates (triazolylalanine and triazolylacetic acid) using an LC/MS/MS method (Morse Meth-160). The validated LOQ was 0.01 ppm for 1,2,4-triazole, and ranged 0.01-0.05 ppm for the triazole conjugates.

Multiresidue Methods

A multiresidue method testing study was previously submitted in support of PP#4F6830. The study investigated the recovery of prothioconazole, prothioconazole-desthio, prothioconazole-4-hydroxy, and the triazole-related compounds (triazole, triazolylalanine and triazolylacetic acid) through the multiresidue methods of PAM Vol. I. Based on a cursory review of the study results, HED concluded that the multiresidue methods are not appropriate for determining residues of prothioconazole residues of concern, or for determining triazole residues. The study has been forwarded to FDA for further review.

4.1.5 Storage Stability Data

Plant commodities

The interim results of several storage stability studies for prothioconazole and its desthio metabolite in plant commodities were previously reported in PP#4F6830. The interim results indicate that residues of prothioconazole appear to be stable for 12.5 to 12.7 months in canola oil (14% decomposition), canola seed (20% decomposition), mustard green (22% decomposition), tomato fruit (14% decomposition), turnip roots (0% decomposition), wheat flour (12% decomposition), wheat forage (16% decomposition), wheat grain (27% decomposition), and wheat straw (15% decomposition). Prothioconazole showed 33% and 36% decomposition in tomato paste and wheat bran, respectively. However, the plant metabolism studies in three dissimilar crops have shown that prothioconazole is expected to contribute only 0 to 7% (0 to 20% normalized) of the total residues measured in the field crop residue studies. Therefore, the initial prothioconazole petition concluded that the apparent slight instability of prothioconazole in tomato paste and wheat bran would not be expected to have any significant effect on the total prothioconazole residue levels measured in the field crop residue studies. Prothioconazole-desthio, the major residue anticipated in crop matrices, was found to be stable in all matrices after 12.5 to 12.7 months of freezer storage. Percent decomposition of prothioconazole-desthio was equal to or less than 5% in all matrices. Prothioconazole-desthio would be expected to contribute 6 to 58% (80 to 100% normalized) of the residues measured in the prothioconazole field crop residue trials.

Additional data from a marginally acceptable study (Study 1; MRID 46477701) indicate that combined residues of prothioconazole and prothioconazole-desthio appear to be stable in/on wheat forage, hay, and straw stored frozen for up to ~35 months. Combined residues of prothioconazole and prothioconazole-desthio were found to decline during frozen storage for ~35 months by ~18% in/on canola seed, ~13% in/on mustard greens, ~20% in/on tomato, ~17% in/on turnip root, and ~32% in/on wheat grain.

It was also reported that 1,2,4-triazole residues are stable at -15 ºC for up to 24 months in/on turnip roots, mustard greens, wheat straw and wheat grain, but less stable in wheat forage (48% decomposition) and canola seed (73% decomposition), and that total residues for triazole conjugates are stable at -15 ºC for up to 24 months in turnip roots, mustard greens, wheat forage, wheat straw and wheat grain, and relatively stable in canola seed (≤36% decomposition).

Conclusions: The available storage stability data are tentatively adequate to support the storage intervals and conditions of samples analyzed for prothioconazole residues of concern from the submitted crop field trial and processing studies. The final reports of the ongoing storage stability studies with prothioconazole and prothioconazole-desthio (up to 45 months) must be submitted as confirmatory data. Storage stability data for processed commodities are not required as processed matrices were analyzed within ~1 month of collection in the soybean and sugar beet processing studies and storage stability data for the RAC will support the storage conditions and durations of AGF samples from the soybean study.

The adequacy of the triazole storage stability study to support the requested uses of prothioconazole will be determined when the final results of an ongoing triazole storage stability study are submitted to the Agency (6-month interim data were submitted in MRID 46246211).

Livestock commodities

Storage stability data were submitted in conjunction with the previously submitted livestock feeding studies. The petitioner has repeated a storage stability study in fat samples for prothioconazole and the prothioconazole-4-hydroxy metabolite for a period of 45 days at the 1.4-fold and 4.7-fold feeding level as confirmatory data. The results indicated some instability of the prothioconazole over the 45 days, but the previously established tolerance is adequate to cover this loss.

4.1.6 Magnitude of the Residue in Plants

Soybean

DER Reference: 46841001.der.doc

Bayer CropScience has submitted field trial data for prothioconazole on soybeans. A summary of residue data from the soybean field trials is presented in Table 4.1.. The maximum total prothioconazole-derived residues were 4.45 and 18.9 ppm in/on soybean forage and hay, respectively, harvested 5-7 days following treatment at 0.391-0.449 lb ai/A. For mature seed harvested 19-23 days following treatment at 0.393-0.413 lb ai/A, the maximum total prothioconazole-derived residues were 0.142 ppm.

Table 4.1.1. Summary of Residue Data from Soybean Field Trials with Prothioconazole.

Matrix	Total Rate (lb ai/A)	PHI (days)	Residues (ppm)						
			N	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Proposed use pattern: Multiple broadcast postemergence foliar applications at maximum seasonal rates of 0.281 lb ai/A (Proline®) or 0.402 lb ai/A (Provost™). A 21-day preharvest interval (PHI) is proposed for both products.									
Total Prothioconazole-Derived Residues									
Forage	0.391-0.449	5-7	42	<0.05	4.45	4.25	1.37	1.39	0.95
Hay		5-7	42	1.46	18.9	18.3	5.56	5.97	3.36
Seed	0.393-0.413	19-23	42	<0.05	0.142	0.12	0.05	0.05	0.02
1,2,4-Triazole Residues									
Forage	0.391-0.449	5-7	21	<0.01	0.01	NA	0.01	0.01	0.00
Hay		5-7	21	<0.01	0.01	NA	0.01	0.01	0.00
Seed	0.393-0.413	19-23	8	<0.01	<0.01	<0.01	<0.01	<0.01	0.00
Triazole Conjugate Residues									
Forage	0.391-0.449	5-7	21	<0.05	0.27	NA	0.06	0.08	0.06
Hay		5-7	21	0.04	0.40	NA	0.17	0.15	0.09
Seed	0.393-0.413	19-23	8	0.04	0.08	0.08	0.06	0.06	0.01

Based on the decline trial data, residues in/on soybean forage and hay generally declined with later harvest intervals. In the two residue decline tests, prothioconazole-derived residues in/on forage declined from averages of 2.8 ppm and 3.7 ppm at 0 DAT to 0.35 ppm and 0.46 ppm at 14 DAT, respectively. Prothioconazole-derived residues in/on hay declined from averages of 16.2 ppm and 18.9 ppm at 0 DAT to 1.40 ppm and 1.81 ppm at 14 DAT. For seeds, prothioconazole-derived residues were too low (<0.05 ppm) to determine decline trends.

The 1,2,4-triazole residues were <0.01-0.01 ppm for both forage and hay samples harvested 5-7 DAT. The triazole conjugate residues were <0.05-0.27 ppm and 0.04-0.40 ppm in the respective forage and hay samples. For composite samples of seed harvested 19-23 DAT, residues of 1,2,4-triazole were <0.01 ppm, and residues of triazole conjugates were 0.04-0.08 ppm.

Conclusions: The submitted residue data for soybeans are adequate to fulfill data requirements pending submission of the final study reports from ongoing storage stability studies and revision of product labels to specify appropriate preharvest intervals for certain soybean commodities. The number and location of field trials are in accordance with OPPTS Guideline 860.1500, and the conducted field trials reflect the maximum proposed seasonal rate for Provost™ as well as the proposed 21-day PHI for soybean seed.

The field trial data for soybean forage and hay were entered into the Agency's tolerance spreadsheet as described in a document entitled *Statistical Basis of the NAFTA Method for Calculating Pesticide Maximum Residue Limits from Field Trial Data* to determine appropriate tolerance levels; see Appendix I of DP# 331663, 12/19/07, S. Funk (PP#6F7073 and PP#6F7134). The tolerance spreadsheet was not used for soybean seed because >60% of treated samples bore residues below the LOQ. The tolerance spreadsheet recommends tolerances of 4.5 ppm for soybean forage and 17 ppm for soybean hay. Based on the maximum residues of 0.142 ppm obtained from the field trials, HED recommends a tolerance of 0.15 ppm for soybean seed which is identical to the level proposed by the petitioner. A revised Section B is required to specify a minimum preharvest interval of 7 days for soybean forage and hay.

Sugar Beet

DER Reference: 46974608.der.doc

Bayer CropScience has submitted field trial data for prothioconazole on sugar beets. A summary of residue data from the sugar beet field trials is presented in Table 4.1.2. The maximum total prothioconazole-derived residues were 4.18 and 1.97 ppm in/on sugar beet tops harvested at 6/7 and 13/14 days, respectively, following late-season foliar applications of the 4 lb/gal FlC formulation at a total rate of 0.529-0.548 lb ai/A. The maximum total prothioconazole-derived residues were 0.24 and 0.14 ppm in/on roots harvested 6/7 and 13/14 DAT, respectively.

Table 4.1.2. Summary of Residue Data for Sugar Beet Field Trials with Prothioconazole.									
Matrix	Total Rate (lb ai/A)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Proposed use pattern: Multiple broadcast postemergence foliar applications at a maximum seasonal rate of 0.534 lb ai/A. The proposed PHIs are 7 days (Proline®) or 21 days (USF 0728 325 SC Fungicide).									
Total Prothioconazole-Derived Residues									
Tops	0.529-0.548	6-7	24	0.39	4.18	3.87	1.64	1.80	1.17
		13-14	24	0.20	1.97	1.75	1.04	1.03	0.60
Roots		6-7	24	<0.05	0.24	0.17	0.05	0.07	0.05
		13-14	24	<0.05	0.14	0.11	0.05	0.07	0.06
1,2,4-Triazole Residues									
Tops	0.529-0.548	6-7	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
		13-14	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
Roots		6-7	12	<0.01	0.012	<0.011	<0.01	<0.01	0.001
		13-14	12	<0.01	<0.01	<0.01	<0.01	<0.01	--
Triazole Conjugate Residues									
Tops	0.529-0.548	6-7	12	<0.01	0.018	0.018	0.01	0.012	0.003
		13-14	12	<0.01	0.021	0.021	0.01	0.012	0.004
Roots		6-7	12	<0.01	0.014	0.014	0.01	0.011	0.002
		13-14	12	<0.01	0.017	0.017	0.012	0.013	0.003

Based on the residue decline trial data, residues in sugar beet tops and roots generally declined with later harvest intervals. Prothioconazole-derived residues declined from 5.0 and 0.07 ppm at the 0-day PHI to 0.74 and 0.06 ppm at the 27-day PHI in/on tops and roots, respectively.

Residues of 1,2,4-triazole were below the LOQ (<0.01 ppm) and <0.01-0.01 ppm, respectively, in/on sugar beet tops and roots harvested 6/7 and 13/14 days after treatment. Total residues of the triazole conjugates were <0.01-0.02 ppm in/on sugar beet tops and roots harvested 6/7 and 13/14 DAT.

Conclusions: The submitted residue data for sugar beet are adequate to fulfill data requirements pending submission of the final study reports from ongoing storage stability studies. The number and location of field trials are in accordance with OPPTS Guideline 860.1500, and the conducted field trials reflect the maximum proposed seasonal rate and the proposed 7-day PHI.

The Agency's tolerance spreadsheet was not used for sugar beet root because >60% of treated samples bore residues below the LOQ. Based on the maximum residues of 0.24 ppm obtained from the field trials (7 day PHI), HED recommends a tolerance of 0.25 ppm for sugar beet root which is identical to the level proposed by the petitioner. According to the Minutes of the 1/17/2007 ChemSAC meeting, a tolerance for sugar beet tops need not be established because they are not a human food commodity and are being eliminated from Table 1 Feedstuffs (October 2006).

4.1.7 Magnitude of the Residue in Processed Food/Feed

Soybean

DER Reference: 46841002.der.doc

Bayer CropScience has submitted a processing study with prothioconazole on soybeans. A summary of processing factors from the soybean processing study is presented in Table 4.1.3.

Table 4.1.3. Summary of Processing Factors for Prothioconazole from the Soybean Study.

RAC	Processed Commodity	Average Processing Factor [1]		
		Prothioconazole	1,24-Triazole	Total Triazole Conjugates [2]
Soybean	Aspirated grain fractions	76x	>1.3x	2.1x
	Meal	0.2x	NC	1.5x
	Hulls	0.6x	NC	0.6x
	Refined oil	<0.2x	NC	<0.1x

[1] NC = Not calculated; residues were below the LOQ in the RAC and the processed commodity.
[2] Total triazolylalanine and triazolylacetic acid residues.

The observed processing factors do not exceed the theoretical concentration factors of 11.3x for soybean hulls, 2.2x for meal, and 12.0x for oil (OPPTS 860.1520, Table 3, based on separation of components).

*Conclusion*s: The soybean processing study is acceptable to satisfy data requirements pending submission of the final study reports from ongoing storage stability studies. The treated samples of soybean seed (RAC) used for processing bore an average prothioconazole-derived residue of 3.06 ppm. Following processing of the RAC, residues did not concentrate in meal (processing factor of 0.2x), hulls (0.6x), and refined oil (<0.2x) but concentrated in soybean aspirated grain fractions (76x). The maximum expected residues in soybean AGF is 9.12 ppm [HAFT (0.12 ppm; see Table 7) X processing factor (76x)]. The established tolerance (11 ppm) for aspirated grain fractions (based on barley and wheat) will cover residues of prothioconazole-derived residues in soybean AGF as a result of the proposed use.

