UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 08/21/2006

Subject: 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 Numbers:	D303508 & D314517	Decision Number:	341716 & 341717
PC Code:	113961	MRID Numbers:	46246139, 46246141-46246150, 46246201-46246211, 46246213-46246227, 46477701-46477704
40 CFR 180.		Chemical Class:	Fungicide

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This document was originally prepared under contract by Dynamac Corporation (20440 Century Boulevard, Suite 100; Germantown, MD 20874; submitted 05/31/2005). The document has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

Executive Summary

Bayer CropScience has proposed, in PP#4F6830, the establishment of permanent tolerances for 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 its desthio metabolite in/on the following agricultural commodities:

Barley, grain	0.2 ppm
Barley, hay	7.0 ppm
Barley, straw	2.0 ppm
Barley, pearled barley	0.2 ppm
Barley, bran	0.4 ppm
Black mustard, seed	0.1 ppm
Borage, seed	0.1 ppm
Canola, seed	0.1 ppm
Crambe, seed	0.1 ppm
Field mustard, seed	0.1 ppm
Flax, seed	0.1 ppm
Grain, aspirated fractions	13. ppm
Indian mustard, seed	0.1 ppm
Indian rapeseed	0.1 ppm
Pea and bean, dried, shelled, except soybean, subgroup	0.8 ppm
Peanut, nutmeat	0.02 ppm
Peanut, hay	5.0 ppm
Peanut, meal	0.3 ppm
Rapeseed, seed	0.1 ppm
Rice, grain	0.25 ppm
Rice, straw	1.5 ppm
Rice, hulls	1.0 ppm
Wheat, grain	0.06 ppm
Wheat, forage	7.0 ppm
Wheat, hay	4.0 ppm
Wheat, straw	2.3 ppm
Wheat, bran	1.5 ppm
Wheat, germ	0.15 ppm

Bayer is also proposing the establishment of permanent tolerances for residues of prothioconazole, its desthio and 4-hydroxy metabolites, and conjugates that can be converted to these three compounds by acid hydrolysis in/on the following animal commodities:

Milk	0.006 ppm
Cattle, fat	0.1 ppm
Cattle, meat	0.01 ppm
Cattle, meat byproducts	1.2 ppm

Prothioconazole is a systemic demethylation inhibitor fungicide (Group 3 fungicide) of the triazolinthione chemical class. Prothioconazole has demonstrated protective, curative, and

eradicative action against plant diseases caused by ascomycetes, basidiomycetes, and deuteromycetes fungi in many crops, and is intended to be used for the control of fusarium head blight and reduction of deoxynivalenol levels in barley and wheat.

This chemical has been submitted for joint EPA and PMRA review by Bayer CropScience. The crops proposed for joint review include barley, the oilseed crop group, the dried shell and bean subgroup, and wheat. Uses on peanuts and rice are being proposed for the U.S. only.

In conjunction with the subject tolerance petition, Bayer CropScience has submitted an application for Section 3 registration of a 4 lb a.i./gal suspension concentrate (equivalent to a flowable concentrate; FlC) formulation (Proline® 480 SC Fungicide; EPA File Symbol No. 264-IEL). The product is to be applied as broadcast postemergence foliar or soil sprays (application to soil for peanuts only) using ground or aerial equipment at 0.088-0.178 lb ai/A/application (0.100-0.200 kg ai/ha/application). The proposed maximum seasonal rates range 0.285-0.713 lb ai/A (0.320-0.800 kg ai/ha), and the proposed retreatment intervals are 5-21 days. The proposed PHIs range from 7 days for dried shelled peas and beans to 40 days for rice.

The available data from metabolism studies with wheat, peanut, and sugar beet indicate that 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% of the total radioactive residues (TRRs) 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% of the TRRs in wheat matrices, 24-28% of the TRRs in peanut hay, 6.2% of the TRRs in peanut nutmeat, and 19-58% of the TRRs in sugar beet tops and root. In triazole-label studies, triazolylalanine accounted for 71% of the TRRs in wheat grain, 4.1-25% of the TRRs in wheat forage, hay, and straw, 50% of the TRRs in peanut nutmeat, 29% of the TRRs in sugar beet root, and <2% of the TRRs in peanut hay and sugar beet tops. Triazolylacetic acid accounted for 19% of the TRRs in wheat grain, <5% of the TRRs 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. Based on the results of the confined rotational crop studies, metabolism in rotational crops was similar to that in peanut, sugar beet, and wheat.

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. Additionally, the contribution of triazole, triazolylalanine (TA), and triazolylacetic acid (TAA) from the use of prothioconazole to the aggregate exposure for human-health risk assessment has been considered (DP322215, 02/07/2006).

The available data indicate that the metabolism of prothioconazole is similar in goats and hens. Prothioconazole was found to be a major residue in liver, kidney (goat only) and fat, at 11-31% of the TRRs and was identified in muscle at 2.5-13% of the TRRs; prothioconazole was found at lower levels in milk and egg (<4% of the TRRs). Desthio-Prothioconazole was a major metabolite in fat and egg, at 15-29% of the TRRs, but was found at lower levels in other tissues and milk (<8% of the TRRs). 4-Hydroxy prothioconazole was found at ~11% of the TRRs in goat liver and at <8.5% of the TRRs 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% of the TRRs in goat kidney and 4.4%-23.7% of the TRRs 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% of the TRRs) and hen muscle (19% of the TRRs); 1,2,4-triazole was found at lower levels in hen liver and fat (<2% of the TRRs) 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% of the TRRs; thiocyanate was found at lower levels in goat liver (~2% of the TRRs) and hen matrices (<10% of the TRRs). JAU6476-triazolyl-ethanol was a major metabolite in egg (16% of the TRRs) and hen muscle (28% of the TRRs), was found at lower levels in hen liver and fat (<4% of the TRRs), and was not detected in goat matrices. Additional metabolites found at significant levels were JAU6476-S-methyl, at 20-28% of the TRRs in hen fat (found at <7% of the TRRs in hen matrices and <1% of the TRRs in goat liver), and JAU6476-hydroxy-glucuronide, at 11% of the TRRs in goat fat (<7% of the TRRs in other goat matrices and in hen liver).

The residue of concern for tolerance enforcement in livestock commodities is 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 residue of concern for risk assessment for livestock commodities is 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. Additionally, for livestock commodities, aggregate exposure from triazole and the triazole derivatives has been considered (DP322215, 02/07/2006). Prothioconazole was included in that assessment.

Crop field trial data have been submitted reflecting the proposed use pattern for the 4 lb a.i./gal FlC formulation; however, confirmatory storage stability data are required to support all crop field trials. Adequate processing data have been submitted for canola, peanut, rice, and wheat, which indicate that a tolerance is needed for rice hulls; additional storage stability data are required to support the processing studies. Adequate cattle feeding studies with prothioconazole have been submitted; a poultry feeding study was not submitted, but based on the results of poultry metabolism study no residues are anticipated in poultry commodities for the currently proposed uses, except poultry liver (which is at the LOQ). A poultry feeding study is required to confirm these findings.

The available rotational crop data indicate that the proposed rotational crop restrictions (30 day PBI) are appropriate; no rotational crop tolerances are needed to support this petition. However, finite residues of triazole and triazole derivatives are found at the proposed PBI. Triazole and triazole derivatives in rotational crops have been considered as part of the aggregate exposure issue (DP322215, 02/07/2006).

There are currently no U.S., Canadian, Mexican, or international Codex tolerances established for prothioconazole.

The petitioner included residue data for 1,2,4-triazole and triazole conjugates triazolylalanine and triazolylacetic acid with the crop field trial, processing, and field rotational crop studies submitted with this petition. The data indicate that quantifiable residues of the triazole

conjugates will occur in primary crop, processed, and field rotational crop commodities following treatment of primary crops with prothioconazole. Radiovalidation data for the method used to collect triazole and triazole conjugates data and completion of the ongoing storage stability study with these compounds are needed to support the residue data.

Regulatory Recommendations and Residue Chemistry Deficiencies

HED has examined the residue chemistry database for the new active ingredient prothioconazole. Pending resolution of the deficiencies noted below, there are no residue chemistry issues that would preclude granting a conditional registration for this fungicide or establishment of tolerances for prothioconazole as follows:

Tolerances for 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]-1H-1,2,4- triazole-1-ethanol], calculated as prothioconazole :

Barley, grain	0.35	ppm
Barley, hay	7.0	ppm
Barley, straw	4.0	ppm
Grain, aspirated grain fractions	11	ppm
Pea and bean, dried shelled, except soybean, subgroup 6C	0.90	ppm
Peanut	0.02	ppm
Peanut, hay	6.0	ppm
Rapeseed, seed	0.15	ppm
Rice, grain	0.20	ppm
Rice, straw	1.4	ppm
Rice, hulls	0.90	ppm
Wheat, grain	0.07	ppm
Wheat, forage	6.0	ppm
Wheat, hay	4.5	ppm
Wheat, straw	5.0	ppm

Tolerances for 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] and conjugates convertible to these two compounds by acid hydrolysis, calculated as prothioconazole

Cattle, fat	0.10	ppm
Cattle, meat	0.02	ppm
Cattle, meat byproducts	0.20	ppm
Goat, fat	0.10	ppm
Goat, meat	0.02	ppm
Goat, meat byproducts	0.20	ppm
Hog, meat byproducts	0.05	ppm
Horse, fat	0.10	ppm
Horse, meat	0.02	ppm
Horse, meat byproducts	0.20	ppm
Milk	0.02	ppm
Poultry, liver	0.02	ppm
Sheep, fat	0.10	ppm
Sheep, meat	0.02	ppm
Sheep, meat byproducts	0.20	ppm

A human health risk assessment will be conducted and described in a separate document.

The following deficiencies in the studies submitted in support of the establishment of tolerances for prothioconazole must be successfully addressed:

The available storage *stability data* are tentatively adequate to support the storage intervals and conditions of samples from the submitted crop field trial, processing, and field rotational crop studies. The final reports of the ongoing storage stability studies with prothioconazole and prothioconazole desthio (interim results for which were reported in MRID 46477701) must be submitted as confirmatory data.

The available poultry metabolism study and analytical method for ruminant commodities are tentatively adequate to establish tolerances for poultry commodities. A *poultry feeding study* and fully validated *analytical method* for poultry commodities are required as conditions of the registration of prothioconazole.

The proposed *enforcement analytical method* for livestock commodities must undergo successful method validation at EPA.

860.1200 Directions for Use

- The applicant has proposed use on an "Oilseed Crop Subgroup" which consists of the members of the Oilseed Crop Group 20 with the exception of safflower seed and sunflower seed. The representative crops of Crop Group 20 are canola and sunflower. Currently, no crop subgroups have been defined by HED for Crop Group 20. The applicant has submitted crop field trial data for canola but not for sunflower. In the absence of crop field trial data for sunflower, the applicant must modify the use directions to remove reference to the Oilseed Crop Subgroup and to delete the following commodities from the label: Indian mustard (Brassica juncea); black mustard (Brassica nigra); flax (Linum usitatissimum); and borage (Borago officinalis).

- The retreatment intervals proposed by the applicant are not in agreement with the retreatment intervals used in the crop field trials for several crops, and the applicant did not propose a retreatment interval for rice. For barley, rice, wheat, and canola and the oilseed crops of rapeseed, Indian rapeseed, field mustard seed, and crambe, the applicant must propose a minimum retreatment interval of 14 days.

- Although the label specifies use of a spray adjuvant for all uses except soil application to peanuts, the only crops for which surfactants were used in the field trials were those in the dried pea/bean crop subgroup. In the absence of data supporting their use, the label must be modified to remove the recommendation regarding spray adjuvants for all crops except chickpea, lentils, and the dried shelled peas and beans subgroup.

- We note that the use directions for barley and wheat specify that the maximum single application rate is 0.178 lb ai/A (200 g ai/ha) and that a maximum of two applications may be made. The maximum seasonal application rate for barley and wheat is 0.293 lb

ai/A (328 g ai/ha) which is less than two times the maximum single application rate. For wheat and barley, the applicant may wish to note on the product label that the maximum seasonal rate would be exceeded if two applications were made at the maximum single application rate.

860.1340 Residue Analytical Methods

- 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 applicant must submit a poultry feeding study with prothioconazole.

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:
  - destihio 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

860.1650 Proposed Tolerances

- The proposed tolerance expression for plant commodities should be revised to be calculated in terms of the "combined residues of the fungicide prothioconazole [2-[2-(1-

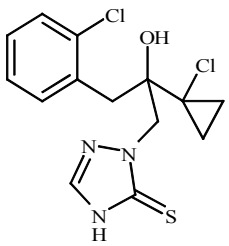
chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione] and prothioconazole desthio [α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-1H-1,2,4-triazole-1-ethanol], calculated as prothioconazole."

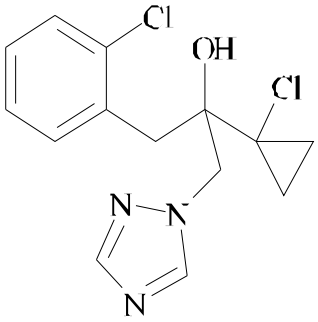
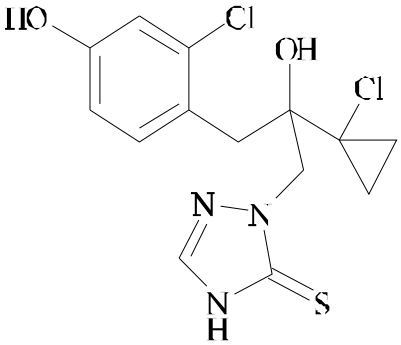
- The proposed tolerance expression for livestock commodities should be revised to be calculated in terms of the "combined residues of the fungicide prothioconazole [2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione] and prothioconazole desthio [α-(1-chlorocyclopropyl)-α -[(2-chlorophenyl)methyl]-1*H*-1,2,4-triazole-1-ethanol] and conjugates convertible to these two compounds by acid hydrolysis, calculated as prothioconazole."

- The proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 9. In addition, revisions to the proposed tolerance levels for certain commodities and deletion of certain tolerances are required, as specified in Table 9.

Background

The subject petition, PP#4F6830, represents the first food/feed uses of prothioconazole proposed in the U.S. or Canada. The chemical structure and nomenclature of prothioconazole and its metabolites to be regulated and the physicochemical properties of prothioconazole are presented in the tables below. The chemical names and structures of prothioconazole and all transformation products identified in plant and livestock commodities are presented in Appendix I.

Prothioconazole Nomenclature	
Chemical structure	
Common name	Prothioconazole
Company experimental name	JAU6476
IUPAC name	2-[(2RS)-2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2H-1,2,4-triazole-3(4H)-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
PC Code	113961
End-use product (EP)	Proline® 480 SC (4 lb/gal suspension concentrate)

Prothioconazole Nomenclature	
Chemical structure of prothioconazole desthio	 α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-1*H*-1,2,4-triazole-1-ethanol
Chemical structure of 4-hydroxy prothioconazole	 2-[2-(1-chlorocyclopropyl)-3-(2-chloro-4-hydroxyphenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione

Physicochemical Properties of Prothioconazole		
Parameter	Value	Reference
Melting point/range	139.1 to 144.5°C	MRID 46246003
pH	5.8	MRID 46246003
Density	1.36 g/mL	MRID 46246003
Water solubility	mg/L (20°C) pH 4 5 pH 8 300 pH 9 2000	MRID 46246003
Solvent solubility	g/L at RT Acetone >250 Acetonitrile 69 Dichloromethane 88 Dimethylsulfoxide 126 Ethyl acetate >250 n-Heptane <0.1 1-Octanol 58 Polyethylene glycol >250 2-Propanol 87 Xylene 8	MRID 46246003

Physicochemical Properties of Prothioconazole		
Parameter	Value	Reference
Vapor pressure	<<4 x 10^{-7} Pa at 20 or 25°C (calculated from determinations at 70°C)	MRID 46246003
Dissociation constant, pK_a	6.9 (calculated from K_{OW})	MRID 46246003
Octanol/water partition coefficient, Log(K_{OW}) at 20°C	unbuffered water 4.05 pH 4 4.16 pH 7 3.82 pH 9 2.00	MRID 46246003
UV/visible absorption spectrum	Peak maximum at 257 nm	MRID 46246003

860.1200 Directions for Use

Use directions for the U.S. label (EPA File Symbol 264-IEL) are from a draft label dated 3/31/04 for the 4 lb/gal suspension concentrate formulation (equivalent to an FlC formulation), and are summarized in Table 2.