Processing factors could not be calculated for 1,2,4-triazole in meal, hulls, and refined oil because residues were below the LOQ in the RAC and processed matrices. Residues of the triazole conjugates did not appear to concentrate in refined oil and hulls, but appeared to concentrate in meal (1.5x). The processing factors for residues of 1,2,4-triazole and triazole conjugates in AGF were 1.3x and 2.1x, respectively.

Sugar Beet

DER Reference: 46974609.der.doc

Bayer CropScience has submitted a processing study with prothioconazole on sugar beets. A summary of processing factors from the sugar beet processing study is presented in Table 4.1.4.

Table 4.1.4. Summary of Processing Factors for Prothioconazole from the Sugar Beet Study.				
RAC	Processed Commodity	Average Processing Factor [1]		
		Prothioconazole	1,2,4-Triazole	Total Triazole Conjugates [2]
Sugar beet	Refined sugar	<0.1x	NC	<0.7x
	Dried pulp	<0.1x	NC	<0.7x
	Molasses	0.2x	NC	5.3x

[1] NC = Not calculated; residues were below the LOQ in the RAC and the processed commodity.
[2] Total triazolylalanine and triazolylacetic acid residues.

The observed processing factors do not exceed the theoretical concentration factors of 12.5x for sugar beet sugar (OPPTS 860.1520, Table 3, based on separation of components) or 20x for sugar beet dry pulp (OPPTS 860.1520, Table 4, maximum experimental factor).

*Conclusion*s: The sugar beet processing study is acceptable to satisfy data requirements pending submission of the final study reports from ongoing storage stability studies. The treated samples of sugar beet root (RAC) used for processing bore an average prothioconazole-derived residue of 1.82 ppm. Following processing of the RAC, residues did not concentrate in refined sugar (<0.1x), dried pulp (<0.1x), and molasses (<0.1x). The results suggest that tolerances are not needed for the processed commodities of sugar beet.

Residues of the triazole conjugates did not appear to concentrate in refined sugar and dried pulp (<0.7x processing factors), but appeared to concentrate in molasses (5.3x) with processing. Processing factors could not be calculated for 1,2,4-triazole because residues were below the LOQ in the RAC and processed refined sugar, dried pulp and molasses.

4.1.8 Magnitude of the Residue in Meat, Milk, Poultry, and Eggs

Residue Chemistry Memo DP#s 303508 & 314517, 8/21/06, S. Funk (PP#4F6830)

Livestock dietary burdens

The potential for secondary transfer of prothioconazole residues of concern in meat, milk, poultry, and eggs exists because there are several livestock feedstuffs (soybean seed, forage, hay, aspirated grain fractions, meal, hulls and silage; and sugar beet dried pulp and molasses) that are associated with the proposed uses in the current petitions. Sugar beet tops are no longer considered a significant feed item and have been removed from Table 1 Feedstuffs (October 2006). The livestock dietary burdens of prothioconazole are presented in Table 4.1.5, and the calculations made reflect the most recent guidance from HED concerning revisions of feedstuff percentages in Table 1 and constructing reasonably balanced livestock diets (RBDs). The calculated dietary burdens of prothioconazole are 9.24 ppm for beef cattle, 9.79 ppm for dairy cattle, 0.29 ppm for poultry, and 0.10 ppm for swine.

Table 4.1.5. Calculation of Dietary Burdens of Prothioconazole Residues to Livestock.					
Feedstuff	Type[1]	% Dry Matter[2]	% Diet[2]	Recommended/ Established Tolerance (ppm)	Dietary Contribution (ppm)[3]
Beef Cattle					
Soybean hay	R	85	30	17.0	6.00
Wheat forage	R	25	10	6.0	2.40
Barley grain	CC	88	40	0.35	0.16
Aspirated grain fractions	CC	85	5	11.0	0.65
Soybean seed	PC	89	15	0.15	0.03
TOTAL BURDEN	--	--	100	--	**9.24**
Dairy Cattle					
Soybean hay	R	85	30	17.0	6.00
Wheat forage	R	25	15	6.0	3.60
Barley grain	CC	88	40	0.35	0.16
Soybean seed	PC	89	15	0.15	0.03
TOTAL BURDEN	--	--	100	--	**9.79**
Poultry					
Barley grain	CC	88	70	0.35	0.25
Wheat grain	CC	89	10	0.07	0.007
Soybean seed	PC	89	20	0.15	0.03
TOTAL BURDEN	--	--	100	--	**0.29**
Swine					
Barley grain	CC	88	20	0.35	0.07
Untreated	CC	NA	60	NA	--
Soybean seed	PC	89	20	0.15	0.03
TOTAL BURDEN	--	--	100	--	**0.10**

[1] R: Roughage; CC: Carbohydrate concentrate; PC: Protein concentrate.
[2] Revision of feedstuffs in OPPTS 860.1000 Table 1 referenced as "Table 1 Feedstuffs (October 2006)."
[3] Contribution = ([tolerance /% DM] X % diet) for beef and dairy cattle; contribution = ([tolerance] X % diet) for poultry and swine.

Established livestock tolerances

Tolerances have been established for the combined residues of prothioconazole, prothioconazole-desthio, and conjugates that can be converted to these two compounds by acid hydrolysis, calculated as parent, at 0.02 ppm for milk; 0.02, 0.1, and 0.2 ppm, respectively, for the meat, fat, and meat byproducts of cattle, goat, and sheep; 0.05 ppm for the meat byproducts of hog; and 0.02 ppm for poultry liver.

The prothioconazole tolerances for livestock commodities were established based on results from the submitted feeding studies and the Agency's estimated dietary burdens for prothioconazole residues, which were originally calculated to be 12.97 ppm for beef cattle, 20.86 ppm for dairy cattle, 0.45 ppm for poultry, and 2.71 ppm for swine. These values represented the maximum

theoretical burden with no consideration of a reasonably balanced diet, i.e., the diet was excessive in forage/hay.

Animal feeding studies

Residue Chemistry Memo DP#s 303508 & 314517, 8/21/06, S. Funk (PP#4F6830)

Two cattle feeding studies were previously reviewed in PP#4F6830, one in which cattle were dosed with prothioconazole (MRID 46246213) and one in which cattle were dosed with prothioconazole-desthio (MRID 46246214). The results of the first study are summarized below; the second study was deemed supplemental.

Prothioconazole was administered orally (via gelatin capsules) to three groups of dairy cattle (3 cows per group) once daily for 29 consecutive days. Dosing was made at levels equivalent to 9.9, 29.5, and 98.4 ppm in the feed. The dosing levels correspond to ~1x, 3x, and 10x the recalculated dietary burden for dairy cattle based on a reasonably balanced diet. Milk and tissue samples were analyzed using the proposed enforcement method for animal commodities, which was an LC-MS/MS method (Bayer Report No. 200537). This method determined residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy, plus any metabolites hydrolysable to these compounds. The maximum residues of prothioconazole, prothioconazole-desthio, and prothioconazole-4-hydroxy in milk and tissues are listed in Table 4.1. below. Because low residue levels were observed in samples from the mid and high dose groups, milk and muscle samples from the low dose group (9.9 ppm) were not analyzed.

Table 4.1.6. Maximum Residues of Prothioconazole (A), Prothioconazole-desthio (B), and Prothioconazole-4-hydroxy (C), as prothioconazole equivalents, by Feeding Level Following Dosing of Dairy Cattle with Prothioconazole for 29 Days.

Matrix	Residues (ppm)								
	9.9 ppm			29.5 ppm			98.4 ppm		
	A	B	C	A	B	C	A	B	C
Milk (day 29)	--	--	--	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005
Skim milk	--	--	--	--	--	--	<0.01	<0.01	<0.01
Cream	--	--	--	--	--	--	<0.01	<0.01	<0.01
Fat	<0.05	<0.05	<0.05	<0.05 (0.019)[1]	<0.05 (≈0.003)[1]	<0.05 (≈0.006)[1]	0.062	<0.05	<0.05
Kidney	0.062	<0.01	0.017	0.176	<0.01	0.063	0.79	0.011	0.356
Liver	0.063	<0.01	0.054	0.120	0.011	0.181	0.467	0.030	0.518
Muscle	--	--	--	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[1] At/near the limit of *detection*; in fat, 0.012 ppm for prothioconazole, 0.005 ppm for prothioconazole desthio, 0.008 ppm for prothioconazole-4-hydroxy.

Quantifiable residues (of prothioconazole, 0.005-0.006 ppm) were observed in only two samples of milk (over the entire dosing period) from the highest dosing level. However, detectable residues of prothioconazole were observed in several samples. Based on these residues, it appeared that residues had reached a plateau within the first week of dosing.

A poultry feeding study is not available. HED *provisionally* concluded in PP#4F6830 that residues are unlikely in poultry commodities except liver and that, therefore, poultry commodity tolerances are not needed, except for liver. The extreme extrapolation required and the short interval of the poultry metabolism study (3 days) makes the conclusions on the need for poultry tolerances tentative. Therefore, a poultry feeding study and fully validated analytical method for poultry commodities are required as conditions of the registration of prothioconazole.

Conclusions: Based on the dietary exposure levels and the residue data from the ruminant feeding study, the existing prothioconazole tolerances for animal commodities are adequate to support the proposed uses. As requested in PP#4F6830 and to support the current petitions, a poultry feeding study and fully validated analytical method for poultry commodities are required.

4.1.9 Confined and Field Rotational Accumulation in Rotational Crops

Residue Chemistry Memo DP#s 303508 & 314517, 8/21/06, S. Funk (PP#4F6830)

Two acceptable confined crop rotation studies were previously submitted in PP#4F6830. HED review of these studies indicate that the metabolism of prothioconazole in rotational crops was similar to that in the primary crops peanut and wheat, as the same major metabolites were detected. The presence of minor unknown polar compounds indicated that composition of metabolites in rotational crops was influenced by the metabolism of prothioconazole in soil. It appeared that conjugation was more prevalent in rotational crop metabolism than in primary crop metabolism, and that metabolism/degradation of the triazole ring to triazole conjugates was more extensive in rotational crops than in primary crops. The submitted confined rotational crop studies indicate the potential for quantifiable prothioconazole and triazole-conjugate residues in rotated crop commodities. No metabolites were identified in the confined rotational crop studies that were not identified in one or more of the primary crop metabolism studies. The residue definition in rotational crop commodities (for tolerance enforcement and for dietary intake assessment) is the same as for primary crop commodities, prothioconazole and the desthio metabolite.

Bayer previously submitted a limited field rotational crop study in PP#4F6830 on the representative crops mustard greens (leafy vegetable), turnip (root vegetable), and wheat (cereal grain). HED has determined that these data are adequate to satisfy data requirements. The petitioner has proposed the following rotational crop restrictions: crops listed on the label may be planted as soon as practical after last application; all other crops may be planted 30 days following last application. The submitted field rotational crop data, which indicated no quantifiable total prothioconazole-derived residues in mustard greens, turnip root and top, and wheat forage, hay grain, and straw at the 1-month plantback interval (PBI), are adequate to support the proposed rotational crop restrictions, provided that the required storage stability data do not indicate significant decline of prothioconazole residues in these commodities during storage.

4.1.10 Drinking Water Residue Profile

Reference: *Drinking Water Assessment for the Section 3 New Use Petitions for the Use of Prothioconazole on Soybeans and Sugar Beets. DP#'s 341457 & 341458, C. Sutton, 10/10/07.*

A detailed characterization of the environmental fate and transport of prothioconazole and its' degradates was previously provided in the following document: "*Prothioconazole Section 3: Environmental Fate and Ecological Risk Assessment", DP Barcode: 324660, Decision #: 341716, C. Salice and R. Kashuba, 06/01/06.*

Prothioconazole has the potential to reach surface water via runoff, erosion, and spray drift. Prothioconazole appears to degrade relatively quickly in the environment. Its major degradates are prothioconazole-desthio and prothioconazole-S-methyl. These degradates are detected in major amounts in almost all fate laboratory studies, and therefore, it is assumed that these degradates are likely to result in significant environmental concentrations. Estimated environmental concentrations are based on total toxic residues, i.e., the parent prothioconazole compound plus prothioconazole-desthio and prothioconazole-S-methyl. Two other major degradates were not included in this assessment: prothioconazole-thiazocine (not considered a degradate of concern) and 1,2,4-triazole (since it is assessed separately as a common degradate in the conazole aggregate risk assessment). The prothioconazole-desthio and prothioconazole-S-methyl degradates are persistent, moderately to slightly mobile, and may reach ground water; because of this and their toxicity they have been included in the drinking water exposure estimates.

EFED provided estimated drinking water concentrations (EDWCs), which were determined using the PRZM-EXAMS screening model. EDWC point estimates were provided for both lower and upper bounds to account for two major uncertainties in the drinking water modeling. First, some prothioconazole residues remained in the bound phase in EFED studies used to characterize persistence. To address this uncertainty, modeling was bounded based on inclusion and exclusion of unextracted residues in half-life calculations. Secondly, the two major water degradates of prothioconazole formed rapidly after application and have different mobilities. To address this uncertainty, modeling was conducted using K_{OCs} (soil organic carbon-water partitioning coefficients) for prothioconazole-desthio and prothioconazole-S-methyl. The lower bound EDWCs represent the exclusion of unextracted residues and the use of the higher K_{oc} (less mobility). Conversely, the higher bound estimates represent the inclusion of unextracted residues and the use of the lower K_{oc} (more mobility).

EDWCs were further refined for peanuts and sugar beets. Regional default Percent Cropped Area (PCA) factors have been applied to estimated concentrations of these crops. Surface water EDWCs used in this assessment are summarized in Table 4.1.7 below. DEEM analyses were performed using both the upper and lower bound estimates and the peanut (previous registration) and sugar beet (proposed registration) crop scenarios shown below, since these EDWC values were the highest reported for the respective acute and chronic exposure durations.

Table 4.1.7. Summary of Estimated Drinking Water Concentrations for Prothioconazole Used for Dietary Assessment					
DRINKING WATER SOURCE (MODEL USED)	**USE SCENARIO (rate modeled)**	**ESTIMATED DRINKING WATER CONCENTRATION (ppb)**			
		ACUTE		CHRONIC	
		Lower Bound	Upper Bound	Lower Bound	Upper Bound
Surface water (PRZM/EXAMS)	Peanut	13	29	--	--
	Sugar Beet	--	--	8.4	13

4.1.11 Proposed Tolerances

HED has determined that the residues of concern for tolerance enforcement and for risk assessment in plant and rotational crop commodities are defined as the sum of prothioconazole and its metabolite prothioconazole-desthio, calculated as prothioconazole. The residues of concern in livestock commodities for tolerance enforcement are defined as the sum of prothioconazole, prothioconazole-desthio, and conjugates that are converted to prothioconazole or prothioconazole-desthio via acid hydrolysis, calculated as prothioconazole. The residues of concern for risk assessment in livestock commodities are defined as the sum of prothioconazole, prothioconazole-desthio, 4-hydroxy prothioconazole, and conjugates that are converted to prothioconazole or prothioconazole-desthio or 4-hydroxy prothioconazole via acid hydrolysis, calculated as prothioconazole.

Prothioconazole tolerances for plant commodities listed in 40 CFR §180.626(a)(1) are expressed in terms of the combined residues of the fungicide prothioconazole, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione, and prothioconazole-desthio, α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-1*H*-1,2,4-triazole-1-ethanol, calculated as parent.

Prothioconazole tolerances for animal commodities are listed in 40 CFR §180.626(a)(2) and are expressed in terms of the combined residues of the prothioconazole and prothioconazole-desthio, and conjugates that can be converted to these two compounds by acid hydrolysis, calculated as parent.

The tolerance expression proposed by Bayer in #6F7073 and PP#6F7134 is consistent with the tolerance definition for plant commodities listed in 40 CFR §180.626(a)(1). However, a revised Section F must be submitted to incorporate the CAS name of prothioconazole-desthio in the tolerance expression and to specify that residues of the metabolite are calculated as parent.

The field trial data for soybean forage and hay were entered into the Agency's tolerance spreadsheet as described in a document entitled *Statistical Basis of the NAFTA Method for*

Calculating Pesticide Maximum Residue Limits from Field Trial Data to determine appropriate tolerance levels; see Appendix I. The tolerance spreadsheet was not used for soybean seed because >60% of treated samples bore residue below the data-collection method LOQ. The tolerance spreadsheet recommends tolerances of 4.5 ppm for soybean forage and 17 ppm for soybean hay. Based on the maximum residues of 0.142 ppm obtained for seed from the field trials, HED recommends a tolerance of 0.15 ppm for soybean seed.

The field trial data for sugar beet root were not entered into the Agency's tolerance spreadsheet because >60% of treated samples bore residues below the LOQ. Based on the maximum residues of 0.24 ppm obtained from the field trials and excluding an apparent invalid value (1.26 ppm), HED recommends a tolerance of 0.25 ppm for sugar beet root. According to the Minutes of the 1/17/2007 ChemSAC meeting, a tolerance for sugar beet tops need not be established because they are not a human food commodity and are being eliminated from Table 1 Feedstuffs (October 2006).

The submitted soybean and sugar beet processing studies indicate that tolerances are not needed for the processed commodities of these crops. No concentration of prothioconazole-derived residues was observed in soybean meal (0.2x), hulls (0.6x), and refined oil (<0.2x) and in sugar beet refined sugar (<0.1x), dried pulp (<0.1x), and molasses (<0.1x). Residues concentrated in soybean aspirated grain fractions (76x); the established tolerance (11 ppm) for aspirated grain fractions (based on barley and wheat) will cover residues of prothioconazole-derived residues in soybean AGF as a result of the proposed use.

No tolerances are needed for rotational crops based on previously submitted studies which showed no quantifiable total prothioconazole-derived residues in/on rotated mustard greens, turnip root and top, and wheat forage, hay grain, and straw at the 1-month PBI. The 30-day rotational crop restriction on the proposed product labels is appropriate.

Adequate ruminant feeding studies are available, and these data indicate that the established tolerances for milk, and fat, meat, and meat byproducts of cattle, goat, hog, horse, and sheep remain adequate to support the proposed uses and the re-calculated dietary burdens. Consistent with the determination made in PP#4F6830, HED *tentatively* concludes that the established tolerance for poultry liver is adequate based on extrapolation made from the results of previously submitted poultry metabolism studies. A poultry feeding study and fully validated analytical methods for poultry commodities were requested in PP#4F6830 as a condition for full registration, and these data gaps apply as well for the current petitions.

A summary of the recommended tolerances for the crop commodities discussed in this Summary Document is presented in Table 4.1.9. The petitioner should submit a revised Section F reflecting the recommended tolerances and correct commodity definitions presented in Table 4.1.9.

Table 4.1.9. Tolerance Summary for Prothioconazole.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Soybean, forage	5	4.5	Tolerance recommendation is contingent upon label revision to specify a 7-day PHI.
Soybean, seed	0.15	0.15	
Soybean, hay	22	17	Tolerance recommendation is contingent upon label revision to specify a 7-day PHI.
Beet, sugar, roots	0.25	0.25	
Beet, sugar, tops	9	Not needed	Tolerances are not currently required for sugar beet tops.

4.1.12 International Residue Limits (IRL)

There are currently no established Codex or Mexican MRLs for prothioconazole. Canada MRLs have been proposed (12/2006) for prothioconazole in/on barley; dry chickpeas and dry lentils; rapeseed (canola); mustard seed; wheat; fat and meat byproducts of cattle, goats, horses and sheep; meat byproducts of hogs; meat of cattle, goats, horses and sheep; milk; and liver of poultry as a result of the previous joint review project (PP#4F6830); no Canadian MRLs are proposed or established for soybean or sugar beet matrices. An International Residue Limit Status sheet is attached to this review.

4.2 Dietary Exposure and Risk

Reference: *Prothioconazole: Acute and Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessments for the Section 3 Registration Actions on Sugar Beets (PP# 6F7134) and Soybeans (PP# 6F7073). DP Barcode 345924, T. Goodlow, 12/19/07.*

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

Acute and chronic dietary (food plus drinking water) exposure analyses were performed to support the registration of the new chemical, prothioconazole. The analyses were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID^{TM}, version 2.03), which used food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and

within population subgroups, but for acute exposure assessment are retained as individual consumption events. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

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

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

Dietary Assessment of Free Triazole and its Conjugates

Prothioconazole is a thio-triazole, and as such, HED notes that a separate risk assessment was conducted for the 1,2,4-triazole and its conjugates. Triazolylalanine (TA), triazolylhydroxoypropionic acid (THPA), and triazolylacetic acid (TAA), metabolites common to the triazole derivative class of fungicides, were also found to be metabolites of prothioconazole.

HED conducted an aggregate risk assessment for the metabolite/degradate 1,2,4-triazole (also referred to as free triazole) and its conjugates TA and TAA, including data review, hazard identification and endpoint selection, to support the extension of existing tolerances and the granting of new parent triazole derivative fungicide tolerances (DP# 322215, 2/7/06, M. Doherty *et al.*). TA and TAA residues are primarily associated with plant commodities whereas 1,2,4-T is associated with rats and livestock. In that assessment, it was concluded that there are no human health risk issues associated with 1,2,4-T or its metabolites that would preclude reregistration of the triazole-derivative fungicides registered at the time the risk assessment memo was issued or conditional registration of the triazole-derivative fungicide uses that have been proposed as of September 1, 2005. The risk assessment included uses of prothioconazole proposed in PP#4F6830; the last prothioconazole risk assessment. Additionally, in that

aggregate triazoles risk assessment, HED concluded that new uses for triazole pesticides (such as the proposed prothioconazole uses addressed in this document) should be examined in terms of potential residues of 1,2,4-T and its conjugates, and that the risk assessment may require revision if new uses are for sites not already addressed by the current list of registered or proposed uses, if the formation of the metabolites exceeds the estimates used in the previous risk assessment, or if required toxicity data raise concerns not addressed by the current risk assessment.

Separate dietary risk assessments, based on conservative residue estimates, have been completed for 1,2,4-T and TA+TAA (combined) and are updated, as needed, for new triazole fungicide uses. The most recent dietary assessments for these compounds (W. Cutchin, DP Numbers 347252 and 347253, 12/19/07) include residue estimates for soybean and sugar beet commodities. Currently registered uses on soybean and sugar beet from the application of other triazole fungicides result in potentially greater residues of 1,2,4-T and TA+TAA (combined) on the resulting crop commodities than are attributable to these proposed uses of prothioconazole. Therefore, an updated assessment is not required to address dietary exposure to 1,2,4-T or to TA+TAA for these new prothioconazole petitions.

Residue Data used for Acute and Chronic Assessments:

Moderately refined acute and chronic dietary assessments were performed for prothioconazole. The refinements used for both exposure durations are summarized below.

- Average field trial residues were used for all plant commodities in both the acute and chronic analyses. Mean values used in this assessment can be found in Stephen Funk's Summary of Analytical Chemistry and Residue Data document under 'crop field trials'. Since all of the crops included in this assessment are blended food forms, no residue data files (RDFs) were required. See Change in Classification of Food Forms with Respect to "Not Blended," "Partially Blended," and "Blended" Status, HED's ChemSAC memo, 8/20/1999 for further details.

- Maximum residues were used in the assessments for livestock commodities. These values were determined using the previously submitted ruminant feeding study, poultry metabolism study, and the calculated reasonably balanced dietary burden (RBDB); see DP# 331663, S. Funk for further details.

- EFED submitted modeled EDWC values. Point estimates were used in the acute and chronic assessments from the peanut and sugar beets application scenarios. See DP#'s 341457 and 341458, Drinking Water Assessment for the Section 3 New Use Petitions for the Use of Prothioconazole on Soybeans and Sugar Beets, by C. Sutton, 10/10/07, for additional information.

- Since there are no water monitoring data available for prothioconazole, drinking water exposure estimates were based on PRZM-EXAMS surface water modeling results. The drinking water inputs may be considered conservative for the following reasons. The model results assume that applications will be made at maximum application rates every year for 30 years. The PRZM-EXAMS models are based on an actual reservoir/watershed system in

Illinois which is known to be a highly vulnerable configuration. Based on these considerations, it is likely that actual exposure to prothioconazole from drinking water is somewhat lower than the estimates provided in this assessment.

- Empirical factors generated in processing studies were also included when appropriate in the acute and chronic assessments. Reduction factors were used for canola refined oil, wheat flour, soybean refined oil, and sugar beet molasses. Concentration factors were incorporated for wheat bran and germ. A default DEEM 7.81 processing factor was also included for dried beef. A processing factor (PF) could not be calculated for peanut butter in the submitted peanut processing study because residues were below the limit of quantification (LOQ) in both the raw agricultural commodity (RAC) and the processed fraction; therefore, no PF was applied for peanut butter. See Summary of Analytical Chemistry and Residue Data document for additional information.

4.2.1 Acute Dietary Exposure/Risk

A moderately refined acute dietary exposure assessment was conducted for prothioconazole. Average field trial values, empirical processing factors, and livestock maximum residues were incorporated into the refined acute assessment. The assessment also assumed 100% CT. No acute endpoint was identified for the general U.S. population; females 13-49 years of age was the only population subgroup included in the acute assessment. Dietary risk estimates were determined considering exposures from food alone and food plus water using drinking water exposures for the peanut application scenario. Ground water sources were not included, as the EDWCs for this water source are minimal in comparison to surface water.

The dietary exposure analyses result in acute dietary risk estimates that are below the Agency's level of concern for food only and food and drinking water. At the 95th percentile, the food only exposure for females 13-49 years old was 0.000167 mg/kg/day, which utilized 8.4% of the aPAD (see Table 4.2.1). The exposure for food plus lower bound drinking water estimates was 0.000737 mg/kg/day, which utilized 37% of the aPAD at the 95th percentile. The exposure for food and upper bound drinking water estimates was 0.001518 mg/kg/day, which utilized 76% of the aPAD at the 95th percentile (see Table 4.2.2).

Table 4.2.1. Results of Acute Dietary Exposure Analysis for Prothioconazole Using DEEM FCID at the 95th Percentile – *Food Only*

Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	% aPAD
Females 13-49 years old	0.002	0.000167	8.4

Table 4.2.2. Results of Acute Dietary Exposure Analysis for Prothioconazole Using DEEM FCID at the 95th Percentile – *Food and Water* (Peanut EDWC value)					
Population Subgroup	**aPAD (mg/kg/day)**	**LOWER BOUND**		**UPPER BOUND**	
		Exposure (mg/kg/day)	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**
Females 13-49 years old	0.002	0.000737	37	0.001518	76

4.2.2 Chronic Dietary Exposure/Risk

A moderately refined chronic dietary exposure assessment was also performed. Empirical processing factors, average residues, and livestock maximum residues were incorporated into the chronic assessment; 100% crop treated was also assumed. Dietary risk estimates were determined considering exposures from food alone and food plus upper or lower bound drinking water EDWC point estimates based on the sugar beet application scenario. The dietary exposure analyses result in chronic dietary risk estimates that are below the Agency's level of concern for food alone and food plus drinking water. The highest exposure and risk estimates were for all infants and children 1-2 years old. The food only exposure was 0.000338 mg/kg/day, which utilized 31% of the cPAD for children 1-2 years old (see Table 4.2.3). The highest exposure and risk estimates for food plus drinking water were for the all infants population subgroup. The exposure for food plus lower drinking water estimates was 0.000712 mg/kg/day, utilizing 65% of the cPAD. The exposure for food plus upper bound drinking water estimates was 0.001030 mg/kg/day, which utilized 94% of the cPAD (see Table 4.2.4).