Table 1. Summary of End-Use Products.

Trade Name	Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Label Date
U.S. Label						
Proline® 480 SC Fungicide	264-IEL	4 lb/gal (41%)	Suspension concentrate	Barley; canola; chickpea; dried shelled peas and beans subgroup; lentils; oilseed crop subgroup; peanut; rice; wheat	Ascomycetes, basidiomycetes, and deuteromycetes diseases	3/31/04 (draft)

Table 2. Summary of Directions for Use of Prothioconazole (U.S. Label).

Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A) [g ai/ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Use Directions and Limitations
Barley						
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	2	0.293 [328]	32	Apply during Feekes stages 10.3-10.5 (70-100% heads on the main stem fully emerged); applications may be made up to Feekes stage 10.52 (heads in full flower). A 7- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.088-0.134 [100-150]	2		32	Apply when earliest disease symptoms appear on leaves or stems. A 7- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Canola						

Table 2. Summary of Directions for Use of Prothioconazole (U.S. Label).						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A) [g ai/ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Use Directions and Limitations
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	2	0.356 [400]	36	Apply during the 20% up to the 50% bloom stage. A 5- to 7-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Chickpea and Lentils						
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	3	0.534 [600]	7	Apply at early flower (lentil) or first sign of disease. A 10- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Dried Shelled Peas and Beans Subgroup : *Lupinius* spp. (grain, sweet, white, and white sweet lupin); *Phaseolus* spp. (field, kidney, dry lima, navy, pinto, and tepary beans); *Vigna* spp. (adzuki bean, blackeyed pea, catjang, cowpea, Crowder pea, moth bean, mung bean, rice bean, southern pea, and urd bean); dry broad bean; guar; lablab bean; and *Pisum* spp. (pea (including field pea), and pigeon pea)						
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	3	0.534 [600]	7	Apply at first sign of disease. A 5- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Oilseed Crop Subgroup: Rapeseed (canola varieties only - see specific instructions above for canola); rapeseed (*Brassica napus* and *Brassica rapa*); Indian rapeseed (*Brassica rapa)*; Indian mustard (*Brassica juncea*); field mustard (*Brassica rapa)*; black mustard (*Brassica nigra*); flax (*Linum usitatissimum*); crambe (*Crambe abyssinica)*; and borage (*Borago officinalis*)						
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	2	0.356 [400]	36	Apply during the 20% up to the 50% bloom stage. A 5- to 7-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Peanut						
Proline® 480 SC Fungicide	Postemergence Broadcast soil Ground or aerial	0.178 [200]	4	0.713 [800]	14	Apply as 4 consecutive applications with a 14-day retreatment interval. The feeding of hay or thrashings or grazing of livestock in treated areas is prohibited.
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.156-0.178 [175-200]	4	0.713 [800]	14	A 14- to 21-day retreatment interval is proposed. Use of a spray surfactant is recommended. The feeding of hay or thrashings or grazing of livestock in treated areas is prohibited.
Rice						

Table 2. Summary of Directions for Use of Prothioconazole (U.S. Label).						
Trade Name	Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A) [g ai/ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A) [g ai/ha]	PHI (days)	Use Directions and Limitations
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.143 [160]	2	0.285 [320]	40	Apply at first sign of disease; usually from panicle differentiation to late boot. A second application may be made up to 70% panicle emergence from the boot. A retreatment interval is not specified. Use of a spray surfactant is recommended.
Wheat						
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.178 [150-200]	2	0.293 [328]	30	Apply during Feekes stages 10.4-10.52 (at least 75% of wheat heads on main stem fully emerged to when 50% of heads on main stem in flower); applications may be made up to Feekes stage 10.52 (heads in full flower). A 7- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.
Proline® 480 SC Fungicide	Postemergence Broadcast foliar Ground or aerial	0.134-0.156 [150-175]	2		30	Apply when earliest disease symptoms appear on leaves or stems. A 7- to 14-day retreatment interval is proposed. Use of a spray surfactant is recommended.

The general use directions for the label specify that ground applications are to be made in a minimum of 10 gal/A, and aerial applications are to be made in a minimum of 5 gal/A. For all uses except soil application in peanuts, the label specifies that the lowest labeled rate of a non-ionic spray surfactant should be tank-mixed with the product. For soil application in peanuts, the label notes that the product must be carried by rainfall or irrigation into the root and pod zone of the plants. Application through any type of irrigation system is prohibited. A restricted entry interval of 24 hours is specified.

The label provides mixing procedures for tank mixes, and notes that the product is compatible with most insecticide, fungicide, herbicide, and foliar nutrient products. It states that physical compatibility of product with tank-mix partners should be tested using a jar test before use.

The following rotational crop restrictions are proposed: 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.

Conclusions: The proposed U.S. label is adequate to allow evaluation of the residue data submitted in support of this petition. Several label amendments are required.

The applicant has proposed use on an "Oilseed Crop Subgroup" which consists of the members of the Oilseed Crop Group 20 with the exception of safflower seed and sunflower seed. The representative crops of Crop Group 20 are canola and sunflower. Currently, no crop subgroups have been defined by HED for Crop Group 20. The applicant has submitted crop field trial data for canola but not for sunflower. In the absence of crop field trial data for sunflower, the applicant must modify the use directions to remove reference to the Oilseed Crop Subgroup and to delete the following commodities from the label: Indian mustard (Brassica juncea); black mustard (Brassica nigra); flax (Linum usitatissimum); and borage (Borago officinalis).

The retreatment intervals proposed by the applicant are not in agreement with the retreatment intervals used in the crop field trials for several crops. For barley, wheat, and canola and the oilseed crops of rapeseed, Indian rapeseed, field mustard seed, and crambe, the applicant must propose a minimum retreatment interval of 14 days. The proposed retreatment intervals for the other crops are supported by the crop field trial data. The applicant did not propose a retreatment interval for rice. The rice crop field trials reflected an application pattern in which the first application was made at panicle differentiation, and the second application was made approximately 14 days later; therefore, the applicant should propose a 14-day retreatment interval for rice.

Although the label specifies use of a spray adjuvant for all uses except soil application to peanuts, the only crops for which surfactants were used in the field trials were those in the dried pea/bean crop subgroup. In the absence of data supporting their use, the label must be modified to remove the recommendation regarding spray adjuvants for all crops except chickpea, lentils, and the dried shelled peas and beans subgroup.

The barley and wheat crop field trials reflect a maximum seasonal rate of 0.293 lb ai/A. HED notes that the use directions for barley and wheat specify that the maximum single application rate is 0.178 lb ai/A (200 g ai/ha) and that a maximum of two applications may be made. The maximum seasonal application rate for barley and wheat is 0.293 lb ai/A (328 g ai/ha) which is less than two times the maximum single application rate. For wheat and barley, the applicant may wish to note on the product label that the maximum seasonal rate would be exceeded if two applications were made at the maximum single application rate.

860.1300 Nature of the Residue - Plants

46246141.der.wpd (Wheat)
46246142.der.wpd (Wheat)
46246143.der.wpd (Wheat)
46246145.der.wpd (Peanut)
46246146.der.wpd (Peanut)
46246147.der.wpd (Sugar beet)
46246148.der.wpd (Sugar beet)

Bayer submitted eight plant metabolism studies to support the proposed uses: (1) a wheat metabolism study reflecting foliar application of [phenyl-^{14}C]-prothioconazole (MRID

46246141); (2) a wheat metabolism study reflecting seed treatment with [phenyl-^{14}C]-prothioconazole (MRID 46246142); (3) a wheat metabolism study reflecting foliar application of [triazole-^{14}C]-prothioconazole (MRID 46246143); (4) a peanut metabolism study reflecting foliar application of [phenyl-^{14}C]-prothioconazole (MRID 46246145); (5) a peanut metabolism study reflecting foliar application of [triazole-^{14}C]-prothioconazole (MRID 46246146); (6) a sugar beet metabolism study reflecting foliar application of [triazole-^{14}C]-prothioconazole (MRID 46246147); (7) a sugar beet metabolism study reflecting foliar application of [phenyl-^{14}C]-prothioconazole (MRID 46246148); and (8) a wheat metabolism study reflecting application of [triazole-^{14}C]-prothioconazole desthio (MRID 46246144), which was not reviewed because it is not useful to support the registration of prothioconazole. Chemical names and structures of prothioconazole and the metabolites identified in the plant metabolism studies are presented in Appendix I.

Wheat - MRID 46246141/46246143:

Phenyl-Label

Bayer CropScience has submitted studies investigating the metabolism of [phenyl-UL-^{14}C]-prothioconazole (specific activity 27.6 mCi/mmol) in wheat as a foliar treatment. The radiolabeled test substances were formulated as emulsifiable concentrate (EC) formulations and applied as two foliar broadcast sprays to wheat plants grown outdoors in planting containers at the beginning of tillering (BBCH 32) and at full flowering (BBCH 65). Applications were made at 0.193 lb a.i./A (216 g a.i./ha) and 0.178 lb a.i./A (199 g a.i./ha), with a 17-day re-treatment interval, for a total seasonal application of 0.371 lb a.i./A (415 g a.i./ha). Forage and hay were harvested 6 and 26 days, respectively, and grain and straw were harvested 48 days following the second application.

The TRRs were 10.45 ppm (forage), 8.90 ppm (hay), 26.74 ppm (straw), and 0.08 ppm (grain) following foliar application of [phenyl-UL-^{14}C]-prothioconazole.
Extraction with organic solvents released the majority of the radioactivity (~61-85% of the TRRs) in all wheat matrices. Cysteine HCl was added to all extracting solvents and to extracts during concentration procedures to prevent oxidative decomposition of prothioconazole. Accelerated solvent extraction (ASE) released an additional ~5-13% of the TRRs (0.02-2.57 ppm) from all matrices. Acid hydrolysis with HCl:dioxane released ~7-8% of the TRRs (0.64-2.18 ppm) in hay and straw. Enzyme hydrolysis of the grain with diastase released an additional ~15% of the TRRs (0.01 ppm). Non-extractable residues remaining following extraction/hydrolysis accounted for <4% of the TRRs (<0.83 ppm) in forage, hay, and straw; and accounted for 18% of the TRRs (0.013 ppm) in grain. Accountabilities were approximately 99-100% for all matrices. Residues were identified primarily by LC-MS, LC-MS/MS, and/or NMR spectroscopy with confirmatory analysis by HPLC and/or TLC co-chromatography. These methods successfully identified the predominant residues in wheat forage, hay, straw, and grain. The stability of prothioconazole and the major metabolite JAU6476-dethio were demonstrated via the co-chromatography of initial (12 – 57 days after harvest) commodity extracts and extracts from crop samples stored frozen for 15 – 18 mo. The stability of minor metabolites was not demonstrated.

Approximately 67-73% of the TRRs were identified in all wheat matrices except in grain where only 34% of the TRRs were identified. Prothioconazole was identified at low levels (1-4% of

the TRRs, <0.01-0.98 ppm) in all wheat matrices. Metabolite JAU6476-desthio was the major identified residue, accounting for 35% of the TRRs (3.7 ppm) in forage, 19% of the TRRs (1.6 ppm) in hay, 22% of the TRRs (6.0 ppm) in straw, and 16% of the TRRs (0.014 ppm) in grain.

All remaining metabolites were identified at <10% of the TRRs. In the phenyl-label study, metabolites JAU6476-α-OH-desthio and JAU6476-triazolinone were identified in all wheat matrices at ~1-9% of the TRRs (<0.01-1.64 ppm). The metabolites JAU6476-3-OH-desthio, JAU6476-4-OH-desthio, JAU6476-6-OH-desthio and JAU6476 sulfonic acid were identified as 1-9% of the TRRs (0.11-2.24 ppm) in forage, hay and straw. In hay, straw and grain, the metabolites JAU6476-α-acetoxy-desthio (along with benzylpropyldiol) and benzylpropyldiol glucoside were identified at <5% of the TRRs (<0.55 ppm). JAU6476 disulfide, JAU6476-OH-desthio (comprised of the 3-OH, 4-OH and/or 6-OH-desthio isomers) and two JAU6476-OH-desthio glucoside isomers were tentatively identified at <6% of the TRRs (≤1.08 ppm) each. The third JAU6476-OH-desthio glucoside isomer was tentatively identified in all matrices except grain at <3% of the TRRs (<0.35 ppm). JAU6476-desthio glucoside was only tentatively identified in hay and straw at <7% of the TRRs (≤1.79 ppm). Characterized radioactivity remaining at the TLC origins accounted for ~12-20% of the TRRs (0.01-3.28 ppm). Unassigned radioactivity was reported as characterized at ~3-10% of the TRRs (<0.01-2.29 ppm). Unknowns accounted for 2-6% of the TRRs (<0.01-0.83 ppm) in each matrix. In grain, ~15% of the TRRs (0.01 ppm) were characterized based on diastase hydrolysis. Another 8% of the TRRs (<0.01 ppm) were extracted by ASE but not analyzed, and 6% of the TRRs (<0.01 ppm) were characterized as polar and aqueous soluble.

Triazole-Label

Bayer CropScience has submitted studies investigating the metabolism of [triazole-3,5-^{14}C]-prothioconazole (specific activity 18.3 mCi/mmol) in wheat as a foliar treatment. The radiolabeled test substances were formulated as emulsifiable concentrate (EC) formulations and applied as two foliar broadcast sprays to wheat plants grown outdoors in planting containers at the beginning of tillering (BBCH 32) and at full flowering (BBCH 65). Applications were made at 0.159 lb a.i./A (178 g a.i./ha) and 0.260 lb a.i./A (292 g a.i./ha), with a 23-day re-treatment interval, for a total seasonal application of 0.420 lb a.i./A (470 g a.i./ha). Wheat forage was harvested 6 days after the second application, 29 days for hay and 64 days for grain and straw.

Total radioactive residues (TRRs) were 7.96 ppm (forage), 11.18 ppm (hay), 7.94 ppm (straw) and 4.97 ppm (grain) following foliar application of [triazole-3,5-^{14}C]-prothioconazole.

Extraction with organic solvents released the majority of the radioactivity (~65-81% of the TRRs) in all wheat matrices. Accelerated solvent extraction (ASE) released an additional ~8-24% of the TRRs (0.61-1.58 ppm) from all matrices. Acid hydrolysis with HCl:methanol and or HCl:dioxane released ~6-11% of the TRRs (0.48-1.05 ppm) in forage, hay and straw. Acid hydrolysis with HCl:dioxane released 1% of the TRRs (0.041 ppm) for grain. Non-extractable residues remaining following extraction/hydrolysis accounted for <6% of the TRRs (<0.45 ppm) in forage, hay, and straw, and 0.1% of the TRRs (<0.01 ppm) in grain. Extraction results were normalized; therefore, accountabilities were 100%. Residues were identified primarily by LC-MS, LC-MS/MS, and/or NMR spectroscopy with confirmatory analysis by HPLC and/or TLC co-chromatography. These methods successfully identified the predominant residues in

wheat forage, hay, straw, and grain. The results of the analysis of some later extracted samples (450 days storage) showed residue profiles which were very similar to the profiles for the samples extracted within 34 days of harvest. No previously unidentified residue was found in the later extracts and the residues identified in the later extracts represented only less than 1 to 3% of the TRRs in the corresponding matrices. No storage stability data were needed for the RACs as the storage duration of the RACs was no more than one month. For the extracts that were stored up to 473 days, residue profiles covering the storage interval indicated no significant changes.