Table 4.2.3. Results of Chronic Dietary Exposure Analysis for Prothioconazole Using DEEM FCID- *Food Only*			
Population Subgroup	**cPAD (mg/kg/day)**	**Refined Assessment**	
		Exposure (mg/kg/day)	**% cPAD**
General U.S. Population	0.0011	0.000105	9.5
All Infants (< 1 year old)	0.0011	0.000132	12
Children 1-2 years old	0.0011	**0.000338**	**31**
Children 3-5 years old	0.0011	0.000275	25
Children 6-12 years old	0.0011	0.000180	16
Youth 13-19 years old	0.0011	0.000095	8.7
Adults 20-49 years old	0.0011	0.000077	7.0
Adults 50+ years old	0.0011	0.000064	5.9
Females 13-49 years old	0.0011	0.000070	6.3

Table 4.2.4. Results of DEEM-FCID Chronic Dietary Exposure Analysis for Prothioconazole Using Lower and Upper Bound EDWC Values for Sugar Beets– *Food and Water*					
Population Subgroup	**cPAD (mg/kg/day)**	**LOWER BOUND**		**UPPER BOUND**	
		Exposure (mg/kg/day)	**% cPAD**	**Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	0.0011	0.000282	26	0.000379	34
All Infants (< 1 year old)	0.0011	**0.000712**	**65**	**0.001030**	**94**
Children 1-2 years old	0.0011	0.000601	55	0.000745	68
Children 3-5 years old	0.0011	0.000521	47	0.000656	60
Children 6-12 years old	0.0011	0.000350	32	0.000443	40
Youth 13-19 years old	0.0011	0.000223	20	0.000294	27
Adults 20-49 years old	0.0011	0.000242	22	0.000333	30
Adults 50+ years old	0.0011	0.000238	22	0.000334	30
Females 13-49 years old	0.0011	0.000234	21	0.000325	30

4.2.3 Cancer Dietary Risk

The available toxicology studies in the mouse and rat showed no increase in tumor incidence, and therefore HED concluded that prothioconazole or its metabolites are not carcinogenic, and classified "Not Likely to be Carcinogenic to Humans" according to the 2005 Cancer Guidelines. Therefore, a dietary cancer assessment was not performed.

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential exposures are not expected, since there are no proposed residential uses.

6.0 Aggregate Risk Assessments and Risk Characterization

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

Based on the proposed and existing Section 3 food crop uses, dietary aggregate exposures (i.e. food plus drinking water) are anticipated. No residential uses are proposed, and therefore, no residential exposures are anticipated. Consequently, only dietary (food plus drinking water) exposures were aggregated for this assessment. Estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate acute and chronic risk. **Refer to section 4.2 for these risk estimates.**

7.0 Cumulative Risk Characterization/Assessment

Prothioconazole 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 prothioconazole, 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.

8.0 Occupational Exposure/Risk Pathway

Prothioconazole: Occupational Exposure and Risk Assessment for Proposed Uses on Soybeans and Sugar Beets and revised postapplicationassessment for: Barley, Oilseed (except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (except Soybean) Subgroup, Peanut, and Wheat. PC Code: 113961, DP Barcode: D331662, S. Winfield, 12/31/07.

Occupational exposure to prothioconazole is expected from registered uses on barley, oilseed crops, dried bean and pea crops, peanuts and wheat; as well as proposed uses on soybeans and sugar beets. Short- and intermediate-term dermal and inhalation exposures are expected from handler activities, and short- and intermediate-term dermal exposures are expected from postapplication activities.

As discussed previously in the hazard section, the short- and intermediate-term dermal exposure scenarios are assessed using the NOAEL from the dermal developmental toxicity study in the rat (30 mg/kg/day, based on an increased incidence of supernumerary rib at the LOAEL of 100 mg/kg/day); and the short- and intermediate-term inhalation exposure scenarios are assessed using the NOAEL from the developmental toxicity study in the rabbit (2 mg/kg/day, based on arthrogryposis and multiple malformations, at the LOAEL of 10 mg/kg/day). A dermal absorption factor was not applied because the study the endpoint was selected from was route specific. A default inhalation absorption factor of 100% was applied to the inhalation exposure estimates because the study the endpoint was selected from was not route specific (*i.e.*, it was an oral study). Also, a body weight of 60 kg was used in the exposure estimates, because the endpoints were developmental effects (and therefore a female-specific body weight is appropriate).

Although the inhalation and dermal exposure scenarios employ different quantitative hazard estimates from different studies for risk calculations – the endpoint/hazard that the quantitative hazard estimates represent is the same. Therefore, the respective risk estimates are combined via the total MOE approach, resulting in a total MOE that reflects risk resulting from exposure via the inhalation and dermal routes, for both short- and intermediate-term exposure durations. As described previously, the LOC is an MOE of less than 1000.

8.1 Short-/Intermediate-Term Handler Risk

Handlers are assumed to have potential short- (1-30 consecutive days) and intermediate-term (1-6 consecutive months) dermal and inhalation exposure to prothioconazole when mixing, loading and applying prothioconazole formulations.

Although prothioconazole-specific handler exposure data were submitted in support of a previous action (D303579, 8/18/06), these data are not used quantitatively in this assessment because of the small scale of the study, the choice of activity combinations, and the use of Bayer employees as study subjects. It is the policy of HED to use data from PHED Version 1.1 as presented in the PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not more-applicable, nor more scenario-specific (HED Science Advisory Council for Exposure [ExpoSAC] Policy .007, "Use of Values from PHED Surrogate Table and Chemical-Specific Data" HED, OPP, 1/28/99). Additionally, typical HED standard values were used for the amount treated per day (ExpoSAC Policy # 9, 7/5/00).

The daily doses presented in this assessment are characterized as mid- to high-end exposure estimates because both upper-percentile and average values were used in the calculations: the unit exposure values from PHED are considered to be central tendency; the areas treated per day values are considered typical-to-high-end; the application rates and other treatment variables used in this assessment are upper-percentile values; and the inhalation absorption factor and body weight values are considered protective. In addition, rather than estimate exposure to prothioconazole and prothioconazole-desthio separately (and then estimate separate risks), the risk assessment team estimated exposure based on prothioconazole assuming no conversion (resulting in protective exposure estimates), and compared these estimates to quantitative hazard estimates from the prothioconazole-desthio toxicology database (protective quantitative hazard estimates, because prothioconazole-desthio is generally considered more toxic than prothioconazole). This approach results in a protective risk assessment.

Prothioconazole is applied aerially and by ground equipment. The following handler scenarios were considered representative of potential exposures expected from use on the proposed crops: mixing and loading for aerial and groundboom equipment; and application with aerial and groundboom equipment; as well as flagging for aerial applications. The following levels of PPE and engineering controls were necessary to reach the LOC for each scenario (except for M/L for aerial application to sugar beets, which did not reach the LOC with engineering controls).

- Mixing and Loading (M/L) for:
  - Aerial: with the engineering controls and PPE of a closed loading system and gloves, the soybean and sugar beet (at the minimum rate of 0.13 lb ai/A on the PROLINE label) scenarios reached the LOC of an MOE of 1000, but the sugar beet scenario (at the maximum rate of 0.18 lb ai/A on the PROLINE label) did not (MOE = 860)
  - Groundboom: with baseline clothing and the PPE gloves, all scenarios reached the LOC of an MOE of 1000

- Application with:
  - Aerial Equipment (closed cockpit): with baseline clothing (and no gloves), all scenarios reached the LOC of an MOE of 1000
  - Groundboom Equipment: with baseline clothing (and no gloves), all scenarios reached the LOC of an MOE of 1000

- Flagging for aerial applications: with baseline clothing (and no gloves), all scenarios reach the LOC of an MOE of 1000

Although the mixing and loading for aerial application to sugar beets at the maximum proposed application rate does not result in an exposure estimate 1000X less than the quantitative hazard estimate (even with engineering controls) this estimate does involve potential overestimation of exposure. As mentioned above, prothioconazole exposure estimates are compared to prothioconazole-desthio endpoints, resulting in a highly protective risk assessment. Had risk from prothioconazole and prothioconazole-desthio been estimated in separate assessments, lower prothioconazole-desthio exposure estimates would have yielded a greater margin of exposure. Therefore, an MOE of 860 at the maximum proposed label rate may not indicate a risk of concern.

Table 8.1 summarizes the handler exposure estimates and risk resulting from the proposed uses of prothioconazole.

Table 8.1. Short- and Intermediate-Term Occupational Exposure and Risk Estimates for Prothioconazole.

Exposure Scenario[1]	Application Rate (lb ai/acre)	Crop	Exposure Route	Acres Treated per Day[2]	PHED Unit Exposure[3] (mg/lb ai)	Daily Dose[4] (mg/kg/day)	Route-specific Short-/Inter Term MOE	Total Short-/Inter Term MOE[5, 6]
Closed M/L Liquids, for Aerial	0.178 (max rate on PROLINE label)	Sugar beet	Dermal	1200	0.0086	0.031	980	860
			Inhalation		0.000083	0.00030	6800	
PPE/Engineering control = Closed system + gloves	0.13 (min rate on PROLINE label)	Sugar beet	Dermal	1200	0.0086	0.022	1300	1100
			Inhalation		0.000083	0.00030	6800	
	0.0938	Soybean	Dermal	1200	0.0086	0.016	1900	1600
			Inhalation		0.000083	0.00016	13000	
Open M/L Liquids, for Groundboom	0.178	Sugar beet	Dermal	200	0.023	0.014	2200	1200
			Inhalation		0.0012	0.00071	2800	
PPE = single layer + gloves	0.0938	Soybean	Dermal	200	0.023	0.0072	4200	2300
			Inhalation		0.0012	0.00038	5300	
Applying Liquid, with Aerial (enclosed cockpit)	0.178	Sugar beet	Dermal	1200	0.005	0.018	1700	1400
			Inhalation		0.000068	0.00024	8300	
Baseline (no PPE, *i.e.*, single layer, no gloves)	0.0938	Soybean	Dermal		0.005	0.0094	3200	2700
			Inhalation	1200	0.000068	0.00013	16000	
Applying Liquid, with Groundboom (open cab)	0.178	Sugar beet	Dermal	200	0.014	0.0083	3600	2000
			Inhalation		0.00074	0.00044	4600	
Baseline (no PPE, *i.e.*, single layer, no gloves)	0.0938	Soybean	Dermal	200	0.014	0.0044	6900	3800
			Inhalation		0.00074	0.00023	8600	
Flagging for Aerial Operations	0.178	Sugar beet	Dermal	350	0.011	0.011	2600	1800
			Inhalation		0.00035	0.00036	5500	
Baseline (no PPE, *i.e.*, single layer, no gloves)	0.0938	Soybean	Dermal	350	0.011	0.0060	5000	3400
			Inhalation		0.00035	0.00019	10000	

[1] All estimates are at different mitigation levels (either the lowest at which the LOC is reached, or the highest available if the LOC is not reached) listed below each scenario description.
[2] Acres Treated Per Day from ExpoSAC Policy # 9, 7/5/00
[3] Unit exposure values are given for PPE/Engineering controls listed under Exposure Scenario (column 1) and taken from PHED Version 1.1 as presented in the PHED Surrogate Exposure Guide (8/98);
[4] Daily Dose = [Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure (mg/lb ai handled) x Absorption Factor]/Body Weight. A dermal absorption factor is not applied, since the endpoint chosen is from a dermal toxicity study. An inhalation absorption factor of 100% was used for inhalation risk, since the endpoint chosen is from an oral toxicity study. A body weight of 60 kg used for all calculations because the endpoints are gender-specific. Short-/Intermediate-term Dermal NOAEL=30 mg/kg/day; LOC = 1000. Short-/Intermediate-term Inhalation LOAEL=2.0 mg/kg/day. LOC = 1000
[5] Total MOE = 1/[(1/Dermal MOE) + (1/Inhalation MOE)] (Risk are combined via the total MOE approach because although the endpoints are selected from different studies and conducted with different species, the adverse effects are similar, and therefore merit combination)
[6] Sugar beets: The Total MOE for single layer, gloves M/L for aerial is 200 without a respirator and 230 with a respirator; the Total MOE for double layer, gloves for M/L for aerial is 240 without a respirator and 270 with a respirator. Soybeans: The Total MOE for single layer, gloves M/L for aerial is 390 without a respirator and 430 with a respirator; the Total MOE for double layer, gloves for M/L for aerial is 460 without a respirator and 510 with a respirator

8.2 Short-/Intermediate-Term Postapplication Risk

Postapplication workers are assumed to have potential short- and intermediate-term dermal exposure (but not inhalation exposure; prothioconazole has a low vapor pressure; therefore, after application, although residues are expected to persist on foliage, these residues are not expected to volatilize) from the registered and proposed uses of prothioconazole. All of the registered and proposed uses are for low to medium height row crops and because of this shared feature, the postapplication exposures expected for different crops are similar when similar postapplication activities are conducted. Postapplication activities expected from the proposed uses are scouting, irrigation, and hand weeding and thinning.

Chemical-specific data relevant to postapplication exposure (*i.e.*, dislodgeable foliar residue [DFR] data) were submitted and determined to be acceptable; therefore, postapplication exposure estimates were calculated using results from the DFR studies, as well as standard HED Exposure SAC assumptions (body weight and exposure duration) and transfer coefficients (SOP # 003.1). The quantitative hazard estimate of 30 mg/kg/day (NOAEL from the dermal developmental study in the rat), as used in the handler assessment (see previous section), is used in the postapplication assessment.

Summary of DFR study* (*MRID 470026-01, DP Barcode: D335477)
Bayer CropScience submitted to the U.S. EPA the study: *JAU 6476 480 SC – Dislodgeable Foliar Residue on Various Crops* in support of the registrations for the fungicide prothioconazole and the prothioconazole formulation PROLINE 480 SC (soluble concentrate). The study objectives were to determine the dissipation of dislodgeable foliar residues (DFR) of prothioconazole and its degradation product, prothioconazole-desthio on the following crops:

- **dry beans** (in Oregon and Washington; applied Proline 480 SC with ground-based boom spray equipment, application rate ~0.18 lb ai/A, 3 times at 10 day application intervals);
- **soybeans** (Nebraska and Minnesota; applied Proline 480 SC with hand boom and field sprayers, application rate ~0.13 lb ai/A, 3 times at 9-10 day application intervals);
- **sugar beets** (Minnesota; applied 480 SC with ground-based spray equipment, application rate 0.18 lb ai/A, 3 times at 9 day application intervals); and
- **peanuts** (in Florida and Georgia; applied Proline 480 SC with ground-based and hand-held spray equipment, application rate ~ 0.18 lb ai/A, 4 times at 14 day application intervals).

The locations, formulation, application rates, number of applications and equipment all reflect scenarios expected based on the crops and usage information provided on the labels (although the labels contain different percentages of prothioconazole, they are all SC formulations and therefore applied as liquids). The study did depart from the label in regards to application intervals for dry beans (the minimum application interval on the label is 5 days, whereas the study employed an application interval of 10 days). Additionally, the study only tested 1 to 2 sites per/crop. However, results from this study indicate prothioconazole and prothioconazole-desthio dissipate quickly, and therefore, this is not a limitation of the study. The study indicated prothioconazole and prothioconazole-desthio do not persist as dislodgeable foliar residues above the LOQ (0.05 µg/cm^2) for more than 3 days after the last treatment. Below the LOQ (but above the LOD; *i.e.*, at low levels), prothioconazole and prothioconazole-desthio persist as dislodgeable residues on foliage for a bit longer, ranging from 3-10 days after treatment. Regression lines were plotted using the natural logarithm (ln) of the residue values versus the days after the final application. HED-calculated R^2 values ranged from 0.86 to 0.93, and half-lives ranged from 0.49 to 1.8 days for total-prothiconazole

(*i.e.*, combined residues of prothiconazole and prothioconazole-desthio converted to prothioconazole-equivalents). Requirements for this type of study are specified by the U.S. EPA OPPT Series 875, Occupational and Residential Exposure Test Guidelines, Group B: Dislodgeable Foliar Residue Dissipation: Agricultural, Guideline 875.2100. The study was reviewed by Versar and by the U.S. EPA.

In the absence of chemical-specific DFR data, HED assumes a default dissipation rate of 10% per day, and that a default fraction of the applied ai is available on the foliage on the day of application (*i.e.*, 20%) when calculating DFR estimates (which in turn are used in postapplication exposure estimates, see footnotes of Table 8.3). However, the chemical-specific DFR data demonstrated that total prothioconazole (prothioconazole and prothioconazole-desthio combined) dissipate more quickly than 10% per day, and that the fraction of applied ai available on the foliage as a percent of the application rate, can be 2-fold lower than 20%. These DFR data were used to calculate 'fraction of ai applied' and 'dissipation rate' estimates (for use in postapplication exposure estimates) for the crops tested, and were extrapolated to those crops for which no DFR data are available.

In order to estimate DFRs for the crops prothioconazole is registered/proposed for use on, an average percent initial DFR value was calculated from the DFR studies conducted on each crop. Additionally, an average daily dissipation rate was estimated for each of the crops tested (see Table 8.2). Although uncertainties are introduced into the assessment when crop-specific residues are used to estimate dissipation parameters, it is believed to be more realistic than using default assumptions.

See Table 8.2 for a summary of these values calculated from the DFR study.

Table 8.2: Results of DFR Study analysis

Crop	Location (state)	R^2	Measured initial DFR (% of appl. rate)		Dissipation (% per day)		Half life (days)	Maximum total-prothioconazole (ug/cm^2) [1]
dry beans	Oregon	0.87	22.2	**Avg: 23.3**	45.1	**Avg: 48.4**	1.2	0.442 0DAT3
	Washington	0.93	24.5		51.7		1.0	0.631 0DAT2
soybeans	Nebraska	0.89	2.6	**Avg: 8.2**	**46.8**	NA	1.1	0.111 0DAT1
	Minnesota	0.86	13.7		75.8		0.49	0.294 0DAT3
sugar beets	Minnesota	0.90	**16.7**	NA[3]	**43.7**	NA	1.2	0.372 0DAT2
peanuts	Florida	0.93	8.8	**Avg: 8.8**	32.3	**Avg: 32.9**	1.8	0.215 0DAT1
	Georgia	0.92	8.9		33.5		1.7	0.248 0DAT3
Average[2]			**14%**		**42%**			

[1] XDATY, where X indicates the number of days after treatment, and Y indicates which treatment the residue was detected after (1-4)

[2]The MN soybean dissipation result was not considered when averaging daily dissipation across crops and when averaging for soybeans only, because there was a rainfall event within 24 hours of the last treatment.

[3] NA, not applicable

The resulting DFRs, exposure estimates and risks are presented below in Table 8.3. For some activities and crops, the REIs of 12 and 24 hours on the proposed labels are not adequate to reach an MOE of 1000. To protect workers conducting all postapplication activities, an REI of 48 hours (2 days) is required (based on scouting barley, canola; and irrigating and scouting beans/peas and sugar beets). [Note: hand harvesting was not evaluated because this practice is

being replaced by mechanical harvesting; the label must indicate that hand harvesting is not permitted].

The estimated REIs were determined using average values calculated from the DFR study.

Table 8.3. Summary of Occupational Postapplication Risks for Prothioconazole.								
Crop	**Appl. Rate (lb ai/A)**	**Fraction of ai Retained on Foliage[1]**	**Daily Dissipation Rate[1]**	**Transfer Coefficient (cm^2/hr)[2]**	**Dislodgeable Foliar Residue (ug/cm2)[3]**	**Time After Application (days)**	**Dermal Daily Dose[4] (mg/kg/day)**	**Short-/Inter-Term Dermal MOE[5]**
Barley, Canola (representative oilseed crops)	0.178	0.23[6]	0.48[6]	Low/min: scouting (100)	0.465	0	0.0062	4800
				High or low/full: scouting (1,500)	0.465	0	0.0930	320
					0.240	1	0.0480	630
					0.13	2	0.0248	1200
Dried shelled peas and beans subgroup	0.178	0.23	0.48	Low/min: irrigation and scouting, Low/full or min: hand weeding (100)	0.465	0	0.0062	4800
				Low/full: irrigation and scouting (1,500)	0.465	0	0.0930	320
					0.240	1	0.0480	630
					0.13	2	0.0248	1200
Peanuts	0.178	0.088	0.33	Hand weeding (100)	0.178	0	0.0024	13000
				Low/full: irrigation and scouting (1500)	0.178	0	0.036	840
					0.119	1	0.024	1300
Soybeans	0.0938	0.082	0.47	Hand weeding, Low/full: scouting (100)	0.086	0	0.0012	26000
				Low/full: irrigation and scouting (1500)	0.086	0	0.0173	1700
Sugar beets	0.178	0.17	0.44	Thinning, Hand weeding, Low/full and min: irrigation (100)	0.343	0	0.0046	6600
				Low/full: irrigation and scouting (1500)	0.343	0	0.0686	440
					0.192	1	0.0384	780
					0.108	2	0.0215	1400
Wheat	0.178	0.17[6]	0.44[6]	Low/min: irrigation and scouting (100)	0.343	0	0.0046	6600
				Low/full: irrigation and scouting (1,500)	0.343	0	0.0686	440
					0.192	1	0.0384	780
					0.108	2	0.0215	1400

[1] Prothioconazole-specific data (MRID 47002801). See Table 5.2a

[2] Transfer coefficients are taken from the HED Science Advisory Council (SAC) for Exposure SOP 003.1 (August 2000)

[3] Dislodgeable Foliar Residue $_{\text{Postapplication day}}$ (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage x (1- Fraction of Residue that Dissipates Daily) $^{\text{postapplication day zero}}$ x 4.54E+8 ug/lb x 2.47E-8 A/cm^2

[4] Daily Dose = [Dislodgeable Foliar Residue x 0.001 mg/ug x Dermal Transfer Coefficient (cm^2/hr) x Exposure Time (8 hours)]/Body weight (60 kg)

[5] MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 30 mg/kg/day. LOC = 1000.

[6] Dry bean data are used as surrogate for barley, canola and oilseed crops; and sugar beet data are used as surrogate for wheat crops.

9.0 Data Needs and Label Recommendations

9.1 Toxicology

The developmental neurotoxicity (DNT) study of prothioconazole-desthio (MRID 46246418) is classified as an acceptable/non-guideline study, because of inadequate data reporting which prevented the identification of the developmental NOAEL. Specifically, an increase in lesions of the peripheral nerves was noted at the high-dose, but mid- and low-dose groups were not evaluated. Changes in brain morphometric measurements were also seen at the high-dose, but mid- and low-dose groups were not evaluated.

- For the Developmental Neurotoxicity Study (MRID 46246418), brain morphometric measurements from the mid and low dose animals must be submitted as well as addressing the other deficiencies listed in the DER to allow the reconsideration of the FQPA database uncertainty factor.

9.2 Residue Chemistry

860.1200 Directions for Use

- A revised Section B is required to specify a preharvest interval of 7 days for soybean forage and hay.

860.1340 Residue Analytical Methods

- Revisions are suggested of the enforcement methods, LC/MS/MS Method RPA JA/03/01 for plants and LC/MS/MS Method Bayer Report No. 200537 for ruminants, to include at least two multiple reaction monitoring (MRM) transitions to preclude the need for a confirmatory method.

- The proposed data collection and enforcement methods for livestock commodities must be validated for poultry commodities.

860.1380 Storage Stability

- The final report of the ongoing storage stability study with prothioconazole and desthio-prothioconazole in plant commodities (interim results for which were reported in MRID 46477701) must be submitted as confirmatory data.

- To support the reported results for 1,2,4-triazole and the triazole conjugates, the final report of the ongoing storage stability study with triazole and triazole conjugates in plant commodities (interim results of which were reported in MRID 46246211) must be submitted.

860.1480 Meat, Milk, Poultry, and Eggs

- The petitioner must submit a poultry feeding study with prothioconazole.

860.1550 Proposed Tolerances

- The petitioner is required to submit a revised Section F to incorporate the CAS name of prothioconazole-desthio in the tolerance expression and to specify that residues of the metabolite are calculated as parent. In addition, the revised Section F should reflect the recommended tolerances and commodity definitions presented in Table 11.

860.1650 Submittal of Analytical Reference Standards

- Based on the proposed tolerance expressions and the proposed enforcement methods, analytical reference standards of the following compounds must be supplied and supplies replenished as requested by the Repository:
  - desthio prothioconazole [JAU6476-desthio; (2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol)]
  - prothioconazole sulfonic acid potassium salt [potassium salt of JAU6476 sulfonic acid; 1-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]1*H*-1,2,4-triazole sulfonic acid, potassium salt]
  - [triazole-^{15}N-^{13}C]prothioconazole
  - [triazole-^{15}N-^{13}C]JAU6476-desthio
  - [triazole-^{15}N-^{13}C]JAU6476 sulfonic acid

The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address (Note that the mail will be returned if the extended zip code is not used.) :

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

9.3 Occupational Exposure

875.1100 Dermal Exposure and 875.1300 Inhalation Exposure

- **PREVIOUS:** Raw data from field fortifications in MRID 46246447 (in addition to the % conversions reported in the study)

875.2100 Foliar Dislodgeable Residue Dissipation

- The registrant indicated prothioconazole-desthio residue measurements were converted to

prothioconazole-equivalents, however, they did not specify the method employed to correct the values. HED has assumed the same technique was used in this study, as was used in the applicator study (submitted with a previous petition). That is, to account for prothioconazole-desthio's lower molecular weight, prothioconazole-desthio was converted to "prothioconazole-equivalents" by applying a molar ratio of the two compounds. HED recommends that RD seek confirmation from Bayer CropScience that this is indeed the approach used in the DFR study (MRID 470026-01).

Label Recommendations

- **PREVIOUS:** State on the label that sunflower and safflower are excluded from the oilseed crop group

- USF 0728 325 SC Fungicide, on page 4 of the proposed label, remove the language describing use directions for chemigation. The label states "apply USF 0728 325 SC through irrigation equipment only to crops for which chemigation is specified on this label." There is one crop on the label (sugar beets), and chemigation is not specified in the use directions (whereas aerial and ground application methods are specified).

- USF 0728 325 SC Fungicide should specify a 30-day plant-back interval for crops not on the label.

- USF 0728 325 SC Fungicide specifies a 10- to 14-day spray interval for soilborne diseases for sugar beets, but the overall restrictions specify a 14- to 30-day spray interval. The spray interval for soilborne diseases should reflect the overall spray interval of 14- to 30 days.

- Change the REI to 48 hours on all labels.

- Remove all references to rice on the Proline 480 SC label.

- Indicate on the labels, that hand-harvesting is prohibited.