Approximately 57-91% of the TRRs were identified in all wheat matrices. Prothioconazole was identified at low levels (3-7% of the TRRs, 0.38-0.53 ppm) in forage, hay and straw. However, in grain, neither prothioconazole nor any metabolites unique to prothioconazole were identified. Metabolite JAU6476-desthio was identified as 9-19% of the TRRs (0.74-1.50 ppm) in forage, hay and straw. In grain, the predominant metabolites were triazolylalanine (TA) at 71% of the TRRs (3.54 ppm) followed by triazolylacetic acid (TAA) accounting for 19% of the TRRs (0.95 ppm) with triazolylhydroxypropionic acid (THPA) constituting the remaining identified residue at 0.4% of the TRRs (0.02 ppm). The triazole-specific metabolite, TA, was also a major residue in hay (25% of the TRRs; 2.77 ppm), and accounted for 12% of the TRRs (0.95 ppm) in forage and 4% of the TRRs (0.32 ppm) in straw. TAA was identified at <5% of the TRRs (<0.5 ppm) in forage, hay, and straw, and THPA was identified at <8% of the TRRs (<0.85 ppm) in these same matrices. Free triazole or *1H*-1,2,4-triazole was not identified in any wheat matrix.

All remaining metabolites were identified at <10% of the TRRs. In the triazole-label study, JAU6476-α-OH-desthio and JAU6476-triazolinone were identified at 1-9% of the TRRs (0.08-0.78 ppm) in forage, hay and straw. JAU6476-OH-desthio and JAU6476-α-acetoxy-desthio were identified in forage and straw at 2-6% of the TRRs (0.16-0.49 ppm). Triazolyl-ethanol-glucoside, JAU6476-OH-desthio-glucoside isomers, and JAU6476-OH-desthio-malonyl-glucoside isomers were identified in forage, hay and straw each at <4% of the TRRs (<0.30 ppm). Unresolved glucoside isomers were found in forage and hay at <5% of the TRRs (<0.52 ppm). Triazolyl-ethanol (found in straw), JAU6476-desthio-malonyl-glucoside (found in forage), JAU6476-desthio-phenyl-cysteine isomers and JAU6476-diOH-desthio-malonyl-glucoside (both found in forage) were identified each at <3% of the TRRs (<0.18 ppm). Unknowns accounted for 6-22% of the TRRs (0.3-1.9 ppm) in each matrix. However, these consisted of multiple components, each generally <3% of the TRRs (≤0.36 ppm). The remaining radioactivity was characterized as HCl hydrolysates at ~6% of the TRRs (<0.49 ppm).

Based on the results of the wheat metabolism study, the applicant concluded that prothioconazole is initially metabolized in wheat by oxidation and loss of sulfur to form JAU6476-desthio, after which two major metabolic processes occur: (1) hydroxylation of the phenyl ring and or benzylic carbon to form isomers of JAU6476-OH-desthio, JAU6476-diOH desthio, and JAU6476-α-OH-desthio, followed by conjugation to form the corresponding glucosides, malonyl-glucosides and acetate; and (2) release of the triazole moiety to form TA and THPA and further metabolism of the triazole conjugates to form TAA. The applicant noted that the absence of 1,2,4-triazole in any wheat matrix suggested that immediate or very rapid conjugation of released triazole occurred. The following minor metabolic pathways were

reported: formation of JAU6476-triazolinone and JAU6476-desthio-phenyl-cysteine; conjugation of JAU6476-desthio with glucose and malonic acid; oxidation of the sulfur atom of prothioconazole to form JAU6476 sulfonic acid; cleavage of the benzylic group to form triazolyl ethanol and its glucoside; and conjugation of the benzylpropyldiol portion of the remaining molecule.

Wheat - MRID 46246142: Bayer CropScience has submitted a study investigating the metabolism of [phenyl-UL-^{14}C]-prothioconazole (specific activity 2.97 MBq/mg) in wheat as a seed treatment. The radiolabeled test substance was applied at 7.3 µg a.i./seed (equivalent to 18.4 g a.i./kg seed; low-rate) and 37 µg a.i./seed (equivalent to 93.3 g a.i./kg seed; high-rate). Wheat plants were grown from the treated seed in the greenhouse. Forage was harvested at BBCH 41, hay was harvested BBCH 83, and grain and straw were harvested at maturity (57, 110, and 153 days, respectively, after planting).

Total radioactive residues (TRRs) in forage, hay, and straw were determined by combustion followed by liquid scintillation counting (LSC). In wheat matrices harvested following the low-rate seed treatment, TRRs were 0.020 ppm in forage and hay, 0.030 ppm in straw, and 0.008 ppm in grain. In wheat matrices harvested following high-rate seed treatment, TRRs were 0.07 ppm in forage, 0.09 ppm in hay, 0.28 ppm in straw, and 0.01 ppm in grain. Only forage, hay, and straw were subjected to further analysis.

Solvent extraction with acetonitrile/water released the majority of the TRRs (~71.2-85.2%) in wheat matrices from both treatment rates. HED notes that cysteine HCl was added to extracting solvents and to extracts during concentration procedures to prevent oxidative decomposition of prothioconazole. Hydrolysis with dioxane/HCl solubilized an additional 7.8% of the TRRs in straw (high-rate treatment only). Non-extractable residues remaining following extraction/hydrolysis accounted for 17.1-28.8% of the TRRs (0.003-0.006 ppm) in wheat matrices from the low-rate treatment, and for 7.7-25.7% of the TRRs (0.01-0.02 ppm) in wheat matrices from the high-rate treatment. Because TRRs were determined by summing extractable and non-extractable radioactivity, accountabilities ranged from 100-119%. Residues were identified primarily by TLC co-chromatography with some confirmatory analysis by HPLC. These methods successfully identified the predominant residues in wheat forage, hay, straw, and grain following seed treatment. Only extracts and hydrolysates from the high-rate treatment were subjected to analysis for characterization/identification of residues. Extraction and analysis of all samples were conducted within 30 days of harvest.

Approximately 18-33% of the TRRs (0.018-0.092 ppm) were identified in wheat forage, hay, and straw. Prothioconazole was identified at <1% of the TRRs in all matrices (≤0.002 ppm). Metabolite JAU6476-desthio was the major identified residue, accounting for 10.9% of the TRRs (0.01 ppm) in forage and 6.4-6.6% of the TRRs (0.005-0.019 ppm) in hay and straw. Metabolites JAU6476-3-OH-desthio and JAU6476-4-OH-desthio together accounted for 3.8-12.0% of the TRRs (≤0.017 ppm). In addition, JAU6476-OH-glucosides were tentatively identified at 10.6% of the TRRs (0.030 ppm) in straw and were tentatively identified but not quantitated in wheat forage and hay. Remaining identified metabolites, including JAU6476-α-OH-desthio, JAU6476-6-OH-desthio, JAU6476-triazolinone, JAU6476 sulfonic acid,

JAU6476-α-acetoxy-desthio, benzylpropyldiol glucoside, and JAU6476-disulfide were present at ≤3.3% of the TRRs (≤0.008 ppm) each.

Based on the results of the phenyl-label seed treatment wheat metabolism study, it is concluded that prothioconazole was extensively metabolized in wheat via: (1) oxidation and loss of sulfur to form JAU6476-desthio; and (2) hydroxylation of the chlorobenzyl methylene C-atom to form JAU6476-α-hydroxy-desthio and hydroxylation of the chlorobenzyl ring at positions 3, 4, and 6 of JAU6476-desthio to form the hydroxy desthio metabolites. Exchange of oxygen for sulfur, the elimination of the triazole moiety and conjugation of the benzylpropyldiol portion of the remaining molecule, and the formation of glucosides of the monohydroxylated JAU6476-desthio isomers were proposed as minor metabolic reactions.

Wheat Metabolism Summary: The submitted wheat metabolism data are adequate to satisfy data requirements. Based on the results of the wheat metabolism studies, the applicant concluded that prothioconazole is initially metabolized in wheat by oxidation and loss of sulfur to form prothioconazole desthio, after which two major metabolic processes occur: (1) hydroxylation of the phenyl ring and/or benzylic carbon to form isomers of JAU6476-OH-desthio, JAU6476-diOH desthio, and JAU6476-α-OH-desthio, followed by conjugation to form the corresponding glucosides, malonyl-glucosides and acetate; and (2) release of the triazole moiety to form triazolylalanine and THPA and further metabolism of the triazole conjugates to form triazolylacetic acid. The applicant noted that the absence of free triazole in any wheat matrix suggested that immediate or very rapid conjugation of released triazole occurred. The following minor metabolic pathways were reported: formation of JAU6476-triazolinone and JAU6476-desthio-phenyl-cysteine; conjugation of prothioconazole desthio with glucose and malonic acid; oxidation of the sulfur atom of prothioconazole to form JAU6476 sulfonic acid; and cleavage of the benzylic group to form triazolyl-ethanol and its glucoside.

A similar metabolic pathway is proposed for the metabolism of prothioconazole in wheat following application as a seed treatment.

Peanut - MRID 46246145/46246146:

Phenyl-Label

Bayer CropScience has submitted studies investigating the metabolism of [phenyl-UL-^{14}C]-prothioconazole (specific activity 2.77 MBq/mg) in peanut plants grown in a greenhouse. The radiolabeled test substances were formulated as an emulsifiable concentrate (EC) formulation. [Phenyl-UL-^{14}C]-JAU6476 were applied to peanut plants 'Georgia Green' as three foliar spray applications with 20 to 22-days interval at growth stages beginning at pod development (BBCH codes 66, 71 and 75). Each treatment was performed at a rate of approximately 0.267 lb a.i./A (299 g a.i./ha) for a maximum seasonal rate of 0.800 lb a.i./A (897 g a.i./ha). A 5-fold rate exaggeration study was also performed to allow for metabolite identification. Peanut plants were harvested at maturity (BBCH growth stages 89-91) at a pre-harvest interval of 21 days. Nuts were removed and cleaned from adhering soil. The plants (hay and nuts with shells) were allowed to dry for 4-5 days. The hay and nutmeat samples were individually homogenized with liquid nitrogen. All samples were stored at -18°C or below. The experimental work from extraction to first analysis (TLC-profiling) was completed within 17-91 days (peanut hay) and

51-99 days (nutmeat). Nutmeat extracted 355 days after harvest using MSPD, indicated similar metabolic distribution.

The overall distribution of TRRs was achieved by combustion and radioassay by liquid scintillation counting (LSC). Identification and characterization of metabolites were performed by HPLC with photodiode array or variable wavelength UV detector and a flow-through radiodetector. Confirmation of residues was by radio-TLC co-chromatography with authentic reference standards or by mass spectrometry (MS) and when possible ^{1}H-NMR. Homogenized peanut hay was extracted with acetonitrile (ACN)/water, with added cysteine hydrochloride to prevent oxidative decomposition of the parent during extraction. Further extraction was achieved using an accelerated solvent extractor (ASE). The homogenized nutmeat samples were extracted by two separate methods; refluxing with hexane and matrix solid phase dispersion (MSPD)/microwave extractions.

The TRRs found in peanut hay and nutmeat were 107.51 ppm and 0.29 ppm, respectively. Solvent extraction with acetonitrile/water released 77.5% of the TRRs in peanut hay. Hexane reflux and/or MSPD extraction with a series of solvents released approximately 67-74% of the TRRs in nutmeat. Accelerated solvent extraction (ASE) and microwave extraction was useful to release additional radioactivity from the peanut matrices. Non-extractable residues remaining following extraction/hydrolysis accounted for <7% of the TRRs (6.73 ppm) in hay and <13% of the TRRs (<0.05 ppm) in nutmeat. Accountabilities ranged from 100-124%.

Approximately 65 to 74% of the TRRs were identified in peanut matrices for the phenyl-label study. Prothioconazole was identified at about 2% of the TRRs (2.0 ppm) in hay. Metabolite JAU6476-desthio was the major identified residue in hay, accounting for 28.2% of the TRRs (30.37 ppm), and one additional metabolite, JAU6476-desthio-dihydroxyolefin glucosides, was identified at 14.1% of the TRRs (15. ppm). All remaining metabolites were identified at <10% of the TRRs and included JAU6476-3-OH-desthio, JAU6476-4-OH-desthio, JAU6476-dihydroxydiene sulfonic, JAU6476-dihydroxyolefin sulfonic acid, glucoside conjugates of the JAU6476-OH-desthio isomers, JAU6476-desthio-hydroxydienyl-cysteine, JAU6476-triazolinone, JAU6476 sulfonic acid, and JAU6476-disulfide. Neither prothioconazole nor JAU6476-desthio were identified in nutmeat. The majority of the TRRs in nutmeat (42.6-47.8%; 0.13-0.14 ppm) were associated with peanut oil and determined as fatty acids, indicating that prothioconazole may be completely metabolized to CO_2 in plants. Identified metabolites (each found at <10% of the TRRs) included JAU6476-desthio-dihydroxyolefin glucosides, JAU6476-desthio-hydroxydienyl-cysteine, JAU6476-OH-desthio glucosides, and JAU6476 sulfonic acid.

Triazole-Label

Bayer CropScience has submitted studies investigating the metabolism of [triazole-UL-^{14}C]-prothioconazole (specific activity 2.11 MBq/mg) in peanut plants grown in a greenhouse. The radiolabeled test substances were formulated as an emulsifiable concentrate (EC) formulation. [Triazole-UL-^{14}C]-JAU6476 was applied to peanut plants 'Georgia Green' as three foliar spray applications with 20 to 22-days interval at growth stages beginning at pod development (BBCH code 66, 71 and 75). Each application was between 0.365-0.267 lb a.i./A (297-299 g a.i./ha) for a maximum seasonal rate of 0.799 lb a.i./ha (895 g a.i./ha). Peanut plants were harvested at

maturity (BBCH growth stages 89-91) at a pre-harvest interval of 14 days (triazole-label study). Nuts were removed and cleaned from adhering soil. The plants (hay and nuts with shells) were allowed to dry for 4-5 days. The hay and nutmeat samples were individually homogenized with liquid nitrogen. All samples were stored at -18°C or below. The experimental work from extraction to first analysis (TLC-profiling) was completed within 17-91 days (peanut hay) and 51-99 days (nutmeat). The aqueous phase of peanut hay and polar fractions of nutmeat were monitored for stability using different HPLC systems throughout the study. No significant changes in the profiles were observed. Adequate storage stability was demonstrated.

The overall distribution of TRRs was achieved by combustion and radioassay by liquid scintillation counting (LSC). Identification and characterization of metabolites were performed by HPLC with photodiode array or variable wavelength UV detector and a flow-through radiodetector. Confirmation of residues was by radio-TLC co-chromatography with authentic reference standards or by mass spectrometry (MS) and when possible ^{1}H-NMR. Isolation and characterization of triazole metabolites was conducted by incubating heterotrophic plant cell suspension cultures prepared from apples with [^{14}C]-triazole for 7 days. Homogenized peanut hay was extracted with acetonitrile (ACN)/water, with added cysteine hydrochloride to prevent oxidative decomposition of the parent during extraction. Further extraction was achieved using an accelerated solvent extractor (ASE). The homogenized nutmeat samples were extracted by two separate methods; refluxing with hexane and matrix solid phase dispersion (MSPD)/microwave extractions.

The TRRs found in peanut hay and nutmeat were 47.38 ppm and 1.4 ppm, respectively. Solvent extraction with acetonitrile/water released 85% of the TRRs in peanut hay. Hexane reflux and/or MSPD extraction with a series of solvents released approximately 77% of the TRRs in nutmeat. Accelerated solvent extraction (ASE) and microwave extraction was useful to release additional radioactivity from the peanut matrices. Non-extractable residues remaining following extraction/hydrolysis accounted for 5.4% of the TRRs (2.55 ppm) in hay and 1.9% of the TRRs (0.03 ppm) in nutmeat. Accountabilities ranged from 100-102%.

Approximately 80-85% of the TRRs were identified in peanut matrices for the triazole-label study. Prothioconazole was identified at 6.6% of the TRRs (3.11 ppm) in hay. Metabolite JAU6476-desthio was the major identified residue in hay, accounting for 23.6% of the TRRs (11.15 ppm). All remaining metabolites were identified at <10% of the TRRs and included JAU6476-3-OH-desthio; JAU6476-4-OH-desthio; JAU6476-triazolinone; JAU6476 sulfonic acid; JAU6476-desthio-phenyl-cysteine; JAU6476-disulfide; glucoside conjugates of JAU6476-3-OH-desthio, JAU6476-4-OH-desthio, unspecified JAU6476-OH-desthio isomers, JAU6476-desthio-dihydroxyolefin, and JAU6476-desthio-dihydroxydiene; JAU6476-malonyl glucoside isomers; JAU6476-dihydroxydiene sulfonic acid; and JAU6476-dihydroxyolefin sulfonic acid. Triazolyl metabolites, including triazolylalanine (TA), triazole acetic acid (TAA), triazolylhydroxy-propionic acid (THPA), JAU6476-triazolyl-ethanol, and JAU6476-triazolyl-ethanol-glucoside were minor components in peanut hay, each accounting for ≤1.5% of the TRRs (≤0.71 ppm). Prothioconazole was not identified in nutmeat, and JAU6476-desthio was identified at 6.2% of the TRRs (0.09 ppm). Triazolyl metabolites were the major identified residues in nutmeat, with TA accounting for 49.8% of the TRRs (0.70 ppm), and THPA accounting for 24.7% of the TRRs (0.35 ppm). TAA was identified at 1.2% of the TRRs (0.02

ppm) and triazolyl unknowns accounted for 4.3% of the TRRs (0.07 ppm). Radioactivity determined as fatty acids in peanut oil accounted for 3.0% of the TRRs (0.05 ppm) in nutmeat.

JAU6476 was extensively metabolized in peanut by: (1) oxidation and loss of sulfur to form JAU6476-desthio; (2) hydroxylation of the chlorobenzyl ring of JAU6476-desthio at positions 3 and 4 to form the hydroxy desthio metabolites; (3) conjugation of the hydroxylated metabolites; (4) exchange of oxygen for sulfur; and (5) release of the triazole moiety to form triazolylalanine (TA) and triazolylhydroxypropionic acid (THPA). Free triazole (1*H*-1,2,4-triazole) was not detected in any peanut matrix.

Peanut Metabolism Summary: The submitted peanut metabolism data are adequate to satisfy data requirements. Based on the results of the peanut metabolism studies, the applicant concluded that prothioconazole is initially metabolized in peanut by: (1) oxidation and loss of sulfur to form prothioconazole desthio; (2) hydroxylation of the chlorobenzyl ring of prothioconazole desthio at positions 3 and 4 to form the hydroxy desthio metabolites; (3) conjugation of the hydroxylated metabolites; (4) exchange of oxygen for sulfur; and (5) release of the triazole moiety to form triazolylalanine and THPA. Free triazole was not detected in any peanut matrix.

Sugar beet - MRID 46246147/46246148:
Phenyl-Label
Bayer CropScience submitted studies investigating the metabolism of [phenyl-UL-^{14}C]-prothioconazole in sugar beet. The radiolabeled test substances were formulated as suspension concentrates and applied as four foliar broadcast sprays at 14-day re-treatment intervals to sugar beet plants. The rate applied for the phenyl-label study was 0.228 lb a.i./A/application (255 g a.i./ha) for a total of 1.028 lb a.i./A/season (1152 g a.i./ha/season). Sugar beet roots and tops were harvested 7 days following the final application.

Following foliar application of [phenyl-UL-^{14}C]-prothioconazole to sugar beets, total radioactive residues (TRRs), determined by combustion and liquid scintillation counting (LSC), were 4.333 ppm in tops and 0.119 ppm in roots. Solvent extraction with acetonitrile/water (4:1) released the majority of the TRRs in tops (92.9 % of the TRRs) and root (69.9 % of the TRRs). Cysteine HCl was added to all extracting solvents to prevent oxidative decomposition of prothioconazole. Additional radioactivity was released from sugar beet matrices by: reflux with methanol/water (4:1) at 60-70°C for 8-9 hours, accelerated solvent extraction with methanol/water (1:1), and acid and base hydrolysis with 0.1% TFA and *1N* NaOH. Non-extractable residues remaining following extraction/hydrolysis accounted for 1.3% of the TRRs (0.056 ppm) in tops, and 8.4 % of the TRRs (0.010 ppm) in root. The applicant normalized the extraction results for accountabilities of 100%. However, the reported accountability in tops prior to normalization was 96%. Residues were identified and quantitated primarily by HPLC co-chromatography with confirmatory analysis and/or structure elucidation by TLC, LC-MS, and LC-MS/MS. These methods successfully identified the predominant residues in sugar beet tops and roots. The interval of storage from harvest to analysis for both the RAC and extracts was less than 28 days for both studies.

Approximately 65% of the TRRs were identified in sugar beet tops, and 60% of the TRRs were identified in roots. Prothioconazole was identified at 7.4% of the TRRs (0.322 ppm) in tops, but was not identified in roots. Metabolite JAU6476-desthio was the major identified residue in both tops and roots, accounting for 28.8% of the TRRs (1.248 ppm) and 57.6% of the TRRs (0.068 ppm), respectively. JAU6476-triazolinone was identified in both tops and roots, at 2.0-2.4% of the TRRs (0.003-0.088 ppm). JAU6476-desthio-hydroxy-dieneyl- cysteine isomers were identified in sugar beet tops only at 10.5% of the TRRs (0.454 ppm). The following additional minor metabolites were identified in sugar beet tops only: JAU6476-OH-sulfonic acid glucoside isomers (8.1% of the TRRs; 0.351 ppm), a JAU6476-OH-desthio glucoside isomer (5.1% of the TRRs; 0.222 ppm), JAU6476-α-OH-desthio and JAU6476-OH-di-sulfonic acid glucoside (≤1.9% of the TRRs each; #0.083 ppm). Remaining radioactivity in sugar beet matrices was characterized as: (1) multicomponent and minor unknowns, accounting for 31.4% of the TRRs in tops (>13 components, each present at ≤4.3% of the TRRs, ≤0.19 ppm); (2) methanol-extractable residues (10.8% of the TRRs in root); and (3) acid- and base-hydrolysable residues (1.6% of the TRRs in tops and 11.0% of the TRRs in root).

Triazole-Label

Bayer CropScience submitted studies investigating the metabolism of [triazole-UL-^{14}C]-prothioconazole (specific activity 18.6 mCi/mmol [MBq/mg]) in sugar beet. The radiolabeled test substances were formulated as suspension concentrates and applied as four foliar broadcast sprays at 14-day re-treatment intervals to sugar beet plants. The rate applied for the triazole-label study was 0.286 lb a.i./A for a total of 1.032 lb a.i./A/season (1157 g a.i./ha). Sugar beet roots and tops were harvested 7 days following the final application.

Following foliar application of [triazole-UL-^{14}C]-prothioconazole to sugar beets, total radioactive residues (TRRs), determined by combustion and liquid scintillation counting (LSC), were 5.154 ppm in tops and 0.130 ppm in roots. Solvent extraction with acetonitrile/water (4:1) released the majority of the TRRs in tops (90.0% of the TRRs) and root (70.2 % of the TRRs). Cysteine HCl was added to all extracting solvents to prevent oxidative decomposition of prothioconazole. Additional radioactivity was released from sugar beet matrices by: reflux with methanol/water (4:1) at 60-70°C for 8-9 hours, accelerated solvent extraction with methanol/water (1:1), and acid and base hydrolysis with 0.1% TFA and *1N* NaOH. Non-extractable residues remaining following extraction/hydrolysis accounted for 1.9 % of the TRRs (0.099 ppm) in tops, and 6.0% of the TRRs (0.008 ppm) in root. The applicant normalized the extraction results for accountabilities of 100%. However, the reported accountabilities prior to normalization ranged from 85-101%. Residues were identified and quantitated primarily by HPLC co-chromatography with confirmatory analysis and/or structure elucidation by TLC, LC-MS, and LC-MS/MS. These methods successfully identified the predominant residues in sugar beet tops and roots. The interval of storage from harvest to analysis for both the RAC and extracts was less than 28 days for both studies.

Approximately 69% of the TRRs were identified in sugar beet tops, and 61% of the TRRs were identified in roots. Prothioconazole was identified at 5.1% of the TRRs (0.265 ppm) in tops, but was not identified in roots. Metabolite JAU6476-desthio was a major identified residue in both tops and roots, accounting for 19.2% of the TRRs (0.988 ppm) and 25.5% of the TRRs (0.033 ppm), respectively. JAU6476-triazolinone was identified in both tops and roots, at 1.6-2.0% of

the TRRs (0.003-0.105 ppm). In the triazole-label study, the triazole-specific metabolite, triazolylalanine, was the major identified residue in sugar beet roots at 28.9% of the TRRs (0.038 ppm) and was identified in tops at 1.6% of the TRRs (0.084 ppm). In the triazole-label study, JAU6476-desthio-hydroxy-dieneyl- cysteine isomers were identified in both tops and roots, at 9.9% of the TRRs (0.512 ppm) and 5.4% of the TRRs (0.007 ppm), respectively. The following additional minor metabolites were identified in sugar beet tops only: JAU6476-OH-sulfonic acid glucoside isomers (6.1% of the TRRs; 0.316 ppm), a JAU6476-OH-desthio glucoside isomer (6.5% of the TRRs; 0.334 ppm), triazolyl-sulfonic acid-ethanol glucoside and triazolyl-ethanol-glucoside (together at 5.1% of the TRRs; 0.263 ppm), triazolylhydroxy-propionic acid (THPA) and triazolyl-ethanol (3.8-4.0% of the TRRs; 0.194-0.207 ppm), JAU6476 sulfonic acid (4.0% of the TRRs; 0.205 ppm), JAU6476-OH-desthio (1.2% of the TRRs; 0.063 ppm). Remaining radioactivity in sugar beet matrices was characterized as: (1) multicomponent and minor unknowns, accounting for 21.4% of the TRRs in tops (9 components, each present at $\leq$4.6% of the TRRs, $\leq$0.24 ppm); (2) methanol-extractable residues (5.3% of the TRRs in tops and 16.1% of the TRRs in root); and (3) acid- and base-hydrolysable residues (2.7% of the TRRs in tops and 7.7% of the TRRs in root). In the triazole-label study, strong anion exchange (SAX) and strong cation exchange (SCX) solid phase extraction cartridges (SPE) eluate/effluents accounted for 3.8% of the TRRs in sugar beet root.

Prothioconazole was extensively metabolized in sugar beet via: (1) oxidation of the sulfur of the triazolinethione ring to the corresponding sulfonic acid and subsequent elimination of the sulfonic acid group to form JAU6476-desthio; and (2) hydroxylation of the phenyl ring or the benzyl carbon to form multiple isomers, with subsequent conjugation with glucose or further reaction to produce JAU6476-desthio-hydroxy-dieneyl-cysteine. Observed in the triazole-label study only was the release of the triazole moiety to form triazolylalanine (TA) and triazolylhydroxypropionic acid (THPA) and elimination of the phenyl ring. Free triazole (1*H*-1,2,4-triazole) was not identified in any of the sugar beet matrices.

Sugar beet metabolism summary: The sugar beet metabolism data are adequate to satisfy data requirements. Based on the results of the sugar beet metabolism studies, the applicant concluded that prothioconazole is extensively metabolized in sugar beet via: (1) oxidation of the sulfur of the triazolinethione ring to the corresponding sulfonic acid and subsequent elimination of the sulfonic acid group to form prothioconazole desthio; (2) hydroxylation of the phenyl ring or the benzyl carbon to form multiple isomers, with subsequent conjugation with glucose or further reaction to produce JAU6476-desthio-hydroxy-dieneyl-cysteine; (3) release of the triazole moiety to form triazolylalanine and THPA; and (4) elimination of the phenyl ring. The applicant noted that free triazole was not identified.

Overall Plant Metabolism Conclusions: The applicant has submitted metabolism studies on three dissimilar crops, wheat, peanut, and sugar beet. The crops selected for the studies are sufficiently representative of the crops for which the applicant is requesting registration: barley, peanut, rice, wheat, the dried shell and bean subgroup, and the oilseed crop group. The application patterns used in the studies are similar to those the applicant is proposing (foliar applications), and bracket the preharvest intervals that are being proposed. The applicant submitted studies reflecting labeling in both rings for all three crops.

The metabolism of JAU6476 was investigated in plants following foliar spray applications of [triazole-UL-^{14}C] JAU6476 or [phenyl-UL-^{14}C] JAU6476 to wheat, peanuts, and sugar beet and seed treatment application of [phenyl-UL-^{14}C] JAU6476 to wheat.

The results of the plant studies showed that JAU6476 was extensively metabolized after the foliar and seed treatment application of [triazole-UL-^{14}C] JAU6476 or [phenyl-UL-^{14}C] JAU6476. The parent compound represented only <1 to 7% of the residues in all matrices. In the phenyl label studies, the major residue found in wheat, peanut, and sugar beet was JAU6476-desthio (6% to 58% of the TRRs in wheat, peanuts, and sugar beet). A second major metabolic process involved hydroxylation followed by conjugation. Since JAU6476 has multiple positions that could potentially undergo hydroxylation, the majority of the remaining metabolites were simply multiple isomers of monohydroxylated JAU6476-desthio and their corresponding glucosides along with JAU6476-hydroxy-diene, dihydroxy-diene, dihydroxy-olefin, and their conjugates. Collectively, these conjugated and/or hydroxylated metabolites compounds represented a major portion (18 to 37%) of the TRRs in the crop matrices and contained both the phenyl and the triazole rings in the molecule. However, none of these hydroxylated metabolites individually reached or exceeded 10% of the TRRs in any target crop matrix. Cleavage of the triazole moiety occurred resulting in the formation of the label-specific metabolite, JAU6476-benzylpropyldiol and its glucoside which represented a minor portion of the TRRs.

A total of 60% to 74% of the residues from the phenyl label foliar studies were identified. An additional 20% to 48% of the TRRs were characterized by extraction and/or chromatographic behaviors. Only 1 to 8% of the residues remained unextracted. The unextrated residues from the wheat seed treatment study ranged from 8% to 26% of the TRRs in the wheat forage, hay, and straw. However, the actual ppm residue levels of unextractable residues ranged from only 0.01 ppm to 0.02 ppm.

The triazole label plant studies showed three major metabolic processes (desulfuration, hydroxylation, and cleavage of the triazole moiety). JAU6476-desthio (6% to 25% maximum levels in wheat, peanuts, and sugar beet) and the label-specific triazole conjugates, triazolylalanine (TA), triazolylacetic acid, and triazolylhydroxypropionic acid (THP) collectively representing a maximum of 29% to 90% of the TRRs in wheat, peanuts, and sugar beet were the major residues found in the triazole label studies. Although the triazole label studies showed greater cleavage of the triazole moiety (compared to the phenyl label), no free triazole was detected in any crop matrix. As was found in the phenyl label studies, numerous minor hydroxylated metabolites and their conjugates comprised the majority of the remainder of the residues. Triazolyl-ethanol and its glucoside and triazolyethanol sulfonic acid glucoside were minor metabolites arising from cleavage of the benzylic group.

A total of 61% to 94% of the residues from the triazole label studies were identified. An additional 6% to 33% of the TRRs were characterized by extraction and/or chromatographic behaviors. The unextractable residues ranged from only <1% to 6% of the TRRs in the plant matrices.