9.4 Triazole Data Requirements

As specified in HED's February 7, 2006 risk assessment (M. Doherty *et al*, DP# 322215) for 1,2,4-triazole and its metabolites triazole alanine and triazole acetic acid, HED recommended that resolution of various issues be a condition of registration for new uses of triazole-derivative fungicides and for new active ingredients which contain the 1,2,4-triazole ring. The requirement for a chronic toxicity/oncogenicity study in male rats and female mice in the 2/7/2006 memo was later modified by HED to a 1-year chronic study in male and female rats (Kit Farwell, DP# 321328, 5/10/2006). Therefore, HED recommends that the registration of the proposed new uses of prothioconazole be conditioned upon resolution of the following issues:

- Chemistry:
  - Final two-year storage stability study with 1,2,4-triazole.

- Toxicology:
  - Free triazole:
    - Developmental neurotoxicity study in rats;
    - Chronic toxicity – 1 year chronic rat study in males and females.
  - Triazole alanine:
    - Developmental toxicity study in rabbits;
    - Chronic toxicity study in rats, conducted according to current guidelines that include neurobehavioral assessments, with additional neuropathology evaluations conducted according to the neurotoxicity guidelines;
  - Triazole acetic acid:
    - Developmental toxicity study in rabbits;
    - Combined 90-day feeding/neurotoxicity study in rats.

References:

1. Prothioconazole. Petition for Establishment of Tolerances for Use on Barley, Oilseed (Except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (Except Soybean) Crop Subgroup, Peanut, Rice, and Wheat. Summary of Analytical Chemistry and Residue Data. PP#4F6830. DP Barcode 303508; S. Funk, 8/21/06.

2. Prothioconazole. Petitions for Establishment of Tolerances for Use on Sugar Beet (PP#6F7134) and Soybean (PP#6F7073). Summary of Analytical Chemistry and Residue Data. DP331663, S. Funk, 12/19/07.

3. Prothioconazole: Acute and Chronic Aggregate Dietary and Drinking Water Exposure and Risk Assessments for the Section 3 Registration Actions on Sugar Beets (PP# 6F7134) and Soybeans (PP# 6F7073). DP Barcode 345924, T. Goodlow, 11/19/07.

4. Drinking Water Assessment for the Section 3 New Use Petitions for the Use of Prothioconazole on Soybeans and Sugar Beets. DP#'s 341457 & 341458, C. Sutton, 10/10/07.

5. Prothioconazole Section 3: Environmental Fate and Ecological Risk Assessment, DP Barcode: 324660, Decision #: 341716, C. Salice and R. Kashuba, 06/01/06.

6. Prothioconazole: Occupational Exposure and Risk Assessment for Proposed Uses on Soybeans and Sugar Beets and revised postapplicationassessment for: Barley, Oilseed (except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (except Soybean) Subgroup, Peanut, and Wheat. PC Code: 113961, DP Barcode: D331662, S. Winfield, 12/31/07.

7. PP# 4F6830. New Chemical – Prothioconazole in/on Plant and Livestock Commodities. Tolerance Method Validation (TMV) Report (MRID #'s 462462-04, 462462-06, 462462-07, and 462462-09) Chemical # 113961. Decision Number: 318440. ACB # B05-39. DP# 318440, 7/30/07, P. Schermerhorn.

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: [2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione	Common Name: Prothioconazole	X Proposed tolerance □ Reevaluated tolerance □ Other	Date: 8/2007

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: PP#s 6F7073 & 6F7134 DP#s: 331663 & 335154 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: L. Cheng/RAB3
	Residue definition: Prothioconazole, 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione and its desthio metabolite

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Soybean, forage	4.5
		Soybean, seed	0.15
		Soybean, hay	17
		Beet, sugar, roots	0.25

Limits for Canada	Limits for Mexico
□ No Limits X No Limits for the crops requested	X No Limits □ No Limits for the crops requested
Residue definition:	Residue definition:

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S. Funk, 10/03/2007

Appendix A: Toxicology Assessment

A. Toxicity Profiles

Table A.1. Acute Toxicity of Prothioconazole technical and Desthio-Prothioconazole technical

Guideline	Study	Species	Results	Tox. Category	MRID No.
Prothioconazole					
870.1100	Acute oral toxicity	Rat	LD_{50} >= 6200 mg/kg (M, F)	IV	46246230
870.1200	Acute dermal toxicity	Rat	LD_{50} >= 2000 mg/kg (M, F)	III	46246244
870.1300	Acute inhalation toxicity	Rat	LC_{50} >= 4.99 mg/L (M, F)	IV	46246246
870.2400	Primary eye irritation	Rabbit	Not an irritant	IV	46246249
870.2500	Primary skin irritation	Rabbit	Not an irritant	IV	46246302
870.2600	Dermal sensitization	Guinea Pig	Not a sensitizer	Negative	46246305
Desthio-prothioconazole					
870.1100	Acute oral toxicity	Rat	LD_{50} = 2806 mg/kg (M, F) (approximate)	III	46246231
870.1100	Acute oral toxicity	Mouse	LD_{50} = 2235 mg/kg (Males) LD_{50} = 3459 mg/kg (Females)	III	46246242
870.1200	Acute dermal toxicity	Rat	LD_{50} >= 5000 mg/kg (M,F)	IV	46246243
870.1300	Acute inhalation toxicity	Rat	LC_{50} >= 5.077 mg/L (M,F)	IV	46246247
870.2400	Primary eye irritation	Rabbit	Slight irritant (iritis, discharge)	III	46246250
870.2500	Primary skin irritation	Rabbit	Not an irritant	IV	46246250
870.2600	Dermal sensitization	Guinea Pig	Not a sensitizer	Negative	46246304

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-day oral toxicity rodents (rat)	46246311 (1999) 0, 20, 100, 500 mg/kg/day Acceptable/Guideline	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on increased water consumption (males and females), increased cholesterol (males and females), liver effects [increased liver weights (females), hepatocellular hypertrophy (males and females) and cytoplasmic change (males and females)] and kidney effects [decreased urinary volume (males and females), increased urine protein levels (males and females), and the increased incidence and severity of basophilic tubules of the renal cortex (males)].
870.3100 90-Day oral toxicity rodents (mouse)	46246427 (1999) 0, 25, 100, 400 mg/kg/day Acceptable/Guideline	NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on increased cholesterol levels and increased liver enzyme activity in females, increased liver weights in both sexes, and increased incidence of hepatocellular hypertrophy and cytoplasmic change in the liver of both sexes.
870.3100 28-Day oral toxicity rodents (rat)	46246429 (1998) 0, 10000 ppm in both neat or stabilized diet 0, 1000 mg/kg/day by gavage Acceptable/Nonguideline	No NOAEL or LOAEL were determined as this was a nonguideline study to compare routes of administration Observations included clinical signs of toxicity, changes in BW, BWG, FC; liver and kidney effects (wt, histopathology), clinical chemistry changes
870.3100 28-Day oral toxicity rodents (rat)	46246428 (1997) 0, 400, 2000, 10000 ppm 0, 18.6/18.8, 145.7/151.0, or 951.7/1032.5 (M/F) mg/kg/day Acceptable/Nonguideline	No NOAEL or LOAEL were determined Observations included changes in body wt, food consumption, liver and kidney effects, clinical chemistry
870.3150 90-day oral toxicity nonrodents (dog)	46246435 (2000) 0, 25, 100, 300 mg/kg/day Acceptable/Nonguideline	No NOAEL or LOAEL were determined in this study, the specific observations included effects on liver and kidney enzyme activities and tissues concentrations of parent and metabolites were determined. This study included a 4 week recovery phase.
870.3150 90-day oral toxicity nonrodents (dog)	46426313 (2001) 0, 25, 100, 300 mg/kg/day Acceptable/Guideline	NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on kidney (histopathological) and thyroid (T4 and TSH) findings at 100 mg/kg. This study included a 4 week recovery phase.
870.3200 21/28-Day dermal toxicity (rat)	46426315 (2000) 0, 100, 300, 1000 mg/kg Acceptable/Guideline	NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a Prenatal develop-mental in rats – oral	46246316 (1996) 0, 80, 500, 1000 mg/kg/day Acceptable/Guideline	**Maternal Toxicity** NOAEL = 80 mg/kg/day LOAEL = 500 mg/kg/day based on increased urination and water consumption, and decreased body weight gain. **Developmental Toxicity** NOAEL = 80 mg/kg/day LOAEL = 500 mg/kg/day based on increased incidence of delayed ossification, increased incidence of dysplastic pubic bone, and increased incidence of left punctiform 14th rib.
870.3700a Prenatal develop-mental in rats – oral	46246317 (2002) 0, 40, 200, 1000 mg/kg/day Acceptable/Nonguideline	Range finding study for above, no endpoints were determined.
870.3700a Prenatal develop-mental in rodents (rat) - dermal	46246323 (2001) 0, Technical 1000 mg/kg/day, 62.5 mg/kg/day diluted EC 250 formulation, 250 mg/kg/day EC 250 formulation Acceptable/Nonguideline	**Maternal Toxicity** NOAEL > 1000 mg/kg/day LOAEL > 1000 mg/kg/day **Developmental Toxicity** NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day
870.3700a Prenatal develop-mental in rats – oral	46923601 (2004) 0, 20, 80, 750 mg/kg/day Acceptable/Nonguideline	**Maternal Toxicity** NOAEL = 80 mg/kg/day LOAEL = 750 mg/kg/day based on increased water consumption, decreased food consumption and decreased body weight gain. **Developmental Toxicity** NOAEL = 80 mg/kg/day LOAEL = 750 mg/kg/day based on increased incidence of rudimentary ribs (comma-shaped).
870.3700b Prenatal develop-mental in nonrodents (rabbit)	46246330 (1997) 0, 80, 100, 300, 480 mg/kg/day pilot study Acceptable/Nonguideline	**Maternal Toxicity** NOAEL < 80 mg/kg/day LOAEL = 80 mg/kg/day based on reduced food consumption and body wts. **Developmenta**l NOAEL = 300 mg/kg/day LOAEL = 480 mg/kg/day based on decreased body wt, and small fetuses.

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal develop-mental in nonrodents (rabbit)	46246328 (1998) 0, 10, 30, 80, 350* mg/kg/day * Additional group added after start of study Acceptable/Guideline	**Maternal Toxicity** NOAEL = 80 mg/kg/day LOAEL = 350 mg/kg/day based on decreased body wt and decreased food consumption. **Developmental Toxicity** NOAEL = 80 mg/kg/day LOAEL = 350 mg/kg/day based on abortions, total resorptions, and lower fetal body weight
870.3800 Reproduction and fertility effects	46246331 (1999) 0, 10, 100, 250, 500 mg/kg/day (pilot) Acceptable/Nonguideline	**Parental Toxicity** NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day based on clinical signs (urine stain) **Reproductive Toxicity** NOAEL = 500 mg/kg/day LOAEL > 500 mg/kg/day **Offspring Toxicity** NOAEL = 500 mg/kg/day LOAEL > 500 mg/kg/day
870.3800 Reproduction and fertility effects	46246334 (2001) 0, 10, 100, 750 mg/kg/day Combined with MRID 46246331 Acceptable/Guideline	**Parental Toxicity** NOAEL = 100 mg/kg/day LOAEL = 750 mg/kg/day based on decreased body weights, body weight gains and increased food consumption, increased liver weights and kidney weights, decreased thymus, testicular, prostate, epicauda and epididymis weights as well as histopathological findings in the liver and kidney. **Reproductive Toxicity** NOAEL = 100 mg/kg/day LOAEL = 750 mg/kg/day based on decreased number of estrous cycles in both generations and increased duration of estrous cycle in the P generation. **Offspring Toxicity** NOAEL = 100 mg/kg/day LOAEL = 750 mg/kg/day based on decreased pup body weight and spleen wt.
870.4100a Chronic toxicity rodents (rat)	46246335 (2000) 0, 5, 50, 750 mg/kg/day Rat, 53 weeks Acceptable/Guideline	NOAEL = 50 mg/kg/day LOAEL = 750 mg/kg/day based on decreased body weight and body weight gain, alterations in hematology and clinical chemistry parameters indicative of liver and kidney damage, increased liver and kidney weights, and accompanying histopathological alterations in the liver, kidney and urinary bladder. FOB conducted at 27 and 52 weeks.
870.4100b Chronic toxicity non-rodent (dog)	46246336 (2001) 0, 5, 40, 125 mg/kg/day one year Acceptable/Guideline	NOAEL = 5 mg/kg/day LOAEL = 40 mg/kg/day based on decreased T3 and T4 thyroid hormones, increased urine volume, and increased incidence of chronic inflammation and pigmentation in the kidneys of the male animals, and decreased T4 thyroid hormone, increased spleen weight, increased incidence of spleen pigmentation, and increased incidence of crystals present in the kidneys of the female animals.

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200 Carcinogenicity rats	46246338 (2001) M: 0, 5, 50, 750/500 mg/kg/day F: 0,5,50,750/625 mg/kg/day 106 weeks Unacceptable/Guideline for Carcinogenicity because dose levels too high.	NOAEL = 50 mg/kg/day LOAEL = 500/625 (M/F) mg/kg/day based **on increased mortality** and decreased body weight/body weight gain, changes in clinical chemistry (APh, creatinine, urea) and hematological parameters, increased liver and kidney weights, and liver (hypertrophy and eosinophilic/clear cell focus) and kidney/urinary bladder pathology.
870.4300 Carcinogenicity mice	46246339 (2001) 0, 10, 70, 500 mg/kg/day 80 weeks Acceptable/Guideline	NOAEL = 10 mg/kg/day LOAEL = 70 mg/kg/day based on kidney (tubular degeneration/regeneration in males) effects. **no evidence of carcinogenicity**
870.6200a Acute neurotoxicity screening battery	46246417 (2000) 0, 200, 750, 2000 mg/kg/day Acceptable/Guideline	NOAEL = 200/750 (M/F) mg/kg/day LOAEL = 750/2000 (M/F) based on the transient effect of reduced motor and locomotor activity.
870.6200b Subchronic neurotoxicity screening battery	46246416 (2001) 0, 100, 500, 1000 mg/kg/day Acceptable/Guideline	**Systemic Toxicity** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on decreased body weight & body weight gain in males. No neurotoxicity was noted at dose levels tested.
870.7600 Dermal Absorption	46246426 (1997) Rat N= 10 Pilot Study	Absorption rate 49.41%
870.7600 Dermal Absorption	46246423 (2003) Monkey N = 1 Pilot Study	Absorption rate 4.06%

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism	46246421 (2001) Aceptable/Guideline	JAU6476 was extensively metabolised in the rat following oral administration. Eighteen metabolites and the parent compound were identified in urine, faeces and bile. The biotransformation of JAU6476 consisted of 3 major reaction types including desulfuration, oxidative hydroxylation of the phenyl moiety and glucuronic acid conjugation. Identification of the metabolites ranged from 26-63% of the administered dose. A higher percentage of metabolite isolation and identification could not be achieved due to difficulties in fecal extraction where 21-33% of the administered dose remained in non-extractable residues in the solids. The parent compound JAU6476 was the most abundant in the faeces (1-22% of the administered dose), followed by the JAU6476-desthio metabolite (3-18% of the administered dose). All other fecal metabolites represented less than 8% of the administered dose. The 1, 2, 4-triazole metabolite was not detected in the faeces. The major urinary metabolite was JAU6476-S- or O-glucuronide (0.1-8% of the administered dose) and was preferentially excreted in females. The 1, 2, 4-triazole metabolite represented 0.8-2.3% of the administered dose following administration of single oral low and/or high doses. The remaining urinary metabolites each accounted for 0-1.4% of the administered dose. JAU6476-S- or O-glucuronide was the most abundant metabolite in the bile, representing approximately 46% of the administered dose. This metabolite was excreted in females only in the urine; however it was noted in the bile in males. Desthio glucuronic acid metabolites in the bile represented 8-10% of the administered dose. Parent compound represented 3-5% of the administered dose in the bile. The 1, 2, 4-triazole metabolite was not detected in the bile.
870.7485 Metabolism	46246419 (2001) Acceptable/Nonguideline	The whole body autoradiography results are in agreement with the absorption, distribution and excretion pattern of JAU6476 in the main metabolism study (MRID 46246421). In summary, peak concentrations in males were noted 1 hour post-administration and continued to decline until sacrifice at 168 hours. In females, absorption was slightly delayed with peak concentrations in some tissues noted at 8 hours post-administration. The highest concentrations were noted in liver (up to 1.78 µg/g in males and up to 0.97 µg/g in females), followed by kidney (renal medulla, up to 0.64 µg/g), brown/perirenal fat (up to 0.36 µg/g), thyroid (up to 0.23 µg/g) and adrenal gland (up to 0.27 µg/g). All other tissues showed peak concentrations of <0.13 µg/g. Concentrations of radioactivity decreased rapidly from 24 to 168 hours post-administration, indicative of continued elimination from the tissues.

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7800 Immunotoxicity	46246438 (2002) Acceptable/Nonguideline	Piloerection was noted in the high-dose males from days 13-21.There were no significant effects on body weight, food consumption or spleen weights. Under the conditions of this study, JAU 6476 did not suppress the humoral immune response in a dose-dependent manner in that it did not significantly decrease the IgM antibody-forming cell response to the T-dependent antigen (sheep erythrocytes). An increase in plaque-forming cells was noted in the high-dose males (↑125%).
870.5100 Bacterial reverse mutation test	46246343 (1996) Acceptable/Guideline	JAU 6476 is considered negative for reverse mutation in this battery of *S. typhimurium* strains up to cytotoxic concentrations.
870.5300 In vitro mammalian cell gene mutation test	46246404 (1996) Acceptable/Guideline	JAU 6476 is considered non-mutagenic in the V79-HGPRT forward mutation assay.
870.5375 In vitro mammalian chromosome aberration test	46246406 (1996) Acceptable/Guideline	JAU 6476 may be considered clastogenic (*i.e.*, induces increases in structural aberrations), but this mutagenic activation may result from secondary cytotoxicity rather than direct structural DNA damage.
870.5395 Mammalian erythrocyte micronucleus test	46246409 (1996) Acceptable/Guideline	The one i.p. dose of 250 mg/kg JAU 6476 (prothioconazole) is considered to be non-clastogenetic *in vivo*.
870.5395 Mammalian erythrocyte micronucleus test	46246411 (2003) Acceptable/Guideline	JAU 6476 (prothioconazole) is not clastogenic or aneugenic in male mice treated up to overtly toxic and cytotoxic doses.
870.5550 Unscheduled DNA synthesis in mammalian cells	46246412 (1998) Acceptable/Guideline	**JAU 6476 is evaluated as equivocal in this assay.** However, these results were clarified based on the negative findings in the *in vivo* UDS assay in rat hepatocytes from adult male rats exposed up to the 5000 mg/kg with the same Batch No. of the test materials. (MRID 46246413).
870.5550 Unscheduled DNA synthesis in mammalian cells	46246413 (1999) Acceptable/Guideline	**JAU 6476 (prothioconazole) is negative for UDS-induction in hepatocytes drawn from male rats administered single oral doses of 2500 and 5000 mg/kg**.

Table A.2: Toxicity Profile for Prothioconazole (JAU6476) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Special Study Inhibition of enzymes in liver microsomes	46246415 (1999) Unacceptable/ Nonguideline	Inhibition was found in microsomes of both rats and mice. The IC50 (Inhibitory Concentration) attained for its ECOD metabolism was 5 *u*M JAU 6476 in rat preparations, and 9 *u*M in mouse microsomes. The inhibition of testosterone hydroxylation in rat microsomes by JAU 6476 was much weaker, since both hydroxylation and oxidation reactions correlated with different cytochrome P450 subtypes had to occur, namely, 16alpha, 2alpha 6beta, and 7alpha hydroxylation; plus oxidation to androstendione. The inclusive IC50 of most of these P450 subtypes was approximately 75 to 100 *u*M; for 7alpha hydroxylation (= subtype 2 A1), the IC50 was about 1000 *u*M. **No conclusions can be reached from this study because of the numerous study deficiencies**
Special Study Interaction with Thyroid Peroxidase in vitro	46246436 (1996) Acceptable/Nonguideline	Thyroid peroxidase (TPO)-catalyzed guaiacol oxidation was inhibited by compounds tested. 3-mercapto-1,2,4-triazole had the lowest IC50 value (i.e.: lowest concentration required to inhibit the reaction by 50%), followed by PTU then JAU 6476 and JAU 6953. This provided initial indication that TPO may be irreversibly inhibited. PTU, ETU, JAU 6476, JAU 6953 and 3-mercapto-1,2,4-triazole dose-dependently suppressed TPO-catalyzed iodine formation temporarily. Following suppression, iodine reappeared. The rate was then similar to controls. 3-mercapto-1,2,4-triazole suppressed the rate of the reappearing iodine formation longer than the other compounds. This study showed inhibition of guaiacol and iodine oxidation with the compounds tested.

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 4-Week oral toxicity rodents (rat)	46246430 (1992) 0, 100, 300, 1000 ppm 0, 11, 34/38, 117/ 121 (M/F) mg/kg/day Acceptable/Guideline	NOAEL = 11 mg/kg/day for males; < 11 mg/kg/day for females LOAEL = 34 mg/kg/day for males and ≤ 11 mg/kg/day for females based increased liver triglycerides and absolute and relative liver weights in males and on decreased relative and absolute ovary weight with histopathology
870.3100 90-Day oral toxicity rodents (rat)	46246309 (1999) 0, 30, 125, 500, 2000 ppm 2.2/3.0, 9.6/12.5, 36.9/50.7, 161.9/210.8 mg/kg/d M/F Acceptable/Guideline	NOAEL = 2.2/3.0 (M/F) mg/kg/day LOAEL = 9.6/12.5 mg/kg/day based on histological changes in the liver of males and increased P450 in females.
870.3100 90-Day oral toxicity rodents (mouse)	46246310 (1999) 0, 40, 200, 1000, 5000 ppm 0, 11.5/16.0, 58.9/79.5, 294.0/392.3, 1454/2073 (M/F) mg/kg/day Acceptable/Nonguideline	NOAEL < 11.5/16.0 (M/F) mg/kg/day LOAEL = 11.5.16.0 (M/F) mg/kg/day based on decreased body weight gain in both sexes.
870.3150 39-Day oral toxicity in nonrodents (dog)	46246431 (1999) 0, 10, 100/5000, 1000 ppm 0, 0.3, 3/150, 30 (M/F) mg/kg/day Acceptable/Nonguideline	Range finding study, no NOAEL or LOAEL were established, observations included dramatic reductions in uterine/oviduct absolute and relative organ weights at 10 ppm.
870.3150 90-Day oral toxicity in nonrodents (dog)	46246314 (2000) 0, 40, 200, 1000 ppm 0, 1.58/1.62, 7.81/8.53, 37.79/42.75 (M/F/) mg/kg/day Unacceptable/Guideline	NOAEL = 37.79/42.75 (M/F) mg/kg/day LOAEL > 37.79/42.75 (M/F) mg/kg/day
870.3465 90-Day inhalation toxicity (rat)	46246432 (1991) - Pilot 46246433 (1992) 0, 11.3, 46.8, 228.4 mg/m^3/day Unacceptable/Guideline	NOAEL = 228.4 mg/m^3/day LOAEL > 228.4 mg/m^3/day

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a Prenatal develop-mental in rodents (rat) - dermal	46246326 (1991) 0, 30 mg/kg/day Pilot study, used with 46246325 Acceptable/Nonguideline	**Discussed in appendix 1 of MRID 46246325** **Maternal Toxicity** NOAEL = 30 mg/kg/day LOAEL > 30 mg/kg/day **Developmental Toxicity** NOAEL = 30 mg/kg/day LOAEL > 30 mg/kg/day
870.3700a Prenatal develop-mental in rodents (rat) - dermal	46246325 (1991) 0, 100, 300, 1000 mg/kg/day Acceptable/Guideline When combined with 46246326	**Maternal Toxicity** NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day **Developmental Toxicity** NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day based on structural alterations (14^{th} rib)
870.3700a Prenatal develop-mental in rodents (rat) - oral	46246322 (1991) 0, 1, 3 mg/kg/day Acceptable/Nonguideline results combined with 46246321	**Maternal Toxicity** NOAEL = 3 mg/kg/day LOAEL > 3 mg/kg/day **Developmental Toxicity** NOAEL = 3 mg/kg/day LOAEL > 3 mg/kg/day Combined with 46246321
870.3700a Prenatal develop-mental in rodents (rat) - oral	46246321 (1991) 0, 10, 30, 100 mg/kg/day Acceptable/Guideline results combined with 46246322	**Maternal Toxicity** NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gains, increased liver weight with histopathology **Developmental Toxicity** NOAEL < 10 mg/kg/day LOAEL < 10 mg/kg/day based on structural alterations (supernumery ribs) and incomplete/delayed ossification at all levels. Combined with 46346322
870.3700a Prenatal develop-mental in rodents (rat) - oral	46246320 (1990) 0, 100 mg/kg/day Acceptable/Nonguideline	**Maternal Toxicity** NOAEL = 100 mg/kg/day LOAEL > 100 mg/kg/day **Developmental Toxicity** NOAEL <100 mg/kg/day LOAEL = 100 mg/kg/day based on developmental delays
870.3700a Prenatal develop-mental in rodents (rat) - oral	46246319 (1992) 0, 30 mg/kg/day oral Acceptable/Nonguideline	**Maternal Toxicity** No NOAEL or LOAEL were determined **Developmental Toxicity** No NOAEL or LOAEL were determined, observations included structural abnormalities, developmental delays, death, shows 14^{th} rib not completely reversible after birth. Follow up of MRID 46246320, 46246321.

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b Prenatal developmental in nonrodents (rabbit) - oral	46246327, (1991) 0, 2, 10, 50 mg/kg/day Acceptable/Guideline	**Maternal Toxicity** NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on decreased body wt gain, decrease food consumption, increased resorptions, decreased number of fetuses, liver histopathology. **Developmental Toxicity** NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on structural alterations including malformed vertebral body and ribs, arthrogryposis, and other multiple malformations.
870.3700b Prenatal developmental in nonrodents (rabbit) - dermal	46246329 (1991) 0, 100, 300, 1000 mg/kg/day dermal pilot study Acceptable/Nonguideline	**Maternal Toxicity** NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on local dermal toxicity **Developmental Toxicity** NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day
870.3800 Reproduction and fertility effects	46246332 (1992) 0, 0.52, 2.49, 53.0, 79.6 mg/kg/day (pilot) Acceptable/Nonguideline	**Parental Toxicity** NOAEL = 0.52 mg/kg/day LOAEL = 2.49 mg/kg/day based on incr. liver wt., liver discoloration **Reproductive Toxicity** NOAEL = 2.49 mg/kg/day LOAEL = 53.0 mg/kg/day based on decreased litter size, birth index, live birth index and viability index **Offspring Toxicity** NOAEL = 2.49 mg/kg/day LOAEL = 53.0 mg/kg/day based on increased liver discoloration (increased cleft palate at 79.6)
870.3800 Reproduction and fertility effects	46246333 (2001) 0, 40, 160, 640 ppm 0, 2.7/3.0, 10.4/12.0, 42.6/49.5 (M/F) mg/kg/day - premating 0, 2.5, 10.0, 41.2 mg/kg/day - gestation 0, 4.8, 18.6, 72.6 mg/kg/day - lactation Acceptable/Guideline	**Parental Toxicity** NOAEL = 10.4/12.0 (M/F) mg/kg/day LOAEL = 42.6/49.5 (M/F) mg/kg/day based on increased liver wt, liver histopathology, decreased food consumption during lactation (females only). **Reproductive Toxicity** NOAEL = 10.4/12.0 (M/F) mg/kg/day LOAEL = 42.6/49.5 (M/F) mg/kg/day based on increased incidence of dystocia, decreased viability and decreased pup body weight. **Offspring Toxicity** NOAEL = 10.4/12.0 mg/kg/day LOAEL = 42.6/49.5 (M/F) mg/kg/day based on decreased pup body weight and increased incidence of cleft palate, dilated renal pelvis, dilated ureters and dilated bladder.