With the exception of the label-specific metabolites, the metabolic profiles were very similar for the target crop studies with both labels. The triazole and phenyl label studies clearly elucidated the metabolic fate of JAU6476 molecule in target crops and were very much complementary to each other. Irrespective of the mode of application (foliar or seed treatment) and the target crop (wheat, peanuts, or sugar beet), the major residues found in all crops were JAU6476-desthio, TA, THP acid, and TAA. The metabolic profiles for the target crop were also similar to the profiles found in the rotational crops. However, the levels of the triazole-based conjugates were much higher in the rotational crops, a finding which was consistent with that expected for confined rotational crop studies with a triazole-based fungicide.

Following the initial metabolism of JAU6476 to JAU6476-desthio (through oxidation of the sulfur to the corresponding sulfonic acid with subsequent elimination of the sulfonic acid group), two major metabolic processes were observed. One major pathway involved the hydroxylation of the phenyl ring and/or benzylic carbon to form multiple isomers of JAU6476-hydroxy-desthio, JAU6476-dihydroxy-desthio, and JAU6476-α-hydroxy-desthio followed by conjugation to form the corresponding glucosides or acetate. The other major pathway involved the cleavage of the H_2C-N bond to release the triazole moiety (and benzylpropyldiol) leading to the formation of TA and THPA and further metabolism of the triazole conjugates to TAA. The fact that no free triazole was found in any target crop matrix suggests an immediate or very rapid conjugation of the released triazole to form the triazole conjugates.

Minor metabolic processes involved the successive reductions of the phenyl ring to form dienes and olefins; formation of JAU6476-triazolinone; and cleavage of the chlorobenzylic group to form triazolyl-ethanol and its glucoside.

Based on these considerations, HED concludes that the submitted studies are adequate to delineate the nature of prothioconazole residues in plants. The residue definition in plant commodities for tolerance enforcement is the sum of prothioconazole and the metabolite prothioconazole desthio, calculated as prothioconazole. The residue definition in plant commodities for risk assessement is the sum of prothioconazole and the metabolite prothioconazole desthio, calculated as prothioconazole. The contribution of triazole derivatives (1,2,4-triazole, triazolylalanine, triazolylacetic acid) from prothioconazole to the aggregate exposure for human-health risk assessment has been considered (DP322215, 02/07/2006).

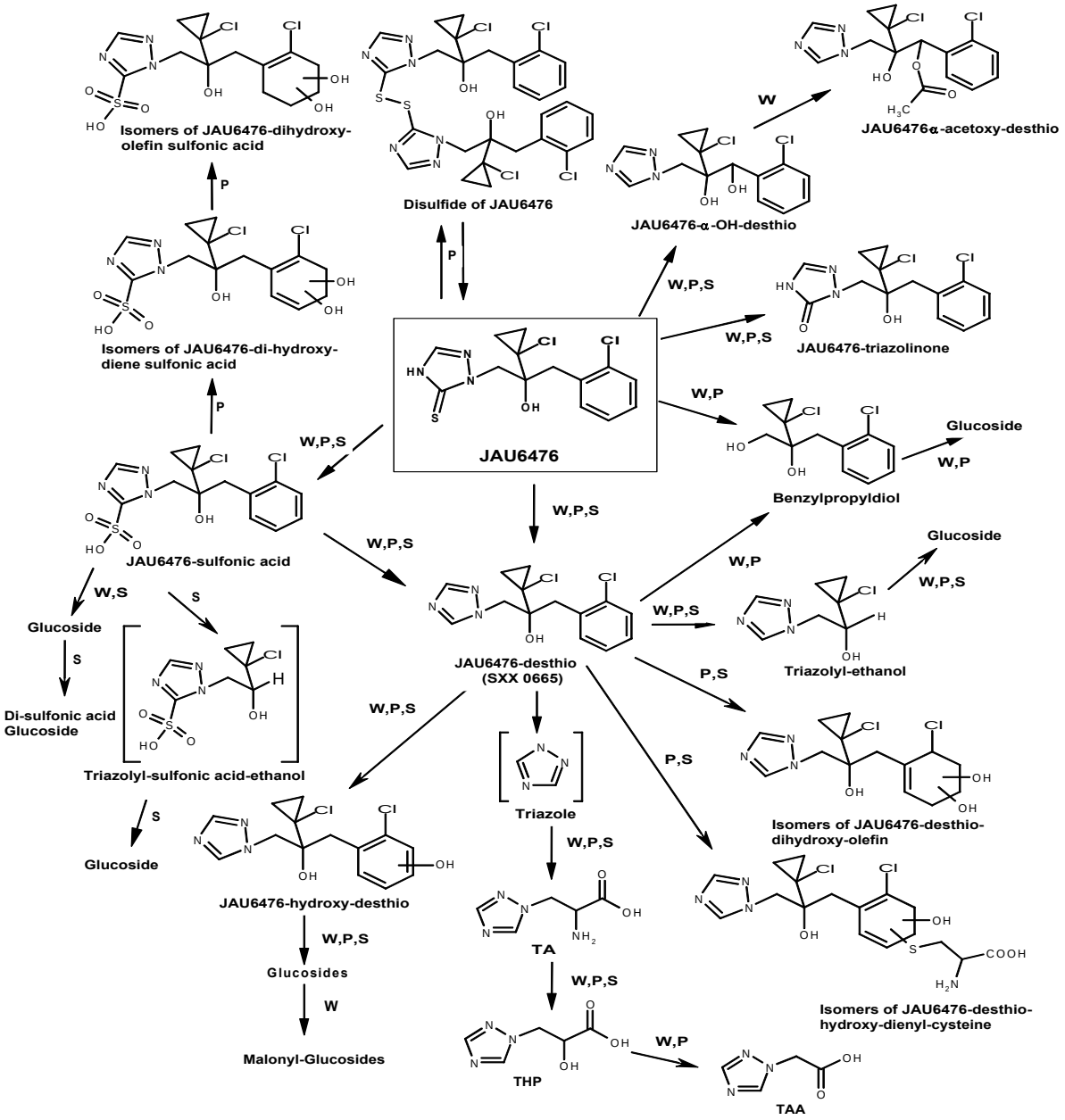


Figure 1. Proposed metabolic profile for [phenyl-UL-^{14}C]-JAU6476 and [triazole-3,5-^{14}C]-JAU6476 in target crops.

8600.1320 Nature of the Residue - Livestock

46246149.der.wpd (Goat)
46246150.der.wpd (Goat)
46246201.der.wpd (Goat)
46246202.der.wpd (Hen)
46246203.der.wpd (Hen)

Bayer submitted five livestock metabolism studies to support the proposed uses: (1) a goat metabolism study reflecting dosing with [triazole-^{14}C]-prothioconazole (MRID 46246149); (2) a goat metabolism study reflecting dosing with [phenyl-^{14}C]-prothioconazole (MRID 46246150); (3) a goat metabolism supplemental study reflecting dosing with [phenyl-^{14}C]-prothioconazole desthio (MRID 46246201); (4) a hen metabolism study reflecting dosing with [phenyl-^{14}C]-prothioconazole (MRID 46246202); and (5) a hen metabolism study reflecting dosing with [triazole-^{14}C]-prothioconazole (MRID 46246203). Chemical names and structures of prothioconazole and its metabolites identified in the livestock metabolism studies are presented in Appendix I.

Goat - MRID 46246149/46246150: Bayer CropScience has submitted studies investigating the metabolism of [phenyl-UL-^{14}C]-prothioconazole (specific activity 0.381 MBq/mg), and [triazole-UL-^{14}C]-prothioconazole (specific activity 369.6 kBq/mg) in lactating goats. The test substances were administered orally to a single goat for each study at 246 ppm (phenyl-label study), and 195 ppm (triazole-label study) in the diet. The goats were dosed once per day for 3 consecutive days. Milk was collected twice daily throughout the studies, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice. Residues were characterized primarily by HPLC analysis, using TLC analyses for confirmation and LC-MS/MS analyses for identification of metabolites. These methods successfully identified the predominant residues in the major extract of each goat matrix. Additionally, adequate storage stability data were submitted demonstrating the stability of the metabolite profile in goat samples and extracts for the duration of the studies.

Phenyl-label study:
The recovered radioactivity accounted for 67.57% of the administered dose. A total of 0.02% of the radioactivity was recovered in milk (0.020-0.071 ppm), while 0.96% was present in the tissues and organs (6.092 ppm in liver, 6.762 ppm in kidney, 0.084-0.106 ppm in muscle, and 0.149-0.172 ppm in fat). Approximately 66% of the total administered dose was excreted in urine and feces. The remaining administered dose was assumed to be absorbed from the intestinal tract prior to excretion. Prothioconazole was monophasically eliminated from plasma with a half-life of 5.3 hours, and the mean residence time (MRT) in plasma was 8.2 hours.

Approximately 29-71% of the TRRs were identified in goat matrices. Prothioconazole was found to be a major residue in liver, kidney, muscle, and fat at 12.94-17.97% of the TRRs (0.012-1.215 ppm), and at 0.89% of the TRRs (<0.001 ppm) in milk. JAU6476-*O*- or *S*-glucuronide and JAU6476-3-hydroxy-desthio were major metabolites in milk and tissues at 34.32% of the TRRs (2.321 ppm) in kidney, and 10.02-14.80% of the TRRs (0.004-0.610 ppm)

in the other matrices. JAU6476-desthio was a major metabolite in fat at 18.98% of the TRRs (0.032 ppm), but <3% of the TRRs (<0.087 ppm) in the other matrices. JAU6476-4-hydroxy was identified at 11.21% of the TRRs (0.683 ppm) in liver, and at <5% of the TRRs (#0.210 ppm) in other goat matrices. Minor metabolites, each at <8% of the TRRs (<0.51 ppm included): JAU6476-4-hydroxy-glucuronide, JAU6476-hydroxy-glucuronide, JAU6476-4-hydroxy-desthio, and JAU6476-*N*-glucuronide. This also included glucuronic acid conjugates of JAU6476-desthio, JAU6476-hydroxy-desthio, JAU6476-dihydroxy-desthio, and JAU6476-hydroxymethoxy-desthio, JAU6476-dihydroxy-diene and JAU6476-desthio-dihydroxy-diene. Unknowns accounted for <8% of the TRRs (<0.182 ppm) in milk, liver, and fat. Accountabilities were normalized to 100%. Non-extractable residues accounted for 16-23% of the TRRs (#0.04 ppm) in milk, muscle, and fat; <3% of the TRRs (0.17 ppm) in kidney; and 17% of the TRRs (1.0 ppm) in liver. The applicant did not attempt to release the non-extractable residues in liver, but it is concluded that an adequate percentage of the TRR was released from liver.

Based on the results of the phenyl-label study, the applicant concluded that prothioconazole is metabolized in goats via several steps: conjugation of the unchanged parent compound with glucuronic acid resulting in an *S*- or *O*-glucuronide; additional glucuronidation of the triazole-thione nitrogen atom of the parent compound to form JAU6476-*N*-glucuronide; hydroxylation of the parent compound to form JAU6476-4-hydroxy and a further hydroxy isomer, followed by conjugation with glucuronic acid; oxidation of the phenyl ring of the parent compound to form JAU6476-dihydroxy-diene; elimination of sulfur to form JAU6476-desthio; further hydroxylation of the chlorophenyl moiety to form JAU6476-3-hydroxy-desthio and JAU6476-4-hydroxy-desthio, followed by conjugation with glucuronic acid; and oxidation of the chlorophenyl moiety of JAU6476-desthio to form JAU6476-desthio-dihydroxy-diene. The presence of JAU6476-dihydroxy-desthio-glucuronides indicated that isomers of JAU6476-dihydroxy-desthio were formed as intermediates. Methylation of JAU6476-hydroxy-desthio-glucuronides to form JAU6476-hydroxymethoxy-desthio-glucuronides occurred to a small extent, as did the glucuronidation of JAU6476-desthio.

Triazole-label study:
The recovered radioactivity accounted for 59.52% of the administered dose. A total of 0.03% of the radioactivity was recovered in milk (0.080-0.249 ppm), while 0.74% was present in the tissues and organs (6.248 ppm in liver, 4.507 ppm in kidney, 0.115-0.142 ppm in muscle, and 0.109-0.213 ppm in fat). Approximately 58% of the total administered dose was excreted in urine and feces. The remaining administered dose was assumed to be absorbed from the intestinal tract prior to excretion. Prothioconazole was monophasically eliminated from plasma with a half-life of 7 hours, and the mean residence time (MRT) in plasma was 10.6 hours.

Approximately 61-84% of the TRRs were identified in goat matrices. Prothioconazole was found to be a major residue in liver, kidney, and fat at 16.12-19.50% of the TRRs (0.028-1.047 ppm), at 3.18% of the TRRs (0.005 ppm) in milk, and at 7.17% of the TRRs (0.008 ppm) in muscle. Thiocyanate accounted for 9.01-41.12% of the TRRs (0.022-0.406 ppm) in milk, kidney, muscle and fat; and at 2.04% of the TRRs (0.128 ppm) in liver. Radioactivity corresponding to 10.76% of the TRRs (0.016 ppm) was attributed to lactose in milk. JAU6476-*S*-glucuronide and JAU6476-3-hydroxy-desthio were major metabolites in kidney, muscle and

fat at 11.92-33.85% of the TRRs (0.016-1.526 ppm), and in milk and liver at <6.1% of the TRRs (<0.38 ppm). JAU6476-desthio was a major metabolite in fat at 15.11% of the TRRs (0.026 ppm), and <5% of the TRRs (<0.31 ppm) in other goat matrices. Other metabolites included JAU6476-4-hydroxy (10.97% of the TRRs; 0.686 ppm) in liver, and <8.5% of the TRRs (<0.164 ppm) in other goat matrices; and JAU6476-hydroxy-glucuronide at 11.15% of the TRRs (0.019 ppm) in fat , but <7% of the TRRs (<0.32 ppm) in other goat matrices. Minor metabolites, each at <7% of the TRRs (<0.41 ppm) included: JAU6476-4-hydroxy-glucuronide, JAU6476-hydroxy sulfate and sulfate conjugate, JAU6476-lactoside, JAU6476-4-hydroxy-desthio, JAU6476-*N*-glucuronide, and JAU6476-*S*-methyl. Unknown metabolites accounted for 5.1-11.0% of the TRRs (<0.32 ppm) in liver and kidney. Accountabilities were normalized to 100%. Non-extractable residues accounted for 16-23% of the TRRs (≤0.04 ppm) in milk, muscle, and fat; <6% of the TRRs (0.237 ppm) in kidney; and ~10% of the TRRs (0.662 ppm) in liver. The non-extractable residues of liver were subjected to microwave extraction which released an additional 4.1% of the TRRs (0.256 ppm).

Based on the results of the submitted goat metabolism studies with prothioconazole, it is concluded that prothioconazole is metabolized in goats via several steps: conjugation of the triazolinethione moiety of the parent compound with glucuronic acid to form the *S*-glucuronide and *N*-glucuronide of the parent; elimination of sulfur to form the metabolite JAU6476-desthio; oxidative hydroxylation of the phenyl moiety in prothioconazole and JAU6476-desthio to monohydroxy, dihydroxy, and dihydroxy-diene compounds, partly followed by conjugation with glucuronic acid; conjugation of the triazolinethione moiety of the parent compound with lactose; conjugation of hydroxylated metabolites of prothioconazole with sulfate; methylation of the triazolinethione moiety of prothioconazole to form JAU6476-*S*-methyl; and cleavage of the parent compound to form thiocyanate.

Goat - (MRID 46246201):

Bayer CropScience has submitted a study investigating the metabolism of [phenyl-UL-^{14}C]JAU6476-desthio (specific activity 0.397 MBq/mg) in a lactating goat; JAU6476-desthio is a metabolite of prothioconazole. The test substance was administered orally to a single goat at 195 ppm in the diet. The goat was dosed once per day for 3 consecutive days. Milk was collected twice daily throughout the study, and tissues (muscle, fat, liver, and kidney) were collected at sacrifice.

Total radioactive residues (TRR) were 0.074-0.31 ppm in milk, 18 ppm in liver, 19 ppm in kidney, 0.23 -0.28 ppm in muscle, and 0.22-0.24 ppm in fat. Radioactivity was highest in liver and kidney and lowest in fat. Residues in milk were generally highest in samples collected 8 hours after dosing, and did not appear to have reached a plateau by the end of the dosing period. A large portion of the administered dose was excreted, with urine and feces accounting for a total of ~74% of the administered dose. Residues were characterized primarily by HPLC analysis, using TLC analyses for confirmation and LC/MS/MS analyses for identification of metabolites. These methods successfully identified the predominant residues in goat matrices, except for liver.

Analysis of the methanol (organic) extracts was completed within 3 months of sample collection for all matrices except milk; analysis of the evening milk extract was completed

within 6 months of sample collection. Additional extractions and analyses of milk and muscle samples were conducted 17-19 months after sample collection to allow for metabolite identification; comparison of the HPLC or HPTLC profiles of the organic extracts with those of the initial extracts indicated that the metabolite profile was stable during storage. The submitted storage stability information and data are adequate to support the goat metabolism study.

Approximately 60-75% TRR were identified in goat matrices. The test substance, JAU6476-desthio, was found to be a major residue in liver and fat, at 31% TRR (5.7 ppm) and 14% TRR (0.032 ppm), respectively. JAU6476-desthio was *not* found in milk and was found in kidney and muscle at <8% TRR. JAU6476-desthio-glucuronide was the major metabolite in kidney, at 24% TRR (4.567 ppm); this metabolite was also found in milk, muscle, and fat, at <7% TRR. Sulfate conjugates of JAU6476-dihydroxy-desthio, JAU6476-hydroxy-methoxy-desthio, and JAU6476-hydroxy-desthio together accounted for 44% TRR in milk; these conjugates were not detected in goat tissues. One diastereomer of JAU6476-desthio-3,4-dihydroxy-dienyl-glucuronide was a major residue in kidney, muscle, and fat, at 13-15% TRR (0.034-2.6 ppm), and was a minor residue in milk and liver (<4% TRR); a second diastereomer of this metabolite was found in all goat matrices, at <9% TRR. JAU6476-4-hydroxy-desthio was a major metabolite in fat, at 15% TRR (0.034 ppm); this metabolite was also found in liver, kidney, and muscle, at <9% TRR. Several additional metabolites were identified in goat matrices, each at <8% TRR: JAU6476-desthio-3,4-dihydroxy-diene in all matrices; glucuronides of JAU6476-dihydroxy-desthio, JAU6476-4,5-dihydroxy-desthio, JAU6476-3-hydroxy-desthio, JAU6476-4-hydroxy-desthio, and JAU6476-hydroxy-methoxy-desthio in all matrices; JAU6476-dihydroxy-desthio in milk, liver, muscle, and fat; JAU6476-4,5-dihydroxy-desthio in milk, liver, and muscle; and JAU6476-3-hydroxy-desthio in liver, kidney, and muscle. Unknown metabolites accounted for a significant portion of the radioactivity in liver and kidney (11.0-14.5% TRR); however, HPLC analyses indicated that individual unknowns were $\leq$5.1% TRR.

Goat Metabolism Summary:
The goat metabolism data are adequate to satisfy data requirements. Based on the results of the goat metabolism studies, it is concluded that prothioconazole is metabolized in goats via several steps: conjugation of the unchanged parent compound with glucuronic acid resulting in an *S*- or *O*-glucuronide; additional glucuronidation of the triazole-thione nitrogen atom of the parent compound to form JAU6476-*N*-glucuronide; hydroxylation of the parent compound to form prothioconazole-4-hydroxy and a further hydroxy isomer, followed by conjugation with glucuronic acid; oxidation of the phenyl ring of the parent compound to form JAU6476-dihydroxy-diene; elimination of sulfur to form prothioconazole desthio; further hydroxylation of the chlorophenyl moiety to form JAU6476-3-hydroxy-desthio and JAU6476-4-hydroxy-desthio, followed by conjugation with glucuronic acid; oxidation of the chlorophenyl moiety of prothioconazole desthio to form JAU6476-desthio-dihydroxy-diene; conjugation of the triazolinethione moiety of the parent compound with lactose; conjugation of hydroxylated metabolites of prothioconazole with sulfate; methylation of the triazolinethione moiety of prothioconazole to form JAU6476-*S*-methyl; and cleavage of the parent compound to form thiocyanate. The presence of JAU6476-dihydroxy-desthio-glucuronides indicated that isomers of JAU6476-dihydroxy-desthio were formed as intermediates. Methylation of JAU6476-hydroxy-desthio-glucuronides to form JAU6476-hydroxymethoxy-desthio-glucuronides occurred to a small extent, as did the glucuronidation of prothioconazole desthio.

The transfer factor (concentration in milk or tissue (ppm) / concentration in feed (ppm)) was generally greater for the [phenyl-UL-^{14}C]JAU6476-desthio metabolite than for the [phenyl-UL-^{14}C]-prothioconazole over the 3 day study period, as summarized:

Chemical	Liver[1]	Kidney[1]	Muscle[1]	Fat[1]	Milk[1]
Prothioconazole + Prothioconazole desthio + Conjugates					
Prothioconazole	6.4	15	0.12	0.29	0.029
Prothioconazole desthio	29	31	0.072	0.22	0.092
4-Hydroxy prothioconazole + 4-Hydroxy prothioconazole desthio + Conjugates					
Prothioconazole	4.6	2.0	0.024	0.041	0.0032
Prothioconazole desthio	10	11	0.12	0.23	0.077

[1] X 10^{-3}

These factors suggest that the feeding of prothioconazole desthio may yield higher residues in livestock commodities than the feeding of prothioconazole. Given that plant metabolism studies generally show a high conversion of prothioconazole to desthtio prothioconazole, feeding studies with both prothioconazole and prothioconazole desthio are evaluated to provide a conservative estimate of residues in livestock commodities (see below).

Hen - MRID 46246202/46246203:

Phenyl-label study

Six laying hens were administered [phenyl-UL-^{14}C]-JAU6476 (0.732 MBq/mg) orally at a mean dose of 9.7 mg/kg b.w. once a day for three consecutive days (corresponding to 171 ppm in the feed). Excreta was collected every 24 hours. Cages were checked for egg production twice daily, and all eggs collected. Five hours after the final dose (53 hours after the initial dose) the hens were sacrificed. Liver (without bile bladder), kidney, leg muscle, breast muscle, skin, subcutaneous fat and eggs from the ovary and oviduct were dissected from the hens. All samples were assayed for total radioactivity by liquid scintillation counting, either directly or by sample combustion. The identification and characterization of metabolites was achieved by high performance liquid chromatography following solvent extraction of tissues.

In [phenyl-UL-^{14}C]-JAU6476 treated hens, the recovered radioactivity accounted for 79.28% of the administered dose. Approximately 78.42% of the administered dose (%AD) was eliminated in the excreta. A total of 0.011 % AD was recovered in eggs, while 0.85% was estimated to have been present in the tissues and organs. A significant portion of the administered dose was absorbed from the intestinal tract prior to excretion, as indicated by the high residue concentrations in the kidney and liver.

Kidney and liver were found to contain the highest total radioactive residues (TRRs), 4.537 ppm and 4.081 ppm, respectively. TRRs in other tissues were 0.597, 0.433, 0.383, 0.107 and 0.058 ppm for eggs from the ovary and oviduct, subcutaneous fat, skin, leg muscle and breast muscle respectively. The major metabolites identified were the parent JAU6476 in muscle (11.33% of the TRRs; 0.010 ppm), fat (30.33% of the TRRs; 0.137 ppm) and liver (24.76% of the TRRs; 0.995 ppm); JAU6476-desthio in fat (28.96% of the TRRs; 0.130 ppm) and eggs (20.13% of the

TRRs; 0.007 ppm); JAU6476-*S*- methyl in fat (19.56% of the TRRs; 0.088 ppm); a glucuronide conjugate of the parent JAU6476 in muscle (15.50% of the TRRs; 0.014 ppm), liver (11.93% of the TRRs; 0.479 ppm) and eggs (16.98% of the TRRs; 0.006 ppm); and sulfate conjugates of hydroxylated JAU6476-desthio in liver (11.07% of the TRRs; 0.445 ppm). Minor metabolites (< 10% of the TRRs) included JAU6476-desthio-3,4-dihydroxy-dienyl-glucuronide, JAU6476-4-hydroxy, JAU6476-4- hydroxy-desthio, JAU6476-*N*-glucuronide, JAU6476-hydroxy-glucuronides and JAU6476- dihydroxy-diene. Attempts were made to further release the bound liver residues by ultrasonic and microwave extractions in the presence of methanol and acidic methanol. These efforts released an additional 6.4% (0.257 ppm) of the TRRs in the liver, leaving 14.4% (0.579 ppm) of the TRRs as non-extractable residues. Total accountabilities ranged from 97-101%.

Triazole-label study

Six laying hens were treated with [triazole-UL-^{14}C]- JAU6476 (0.702 Mbq/mg) orally at a mean dose of 10.4 mg/kg b.w. once daily for three consecutive days (corresponding to 163 ppm in the feed). Excreta was collected every 24 hours. Cages were checked for egg production twice daily, and all eggs collected. Five hours after the final dose (53 hours after the initial dose) the hens were sacrificed. Liver (without bile bladder), kidney, leg muscle, breast muscle, skin, subcutaneous fat and eggs from the ovary and oviduct were dissected from the hens. All samples were assayed for total radioactivity by liquid scintillation counting, either directly or by sample combustion. The identification and characterization of metabolites was achieved by high performance liquid chromatography following solvent extraction of tissues. Mass spectroscopy and ^{1}H-NMR were used to identify a single metabolite in the triazole-label study.

The recovered radioactivity accounted for 66.37% of the administered dose. A large fraction of the administered dose in the [triazole-UL-^{14}C] JAU6476-treated hens was eliminated in the excreta (65.61%). A total of 0.014% of the radioactivity was recovered in eggs, while 0.75% was present in the tissues and organs. A significant portion of the administered dose was absorbed from the intestinal tract prior to excretion, as indicated by the high residue concentrations in the kidney and liver.

Liver and kidney were found to contain the highest mean residues at 3.447 and 3.381 ppm respectively. Mean residues detected in other tissues represented 0.623, 0.342, 0.308, 0.139 and 0.096 ppm for eggs from the ovary and oviduct, subcutaneous fat, skin, leg muscle and breast muscle respectively. The major metabolites identified were parent JAU6476 in fat (15.9% of the TRRs; 0.046 ppm) and liver (30.7% of the TRRs; 1.085 ppm); JAU6476-desthio in fat (26.8% of the TRRs; 0.078 ppm); JAU6476-*S*-methyl in fat (28.5% of the TRRs; 0.083 ppm); JAU6476-*S*-glucuronide in liver (14.9% of the TRRs; 0.526 ppm) and eggs (23.7% of the TRRs; 0.012 ppm); sulfate conjugates of hydroxylated JAU6476-desthio in liver (13.5% of the TRRs, 0.474 ppm); 1*H*-1,2,4-triazole in muscle (18.7% of the TRRs; 0.023 ppm) and eggs (11.4% of the TRRs; 0.006 ppm); and JAU6476-triazolyl-ethanol in muscle (28.3% of the TRRs; 0.035 ppm) and eggs (15.6% of the TRRs; 0.008 ppm). Minor metabolites (<10% of the TRRs) included JAU6476-4-hydroxy, JAU6476-4-hydroxy-desthio, JAU6476-*N*-glucuronide and thiocyanate. Attempts were made to further release the bound liver residues by ultrasonic and microwave extractions in the presence of methanol and acidic methanol. These efforts

released an additional 5.7% (0.202 ppm) of the TRRs in the liver, leaving 12.7% (0.448 ppm) of the TRRs as non-extractable residues. Accountabilities ranged from 100-102%.

The fact that the highest mean residues were found in the kidney and liver indicates that a significant fraction of the administered dose is absorbed through the intestine prior to excretion.

JAU6476 was extensively metabolized following the oral administration of [phenyl-UL-^{14}C] JAU6476 or [triazole-UL-^{14}C] JAU6476 to laying hens. The major metabolic pathways were:

- conjugation of the unchanged parent compound with glucuronic acid forming an *S*-glucuronide,
- methylation of the sulfur atom to form JAU6476-*S*-methyl,
- desulfuration of JAU6476 yielding JAU6476-desthio followed by hydroxylation and conjugation with sulfate, and
- cleavage of the chlorobenzylic group of JAU6476-desthio to JAU6476-triazolyl-ethanol and release of 1*H*-1,2,4-triazole.

Several minor metabolic processes were also elucidated. These minor pathways were:

- conjugation of JAU6476 to the *N*-glucuronide,
- hydroxylation of JAU6476 followed by glucuronidation,
- cleavage of the triazolinthione moiety of JAU6476 to yield thiocyanate,
- hydroxylations of JAU6476 and JAU6476-desthio and reduction of the phenyl ring to the corresponding dihydroxy-dienes followed by conjugation with glucuronic acid, and
- further hydroxylation of JAU6476-4-hydroxy-desthio followed by methylation and/or sulfate conjugation.

Hen Metabolism Summary: The hen metabolism data are adequate to satisfy data requirements. Based on the study results, the applicant concluded that prothioconazole is metabolized in hens via several steps: conjugation of the unchanged parent compound with glucuronic acid to form an S- (more likely) or an O-glucuronide; methylation of the triazolinethione moiety to form JAU6476-S-methyl; elimination of sulfur to form the metabolite prothioconazole desthio; hydroxylation of the chlorophenyl moiety of the metabolite prothioconazole desthio to form JAU6476-4-hydroxy-desthio and possibly JAU6476-3-hydroxy-desthio, followed by conjugation with sulfate; oxidation of the chlorophenyl moiety of prothioconazole desthio, followed by conjugation with glucuronic acid, to form JAU6476-desthio-3,4-dihydroxy-dienyl-glucuronide; cleavage of the aliphatic carbon chain to form 1,2,4-triazole and JAU6476-triazolylethanol; cleavage of the triazolinethione moiety to form thiocyanate; hydroxylation of the parent compound to form prothioconazole-4-hydroxy; glucuronidation of a triazolinethione nitrogen atom of the parent compound to form JAU6476-N-glucuronide; and, to a small extent, methylation of JAU6476-hydroxy-desthio to form JAU6476-hydroxymethoxy-desthio-glucuronides. The presence of sulfate conjugates of JAU6476-dihydroxy-desthio and JAU6476-hydroxymethoxy-desthio indicated that JAU6476-dihydroxy-desthio and JAU6476-hydroxymethoxy-desthio were formed as intermediates.