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b Chronic toxicity dogs	46246337 (2001) 0, 40, 300, 2000 ppm 0, 1.35/1.55, 10.1/11.1, 69.9/77.1 (M/F) mg/kg/day 30 weeks Unacceptable/Guideline Not tested at high enough doses GLP deficiencies	NOAEL = 69.9/77.1 (M/F) mg/kg/day LOAEL > 69.9/77.1 (M/F) mg/kg/day
870.4200 Carcinogenicity rats	46246342 (1999) 0, 20, 140, 980 ppm 0, 1.1/1.6, 8.0/11.2, 57.6/77.4 (M/F) mg/kg/day Acceptable/Guideline	NOAEL = 1.1/1.6 (M/F) mg/kg/day LOAEL = 8.0/11.2 (M/F) mg/kg/day based on clinical chemistry, histopathology (liver). **no evidence of carcinogenicity**
870.4300 Carcinogenicity mice	46246340 (2000) 46246341 (2001) 0, 12.5, 50, 200 ppm 0, 3.1/5.1, 12.8/20.3, 51.7/80.0 (M/F) mg/kg/day 105 weeks Acceptable/Guideline	NOAEL =12.8/20.3 (M/F) mg/kg/day LOAEL = 51.7/80.0 (M/F) mg/kg/day based on decreased body weight gain in males, decreased triglyceride levels in both sexes, decreased cholesterol levels in males, changes in glucose levels in males, increased liver weights in both sexes, increased incidence of histopathological findings in the liver hepatocytes in both sexes, decreased blood urea levels in females, increased kidney weights in females, and increased incidence of eosinophilic droplets in the cortical tubules of the kidneys of females. **no evidence of carcinogenicity**
870.6300 Developmental neurotoxicity rats	46246418 (2004) 0, 40, 160, 500 ppm 0, 3.6, 15.1, 43.3 mg/kg/day during gestation 0, 8.1, 35.7, 104.6 during lactation Acceptable/Nonguideline	**Maternal Toxicity** NOAEL = 15.1 mg/kg/day LOAEL = 43.3 mg/kg/day based on dystocia **Developmental Toxicity** NOAEL = 3.6 mg/kg/day LOAEL = 15.1 mg/kg/day based on deviated snout and malocclusion **Offspring Neurotoxicity** potential could not be determined - Brain morphometric changes and increased incidence of peripheral nerve lesions were observed at high dose level, but not measured at mid- and low-dose levels.
870.7600 Dermal Absorption	46246425 (2003) Monkey N=5	Absorption rate: 18.61%
870.7600 Dermal Absorption	46246424 (2003) Monkey N=1 Pilot Study	Absorption rate 7.11%

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism -rat	46246422 (2001) 46246420 (2001) Pilot study and autoradiography Acceptable/Nonguideline	In whole-body autoradiography experiments, the quick onset of absorption of the test material was demonstrated. Absorption was not complete after one hour. The autoradiograms also showed that the blood concentration was less than the concentration present in the fatty tissues, demonstrating the lipophilic nature of SXX0665, and perhaps of its metabolites. The mucous membrane of the stomach walls were observed with radioactivity throughout the various observation periods, which was considered an indication of extrabiliary secretion of the absorbed radioactivity back into the stomach lumen. The muscle, heart, lung, brain, thyroid, and mineral portion of the bones showed minor concentrations of radioactivity. The testes had a radioactivity distribution pattern indicative of the blood circulation in the organ. Medium amounts of radioactivity were observed in some glandular organs, including the preputial gland and the adrenals. The gums were also observed with increased radioactivity, with unknown physiological significance. The distributions noted at one hour were fairly consistent for 48 hours, though declining due to excretion. The renal cortex contained radioactivity to a much greater extent than did the renal pelvis, indicating that the radioactivity was reabsorbed in the duodenum. As well, the radioactivity that is absorbed is likely not transformed into metabolites that are adequately polar to be eliminated by the kidney. This results in increased passage through the liver by the radioactive test material.
870.7485 Pregnant Metabolism Study (single and multiple oral and dermal low and high dose administration)-Rat	46246439 (2001) Acceptable/Nonguideline	The maximum concentrations (Cmax) were comparable between single and multiple oral administration of 1 mg/kg and 3 mg/kg and dermal application of 30 mg/kg, respectively. The maximum concentration varied after single and multiple dermal application of 100 mg/kg. The time to achieve maximum concentration was prolonged after dermal application compared with oral administration at all doses tested (single and multiple) but the delay was not dose-dependent. The longest terminal half-life was observed in the high dose single dermal application (100 mg/kg) which was 34.4 h. The lowest terminal half-life was observed in the low dose multiple dermal application group (30 mg/kg). The AUC values (representing an indirect measure for the fraction of SXX 0665 absorbed) increased only slightly after large increases in applied dose (both dermal and oral).
870.5100 Bacterial reverse mutation test	46246344 (1990) Acceptable/Guideline	At no concentration up to cytotoxic levels in either assay, however, were increases in revertants induced by SXX 0665, compared to concurrent negative controls, or compared to the laboratory's historical control data. Marked increases were induced in all positive controls.

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300 In vitro mammalian cell gene mutation	46246405 (1999)	SXX 0665 is considered non-mutagenic in the V79-HGPRT Forward Mutation Assay.
870.5375 In vitro mammalian chromosome aberration test	46246407 (1995) Acceptable/Guideline	SXX 0665 is considered to be non-clastogenic in CHO cells up to subcytotoxic concentrations.
870.5395 Mammalian erythrocyte micronucleus test	64246410 (1993) Acceptable/Guideline	SXX 0665 is not considered to be a clastogen or aneugen in mice at the i.p. administration of 350 mg/kg.
870.5550 Unscheduled DNA synthesis in mammalian cells	46246414 (1992) Acceptable/Guideline	There was no evidence that UDS, as determined by radioactive tracer procedures [nuclear silver grain counts], was induced.
Special Study Assessment of Ovarian Findings in Rodents	46246441 (2001) Acceptable/Non Guideline	Currently, the only study where the ovary findings influence the study LOAEL is MRID 46246430 (Krotlinger, 1992). Although there is evidence that the ovary effects seen in this study are coincidental, the reviewers for this submission have decided to consider this effect treatment related. A NOAEL for females was not achieved in this study; however, there is an adequate margin of safety to this LOAEL from the dose levels selected during risk assessment.

Table A.3: Toxicity Profile for Prothioconazole-Desthio (SXX0665) Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Special Study Liver Foci Study-Rat	46246437 (1991) Acceptable/Nonguideline	The incidences of foci of altered hepatocytes (FAH) were slightly increased in males and females administered the test substance (980 ppm) for 6 weeks (groups 1 and 7) compared to their controls (groups 2 and 8). The incidence of FAH was slightly decreased in males and females administered the test substance (980 ppm) for 12 weeks (groups 3 and 9) compared to their controls (groups 6 and 12). The incidences of FAH were higher in the control males compared to the females. Administration of the test substance to animals previously treated with an initiator (NNM) and a regenerative proliferation inducer (DGA) (groups 4 and 10) produced only slightly elevated (no statistical significance) incidences of FAH relative to those in the corresponding control groups (groups 5 and 11). Severe cytoplasmic vacuolation, particularly following the 12-week treatment, was found in the Zone II hepatocytes of nearly all males that had been exposed to the test substance and exhibited this increased activity (this correlation was absent in animal no. 19). These vacuoles appeared void to the eye in sections that had been treated with solvents. In native sections, these vacuoles were highly refractive. Isolated cellular destruction and mitosis of parenchyma1 cells were also observed in these animals." In males administered the test substance, there was an increase in the glucose-6 phosphate dehydrogenase activity in 3/5 animals compared to 0/5 controls after 6 weeks, and in 5/5 animals compared to 1/5 controls after 12 weeks. "This rise in activity was limited to the Rappaport Zone I hepatocytes." The enzyme induction in the periportal hepatocytes was stronger at 13 weeks in the males administered test substance without NNM and DGA than with. There were no clear patterns with the incidence or severity of enzyme induction findings in the females. "No evident hepatocytic vacuolation was observed in the females of any group. However, in animals that had been treated with the test substance, it was noted that the stored glycogen in perivenular cells was distributed very uniformly throughout the cytoplasm, whereas structures having the appearance of densely packed glycogen pools - often concentrated at the cellular periphery - were observed in the pertinent controls."

Table A.4: Toxicity Profile for Prothioconazole - Sulfonic Acid K Salt Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity rodents (rat)	46246312 (2001) 0, 30, 125, 500, 2000 ppm 0, 2.1/2.6, 8.7/9.7, 34.3/40.4, 135.9/163.0 (M/F) mg/kg/day Acceptable/Guideline	NOAEL = 34.3/40.4 (M/F) mg/kg/day LOAEL = 135.9/163.0 (M/F) mg/Kg/day based on microscopic findings in the ovary in females (cysts), and the urinary bladder (transitional cell hyperplasia) and testes (focal degeneration germinal epithelium) in males.
870.3700a Prenatal develop-mental in rodents (rat)	46246318 (2001) 0, 30, 100, 500, 1000 mg/kg/day Range finding study Acceptable/Nonguideline	**Discussed in review of MRID 46246234** **Maternal Toxicity** NOAEL = 500 mg/kg/day LOAEL = 1000 mg/kg/day based on decreased FC, BW, clinical signs and high mortality. **Developmental Toxicity** NOAEL = >1000 mg/kg/day LOAEL > 1000 mg/kg/day
870.3700a Prenatal develop-mental in rodents (rat)	46246324 (2001) 0, 30, 150, 750 mg/kg/day Acceptable/Guideline	**Maternal Toxicity** NOAEL = 150 mg/kg/day LOAEL = 750 mg/kg/day based on clinical signs, decreased food consumption, decreased body wt, mortality **Developmental Toxicity** NOAEL < 30 mg/kg/day LOAEL ≤ 30 mg/kg/day based on increased incidence of supernumerary one ribs.
870.5100 Bacterial reverse mutation test	46246402 (2000) Unacceptable/Guideline	No concentration in either assay did the test article significantly increased the number of revertants over negative control values. However, the spontaneous revertant counts of strain TA100 as well as the response to the S9-activated positive control were lower than expected.

Table A.5: Toxicity Profile for Prothioconazole - Des-chloro Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a Prenatal develop-mental in rodents (rat)	46246317 (2002) 0, 40, 200, 1000 mg/kg/day Acceptable/Nonguideline	**Maternal Toxicity** No NOAEL or LOAEL were established, observations included decreased food consumption, body weight, body weight gain **Developmental Toxicity** No NOAEL or LOAEL were established, observations included decreased fetal wt, increased developmental delays & structural abnormalities

Table A.5: Toxicity Profile for Prothioconazole - Des-chloro Technical		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100 Bacterial reverse mutation test	46246345 (2003) Acceptable/Guideline	No evidence of mutagenicity (increased revertants) was observed in either assay up to cytotoxic levels of the test substance. Therefore, 6476 Des-chloro is considered non-mutagenic in this bacterial test system.
870.5375 In vitro mammalian chromosome aberration test	46246408 (2003) Acceptable/Guideline	JAU 6476 Des-Chloro is considered non-clastogenic in this test system.

Table A.6 Supplemental: Toxicity Profile for other Prothioconazole metabolites		
870.5100 Bacterial reverse mutation test	46246346 (2002) JAU 6476-methyl Acceptable/Guideline	JAU 6476-methyl is considered nonmutagenic in this battery of *S. typhimurium* strains up to cytotoxic levels.
870.5100 Bacterial reverse mutation test	46246347 (2002) JAU 64760-asymmetric isomer Acceptable/Guideline	The asymmetric isomer of JAU 6476 is considered nonmutagenic in this battery of *S. typhimurium* cultures up to cytotoxic concentrations.
870.5100 Bacterial reverse mutation test	46246348 (2001) JAU 6476-asymmetric disulfide Acceptable/Guideline	JAU 6476-asymmetric disulfide does not induce reverse mutation in this bacterial test system up to cytotoxic concentrations.
870.5100 Bacterial reverse mutation test	46246349 (2000) JAU6476-alpha-hydroxy-desthio Acceptable/Guideline	The alpha-hydroxy-desthio derivative of JAU 6476 is considered non-mutagenic in this bacterial test system up to the cytotoxic/limit concentration.
870.5100 Bacterial reverse mutation test	46246350 (2000) JAU 6476-triazolinone Acceptable/Guideline	JAU 6476-triazolinone is considered nonmutagenic in this *S. typhimurium* test system.
870.5100 Bacterial reverse mutation test	46246401 (2000) JAU-6476-alpha-acetoxy-desthio Acceptable/Guideline	JAU 6476-alpha-acetoxy-desthio is considered non-mutagenic in this bacterial test system.

870.5100 Bacterial reverse mutation test	46246403 (2000) JAU-6476-benzylpropyldiol	JAU 6476-Benzylpropyldiol does not induce reverse mutation in this bacterial test system up to cytotoxic concentrations.