Overall Livestock Metabolism Conclusions: The metabolic pathway for JAU6476 was evaluated in livestock following three consecutive daily oral doses of [phenyl-UL-^{14}C] JAU6476 or

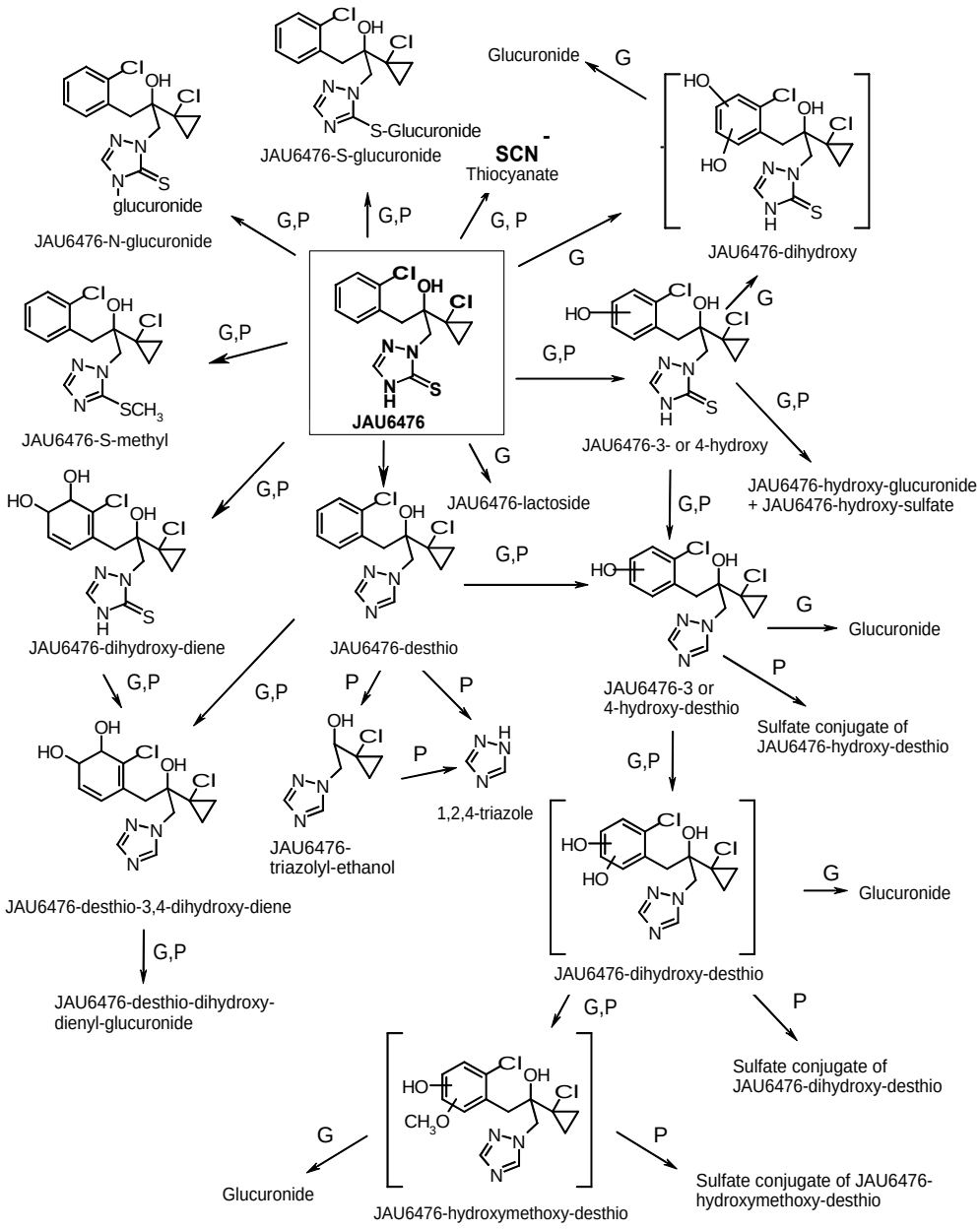
[triazole-UL-^{14}C] JAU6476 to lactating goats and laying hens. Some qualitative and quantitative differences between goats and laying hens were observed. These differences were:

- cleavage of JAU6476 and JAU6476-desthio to release 1,2,4-triazole and triazolylethanol occurred in poultry, but these metabolites were not found in goats (1,2,4-triazole was also found in rats following an oral dose of [triazole-UL-^{14}C] JAU6476),
- methylation of the sulfur atom of the parent compound was a major metabolic process in poultry, but was only a minor pathway in goats,
- cleavage of the triazolinthione ring to yield thiocyanate was a major metabolic process in goats, but was only a minor pathway in poultry, and
- conjugation of JAU6476 with lactose occurred in goats.

With the exception of the above-mentioned differences, the metabolism of JAU6476 was very similar in all livestock. Conjugation of the unchanged parent compound with glucuronic acid forming an S-glucuronide and desulfurization of JAU6476 yielding JAU6476-desthio were major metabolic processes in both poultry and goats. However, the majority of the metabolites found in poultry and goats were products of hydroxylations of JAU6476 and its desthio metabolite (probably through epoxide intermediates) leading to the formation of the corresponding dihydroxy and dihydroxy-dienes.

In goats, the di-hydroxylated metabolites (JAU6476-dihydroxy and JAU6476-desthio-dihydroxy-diene) were further conjugated with glucuronic acid; in poultry, the sulfate and glucuronic acid conjugates of the di-hydroxylated JAU6476-desthio metabolites were formed. Sulfate and glucuronic acid conjugation of JAU6476-3/4-hydroxy and methylation of JAU6476-dihydroxy-desthio occurred in both poultry and goats.

It is concluded that for tolerance enforcement in livestock commodities the residue of concern consists of 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 in livestock commodities, the residue of concern consists 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 hydroysis. Additionally, contribution of triazole derivatives (in poultry commodities) from the use of prothioconazole to the aggregate exposure for human-health risk assessment has been considered (D322215, 02/07/2006).



P = poultry G = goat

Figure 2. Proposed metabolic pathway for JAU6476 in livestock.

860.1340 Residue Analytical Methods

46246206.der.wpd (Plants; also includes review of MRIDs 46246208 and 46246209)
46246215.de2.wpd (Plants)
46477702.der.wpd (Plants; also includes review of MRID 46477703)
46246204.der.wpd (Livestock; also includes review of MRIDs 46246205 and 46246207)
46477704.der.wpd (Livestock; also includes review of 860.1340 data from MRID 46246201)

Plant commodity methods

Enforcement method: Bayer CropScience has proposed the high performance liquid chromatography (with electrospray ionization) and tandem mass spectrometry (LC-MS/MS) method RPA JA/03/01 for data gathering and the enforcement of maximum residue limits (MRLs) for residues of prothioconazole (JAU6476) and the prothioconazole desthio metabolite (JAU6476-desthio) in plant commodities. The LC-MS/MS method is entitled "An Analytical Method for the Determination of Residues of JAU 6476 and desthio-JAU 6476 in Plant Matrices Using LC/MS/MS."

In the method, crop matrices are extracted with a mixture of methanol, 30% hydrogen peroxide, and 5% aqueous sodium bicarbonate at 65°C for 2 hours. Prothioconazole is converted to both prothioconazole sulfonic acid and prothioconazole desthio because of this oxidative extraction procedure. The prothioconazole desthio metabolite remains unchanged after extraction. The cooled extract is spiked with an isotopically labeled internal standard, cleaned up by C18 solid-phase extraction (SPE), and mixed with either 0.1% formic acid or 1% acetic acid for analysis by LC-MS/MS. The results for prothioconazole sulfonic acid and prothioconazole desthio are reported in prothioconazole equivalents and then totaled to yield "total prothioconazole derived residues." The validated LOQs reported in the method are 0.02 ppm for canola seed, peanut nutmeat, and wheat grain; and 0.05 ppm for dried peas, wheat forage, wheat hay, and wheat straw. The calculated LODs range from 0.002-0.005 ppm for prothioconazole and prothioconazole desthio in canola seed, dried peas, peanut nutmeat, and wheat (forage, hay, straw, and grain); and from 0.002-0.007 ppm for prothioconazole sulfonic acid in these same commodities.

Concurrent recovery data from the crop field trials, as well as data from the method validation study adequately bracket the expected residue levels. Method validation data demonstrate adequate method recoveries of prothioconazole, prothioconazole sulfonic acid, and prothioconazole desthio at 0.020 ppm (LOQ) and 0.1 ppm, respectively, for canola seed, peanut nutmeat, and wheat grain; and at 0.05 ppm (LOQ) and 1.0 ppm, respectively, for dried peas, wheat forage, wheat hay, and wheat straw. The ranges of recoveries (and CVs) from these matrices are 71-91% (5.4%) for prothioconazole, 76-102% (5.8%) for prothioconazole sulfonic acid, and 85-106% (4.5%) for prothioconazole desthio over all matrices and spiking levels. Adequate extraction efficiency data have been submitted for the method using samples of sugar beet tops and wheat forage. Adequate independent laboratory validation data have been

submitted for the method using samples of peanut nutmeat and wheat forage from the plant metabolism studies. Confirmatory analysis procedures were not conducted for the proposed enforcement method.

The proposed enforcement method for plant commodities has been successfully validated by the EPA ACL. However, the sponsor needs to modify the method to include at least two multiple reaction monitoring (MRM) transitions. A single MS/MS ion transition as used in the current version of the method is no longer considred sufficient for positive confirmation of the analyte residue.

Data collection methods: The proposed LC-MS/MS enforcement method was used to determine residues of prothioconazole and prothioconazole desthio in/on samples of plant commodities from the crop field trial, processing, and field rotational crop studies associated with DP Barcode D303508. The proposed enforcement method was also used to determine residues of prothioconazole and prothioconazole desthio in the majority of samples from storage stability studies reported in MRID 46477701.

Additional data collection methods: An LC-MS/MS method, Method No. 00598, was used to determine residues of prothioconazole and prothioconazole desthio in one storage stability study (MRID 46246139) and in certain samples from another storage stability study (MRID 46477701). Bayer has submitted a description of Method No. 00598 and its modification 00598/M001; the method determines residues of prothioconazole and its metabolite prothioconazole desthio in cereal grain and canola commodities.

For Method No. 00598, cereal grain matrices are extracted with ACN/water containing cysteine HCl; cysteine HCl is added as an antioxidant to prevent degradation of prothioconazole. The extract is partitioned with n-hexane, and the resulting aqueous phase is partitioned with dichloromethane. The dichloromethane phase is concentrated and diluted with ACN and water for LC/MS/MS analysis.

Method No. 00598/M001 includes instructions for the analysis of cereal grain and canola matrices. The extraction procedures are the same as for Method No. 00598 except that internal standards prothioconazole-$^{15}N_3$-$^{13}C_2$ and prothioconazole desthio-$^{15}N_3$-$^{13}C_2$ are added to the final sample extract just prior to LC-MS/MS analysis.

The validated LOQs are 0.01 ppm for each analyte in cereal grain and canola seed and 0.05 ppm for each analyte in all other matrices. The calculated LODs ranged 0.0008-0.0304 ppm.

Method validation data for Method No. 00598 demonstrated adequate method recoveries of prothioconazole and prothioconazole desthio at 0.01 ppm (LOQ) and 0.10 ppm for barley and wheat grain, and at 0.05 ppm (LOQ), 0.50 ppm, and 5.0 ppm for barley and wheat forage and straw. Recovery ranges (and CVs) from these matrices were 67-112% (9.1%) for prothioconazole and 72-104% (7.1%) for prothioconazole desthio. Method validation data for Method No. 00598/M001 demonstrated adequate method recoveries of prothioconazole and prothioconazole desthio at 0.01 and 0.10 ppm for barley and wheat grain and canola seed, and at 0.05, 0.50, and 5.0 ppm for barley and wheat forage and straw and canola forage, straw, and

pod. Recovery ranges (and CVs) from these matrices were 65-118% (10.2%) for prothioconazole and 64-98% (6.5%) for prothioconazole desthio.

Based on the method validation data, the method is adequate for data collection purposes. However, HED notes that in conjunction with the storage stability study reported in MRID 46477701, the applicant concluded that Method No. 00598 was not adequate for the determination of weathered residues of prothioconazole.

Bayer CropScience has submitted a high performance liquid chromatography (with electrospray ionization) and tandem mass spectrometry (LC-MS/MS) data gathering method for the determination of residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid in plant commodities. The method was not submitted as a separate study but was submitted as an appendix to the crop field trial, processing, and limited field rotational crop studies submitted under DP Barcode D303508. The LC-MS/MS method, entitled "Working Residue Analytical Method for the Determination of Triazole, Triazole Alanine, and Triazole Acetic Acid Residues in Dried Pea, Dried Bean, Rice, Barley, Wheat, Canola, Peanut, Mustard Greens, and Turnip Matrices," was used to determine residues of 1,2,4-triazole, triazolylalanine, and triazolylacetic acid in/on samples of plant commodities from the crop field trial, processing, and field rotational crop studies associated with DP Barcode D303508.

In the method, crop matrices are extracted with aqueous methanol, and three separate aliquots of the extract are removed for determination of each of the three analytes. Isotopically labeled internal standard is added to each aliquot. For 1*H*-1,2,4-triazole, the aliquot is mixed with dansyl chloride to form the dansyl derivative of 1*H*-1,2,4-triazole, which is partitioned into ethyl acetate and then redissolved in acetonitrile (ACN)/water (1:1, v:v) for LC-MS/MS analysis. For triazolylalanine, the aliquot is cleaned up by solid-phase extraction (SPE), derivatized to the butyl ester using butanolic HCl, and then further derivatized using heptafluorobutyric anhydride (HFBA). The mixture is redissolved in ACN/water (1:1, v:v) for LC-MS/MS analysis. For determination of triazolylacetic acid, the aliquot is cleaned up by SPE, derivatized to the butyl ester using butanolic HCl, and then redissolved in ACN/water (1:1, v:v) for LC-MS/MS analysis. In the crop field trial, processing, and field rotational crop studies, the LOQ has been determined from the lowest spiking level with adequate recovery. Validated LOQs range from 0.01-0.05 ppm for 1*H*-1,2,4-triazole and 0.01-1.5 ppm for triazolylalanine and triazolylacetic acid. The calculated LODs range from 0.001 ppm to values that are greater than the reported LOQs for certain matrices. When the calculated LOD exceeded the reported LOQ, the LODs were set at the LOQ value.

Method validation and concurrent method recovery data for the method demonstrated generally acceptable accuracy/precision for barley (grain, hay, and straw), canola (seed, meal, and refined oil), mustard greens, dried shelled bean, dried shelled pea, peanut (nutmeat, hay, meal, refined oil, dry roasted peanuts, and peanut butter), rice (grain, straw, polished grain, bran, and hulls), turnip (top and root), and wheat (forage, hay, grain, straw, aspirated grain fractions, bran, flour, germ, middlings, and shorts). The spiking levels for these commodities range from 0.01-0.5 ppm for 1*H*-1,2,4-triazole, 0.01-4.5 ppm for triazolylalanine, and 0.01-0.8 ppm for triazolylacetic acid. Recovery ranges (and SD) from these matrices were 59-119% (11%) for

1*H*-1,2,4-triazole, 64-126% (10%) for triazolylalanine, and 67-119% (11%) for triazolylacetic acid.

The spiking levels and samples used in method validation are sufficiently representative of the expected residue levels for the plant commodities. Extraction efficiency has not been demonstrated for plant matrices at this time. The method is not being proposed for enforcement purposes, and as such, independent laboratory validation data is not required.

Conclusions: An HPLC-MS/MS method was developed and proposed for data gathering and enforcement purposes. In plant matrices, an oxidative extraction procedure converts prothioconazole residues to a mixture of desthio prothioconazole and prothioconazole sulfonic acid. The results are reported as prothioconazole equivalents. The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70 to 120%) were obtained in plant matrices. Adequate extraction efficiencies were demonstrated using radiolabeled wheat forage, and sugarbeet tops analyzed with the enforcement method. The method has undergone a successful tolerance method validation by EPA ACL.

Based on information reported by the applicant, RAB3 concludes that Method No. 00598 and its modification 00598/M001 should not be used for data collection purposes.

Livestock commodity methods

Enforcement method: Bayer CropScience has proposed a high performance liquid chromatography (with electrospray ionization) and tandem mass spectrometry (LC-MS/MS) method for the data gathering and enforcement of maximum residue limits for residues of prothioconazole, prothioconazole desthio (JAU6476-desthio), prothioconazole-4-hydroxy (JAU6476-4-hydroxy), and conjugates that may be converted to these compounds by acid hydrolysis, in milk and cattle tissues.

Briefly, samples of bovine liver, kidney, and muscle are extracted with acetonitrile (ACN)/water and 25% aqueous L-cysteine HCl. An internal standard solution is added to the extract. The internal standard solution consists of a mixture of [triazole-$^{15}N_3$-$^{13}C_2$]-prothioconazole, [triazole-$^{15}N_3$-$^{13}C_2$]-prothioconazole desthio, and [triazole-$^{15}N_3$-$^{13}C_2$]-prothioconazole-4-hydroxy in ACN containing 50 µg/mL L-cysteine HCl. Fat samples are extracted with n-hexane and then with a mixture of ACN, 25% aqueous L-cysteine HCl, and acetone; the combined extracts are allowed to separate, and internal standard solution is added to the aqueous phase. Samples of milk and cream are mixed with internal standard solution directly. For all matrices, the extract/sample is hydrolyzed using aqueous HCl, and the hydrolysate is partitioned with methylene chloride and acetone. The organic phase is concentrated to aqueous, mixed with ACN and water, and analyzed by LC-MS/MS. Samples are analyzed for residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy, and all results are reported in prothioconazole equivalents. The validated LOQs are 0.005 ppm for each analyte in milk; 0.010 ppm for each analyte in skim milk, cream, muscle, liver, and kidney; and 0.050 ppm for each analyte in fat. The calculated LODs range from

0.0007-0.0021 ppm for milk, 0.001-0.0019 ppm for skim milk, 0.0021-0.0035 ppm for cream, 0.0006-0.001 ppm for muscle, 0.0005-0.0029 ppm for liver, 0.0021-0.0025 ppm for kidney, and 0.0041-0.0115 ppm for fat.

Method validation data (and concurrent recovery data from the livestock feeding study) for the proposed enforcement method has demonstrated adequate method recoveries of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy at 0.005 ppm (LOQ) and 0.010 ppm for milk; 0.010 ppm (LOQ) for skim milk, cream, and muscle; 0.010 ppm (LOQ) and 0.60 ppm for liver; 0.010 ppm (LOQ), 0.050 ppm, and 0.80 ppm for kidney; and 0.050 ppm (LOQ) and 0.080 ppm for fat. The range of recoveries (and CVs) are 77-115% (9.1%) for prothioconazole, 91-117% (6.0%) for prothioconazole desthio, and 63-117% (14.7%) for prothioconazole-4-hydroxy over all matrices and spiking levels. The spiking levels and samples used in method validation and concurrent method recovery are adequate to bracket expected residue levels in milk and livestock tissues for residues of prothioconazole, prothioconazole desthio, prothioconazole-4-hydroxy, and conjugates that may be converted to these compounds by acid hydrolysis.

Adequate extraction efficiency data have been submitted for the method using samples of goat milk, muscle, liver, and fat. Adequate independent laboratory validation data have been submitted for the method using samples of cattle milk and liver. Confirmatory analysis procedures have not been conducted for the proposed enforcement method.

The proposed enforcement method has been validated by EPA ACL. Acceptable recoveries were achieved for cattle liver fortified at 0.010 mg/kg with each of prothioconazole, prothioconazole desthio, and 4-hydroxy prothioconazole. Acceptable recoveries were also achieved for milk fortified with each of these three compounds at 0.005 mg/kg. However, the method needs to be modified to include at least two multiple reaction monitoring (MRM) transitions. A single MS/MS ion transition as used in the current version of the method is no longer considred sufficient for positive confirmation of the analyte residue.

Data collection methods: The proposed enforcement method was used for the determination of residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy in milk and cattle tissues from the prothioconazole dairy cattle feeding study.

Conclusions: An HPLC-MS/MS method was developed and proposed for data gathering and enforcement purposes. In livestock matrices, extracts are acid hydrolysed and residues are reported as prothioconazole equivalents (prothioconazole, prothioconazole desthio, prothioconazole-4-hydroxy). The method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70 to 120%) were obtained in animal matrices. Adequate extraction efficiencies were demonstrated using radiolabeled goat milk, goat liver goat muscle and goat fat analyzed with the enforcement method. The proposed enforcement method has undergone a successful tolerance method validation by EPA ACL.

860.1360 Multiresidue Methods

46246210.der.wpd

Bayer CropScience has submitted multiresidue method data for prothioconazole, the metabolites JAU6476-desthio and JAU6476-4-hydroxy, and the triazole-related compounds triazole, triazolylalanine, and triazolylacetic acid. The test substances were analyzed according to the FDA Multi-Residue Method Test guidelines in PAM Vol. I (dated 1/94). Prothioconazole, JAU6476-desthio, JAU6476-4-hydroxy, triazole and triazolylacetic acid were tested through Protocols A and C. As a result of Protocol C testing, prothioconazole, JAU6476-desthio, and JAU6476-4-hydroxy were tested through Protocol F. JAU6476-4-hydroxy and triazolylacetic acid were tested through Protocol B. Based on the results of the Protocol F testing, testing under Protocols D and E was not required for prothioconazole, and testing under Protocol E was not required for JAU6476-4-hydroxy. Because the test substances are not substituted ureas, no testing under Protocol G was required. A suitable solvent for triazolylalanine could not be found; therefore, testing of this compound could not be conducted.

Sensitivity for triazolylacetic acid was poor using Protocol A, and no response was obtained for the other test compounds. Protocol C testing indicated that further testing using Protocols D, E, and F was not required for triazolylacetic acid and triazole. Triazolylacetic acid and JAU6476-4-hydroxy could not be adequately recovered under Protocol B. Prothioconazole and JAU6476-4-hydroxy were not adequately recovered using the Florisil column cleanup steps of Protocol F, and JAU6476-4-hydroxy did not yield adequate chromatography using Protocol D; thus, no further testing of these compounds was conducted. JAU6476-desthio could not be adequately recovered under Protocols D or E, using wheat hay. Recovery of JAU6476-desthio was variable (66-100%) under Protocol F, using ground beef.

Conclusions: The multiresidue test data will be forwarded to FDA for further evaluation. Based on the results of the testing, the multiresidue methods are not appropriate for determining prothioconazole residues of concern, or for determining residues of triazole, triazolylalanine, or triazolylacetic acid.

860.1380 Storage Stability

46477701.der.wpd (also includes review of 860.1380 data in MRID 46246219)
46246139.der.wpd

Plant commodities

Bayer has submitted the results of three storage stability studies with prothioconazole and the metabolite prothioconazole desthio in plant commodities (MRID 46477701) as well as the results of a storage stability study with prothioconazole and the desthio metabolite in wheat commodities (MRID 46246139).

MRID 46477701: This submission reported results from three separate storage stability studies with prothioconazole and its desthio metabolite in plant commodities. The first study (which

will be referred to herein as Study 1) was initiated January 2001 at Battelle-AgriFood Laboratories. We note that partial results for this study were submitted as an appendix to the wheat crop field trial study submitted under DP Barcode D303508 (in MRID 46246219). In Study 1, samples of untreated canola seed, mustard greens, tomato, turnip root, and wheat forage, straw, hay, and grain were fortified with a mixed standard of prothioconazole and prothioconazole desthio (in a 1:1 ratio) at a total of 0.200 ppm expressed as parent equivalents. Samples were stored frozen (<-10°C) for up to ~35 months. Only limited information pertaining to sample preparation prior to storage was submitted. At the 3-month storage interval, samples were analyzed at Battelle, and at the final storage interval, samples were analyzed by Bayer. No zero-time analyses were conducted.

Because Study 1 did not include any zero-time analyses, Bayer initiated a second storage stability study (Study 2) in August 2004. In Study 2, samples of untreated canola seed, canola oil, mustard greens, tomato, tomato paste, turnip root, and wheat forage, grain, straw, bran and flour were separately spiked with prothioconazole or prothioconazole desthio at 0.250 ppm. Samples were stored frozen (<-15°C) for up to 12.7 months. The interim results of Study 2 were submitted, and the applicant has volunteered to submit interim data on analyses planned for up to 45 months.

To address the stability of weathered prothioconazole residues, Bayer also reanalyzed certain crop field trial samples from the first study after 30 to 46 months of frozen storage (Study 3). Samples of canola seed, barley hay, grain, and straw, dried peas, wheat forage, and wheat hay and straw from crop field trials submitted in conjunction with DP Barcode D303508 (MRIDs 46246215 and 46246219-46246221) were used. These samples were originally analyzed at Battelle within 3 months of collection and were reanalyzed at Bayer after 18-32 months of frozen storage because it was determined that the original analytical methods did not adequately extract weathered residues. For Study 3, Bayer reanalyzed these samples 12-15 months after the initial analyses at Bayer.

Samples that were analyzed at Battelle (canola seed, mustard greens, tomato, turnip root, and wheat forage, hay, straw, and grain from the ~3-month storage interval from Study 1, and samples of canola seed, barley hay, straw, and grain, and wheat forage, hay, and straw from the ~1- to 3-month storage interval from Study 3) were analyzed for combined residues of prothioconazole and prothioconazole desthio using LC-MS/MS Method 00598 or its modification Method 00598/M001. Samples that were analyzed at Bayer (canola seed, mustard greens, tomato, turnip root, and wheat forage, hay, straw, and grain from the ~35-month storage interval from Study 1, all samples from Study 2, and samples of canola seed, barley hay, straw, and grain, dried peas, and wheat forage, hay, and straw from the ~30- to 42-month storage interval from Study 3) were analyzed for total prothioconazole-derived residues (prothioconazole and the metabolite prothioconazole desthio) using the proposed enforcement method, LC-MS/MS method RPA JA/03/01. Because the applicant has indicated that LC-MS/MS method JA/03/01 is the preferred method for analysis of crop samples, sample results that were generated using Method No. 00598 or 00598/M001 will not be used to evaluate storage stability. Adequate concurrent method recovery data were submitted for both methods.

Based on the reported results from Study 1, 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.

Based on the reported results from Study 2, JAU6476 was found 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). JAU6476 showed 33% and 36% decomposition in tomato paste and wheat bran, respectively. However, the JAU6476 plant metabolism studies in three dissimilar crops have shown that JAU6476 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 apparent slight instability of JAU6476 in tomato paste and wheat bran would not be expected to have any significant effect on the total JAU6476 (JAU6476 plus JAU6476-desthio) residue levels measured in the field crop residue studies. JAU6476-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 JAU6476-desthio was equal to or less than 5% in all matrices. JAU6476-desthio would be expected to contribute 6 to 58% (80 to 100% normalized) of the residues measured in the JAU6476 field crop residue trials.

Based on the reported results from Study 3, weathered total prothioconazole-derived residues appear to be stable in/on barley hay, straw, and grain stored frozen for ~13 months beyond initial analyses at Bayer, in/on dried peas stored frozen for 12 months beyond initial analyses, and in/on wheat hay and straw stored frozen for ~15 months beyond initial analyses. Residues were found to decline ~14% in/on canola seed stored frozen for ~12 months beyond initial analyses at Bayer and ~13% in/on wheat forage stored frozen for ~15 months beyond initial analyses. Initial analyses at Bayer were conducted 29-32 months after sample collection for barley, canola, and wheat commodities and 18 months after sample collection for dried peas.

MRID 46246139: Bayer submitted the results of storage stability studies with prothioconazole and prothioconazole desthio. Untreated samples of wheat forage, grain, hay, and straw were separately spiked with prothioconazole and prothioconazole desthio and stored frozen (<-18°C) for up to ~36 months (1088 days; wheat grain) and ~37 months (1126-1128 days; wheat forage and straw). The tested commodities were spiked by spraying the samples with the fortification solution; samples were then homogenized prior to frozen storage. The actual spiking level was determined by analyzing 0-day samples. The results of the storage stability study indicate that under these conditions, residues of prothioconazole are stable in/on wheat forage, grain, and straw for up to ~4, ~6.5, and ~19 months, respectively, before a decrease of $\geq$30% is observed; at the final storage interval, residues had decreased by an average of 50%, 38%, and 31% in forage, grain, and straw, respectively. Residues of prothioconazole desthio were found to be stable for ~36 months in/on wheat grain and ~37 months in/on wheat forage and straw.

Samples of wheat forage, grain, and straw were analyzed for residues of prothioconazole and prothioconazole desthio using LC-MS/MS Method No. 00598. The reported LOQ was 0.01

ppm for wheat grain and 0.05 ppm for wheat forage and straw. Based on acceptable concurrent method recovery data, this method appears to be adequate for data collection. However, the applicant reported in a separate submission (MRID 46477701) that this method was found to be inadequate for determination of weathered residues of prothioconazole.

Storage intervals and conditions of samples from the submitted studies: The storage intervals and conditions of samples from the submitted crop field trial, processing, and field rotational crop studies are presented in Table 3. The reported storage duration represents the interval from sample collection to analysis.

Table 3. Summary of Storage Intervals and Conditions.		
Matrix	Storage Temp. (°C)	Actual Storage Duration
		Total Prothioconazole-Derived Residues
Crop Field Trials; MRIDs 46246215-46246217 and **46246219-46246221**		
Barley grain	-30.0 to -4.8	824-1234 days (27.1-40.6 months)
Barley hay	-30.0 to -4.8	859-1269 days (28.2-41.7 months)
Barley straw	-30.0 to -4.8	825-1240 days (27.1-40.8 months
Bean, dried shelled	-24 to -22	490-536 days (16.1-17.6 months)
Canola seed	-30.0 to -4.8	867-1265 days (28.5-41.6 months)
Pea, dried shelled	-24 to -22	494-542 days (16.2-17.8 months)
Peanut nutmeat	-30.0 to -4.8	1175-1214 days (38.6-39.9 months)
Peanut hay	-30.0 to -4.8	1173-1212 days (38.6-39.8 months)
Rice grain	-30.0 to -4.8	1135-1240 days (37.3-40.8 months)
Rice straw	-30.0 to -4.8	1120-1226 days (36.8-40.3 months)
Wheat hay	-30.0 to -4.8	871-1221 days (28.6-40.1 months)
Wheat grain	-30.0 to -4.8	873-1214 days (28.7-39.9 months)
Wheat straw	-30.0 to -4.8	854-1203 days (28.1-39.5 months)
Wheat forage	-30.0 to -4.8	181-469 days (6.0-15.4 months)
Processing Studies; MRIDs 46246218 and **46246222-46246224**		
Canola seed	-30.0 to -4.8	1261 days (41 months)
Canola meal and refined oil		918 days (30 months)
Peanut nutmeat	-30.0 to -4.8	1090 days (36 months)
Peanut meal, refined oil, dry roasted peanuts, and peanut butter		911 days (31 months)
Rice grain	<-5	1222 days (40 months)
Rice polished grain, bran, and hulls		902 days (30 months)
Wheat grain	<-5	1285 days (42 months)
Wheat aspirated grain fractions, bran, germ, flour, middlings, and shorts		909 days (30 months)

Field Rotational Crop Study; MRID 46246227		
Mustard greens	-30.0 to -4.8	1135-1263 days (37.3-41.5 months)
Turnip tops	-30.0 to -4.8	1136-1243 days (37.3-40.8 months)
Turnip roots	-30.0 to -4.8	1136-1243 days (37.3-40.8 months)
Wheat forage	-30.0 to -4.8	952-1002 days (31.3-32.9 months)
Wheat hay	-30.0 to -4.8	893-943 days (29.3-31.0 months)
Wheat grain	-30.0 to -4.8	869-919 days (28.6-30.2 months)
Wheat straw	-30.0 to -4.8	861-911 days (28.3-29.9 months)

Conclusions: The available storage stability data are tentatively adequate to support the storage intervals and conditions of samples from the submitted crop field trial, processing, and field rotational crop studies. The final reports of the ongoing storage stability studies with prothioconazole and prothioconazole desthio (interim results for which were reported in MRID 46477701) must be submitted as confirmatory data.

For the storage stability data reported in MRID 46477701 for prothioconazole and prothioconazole desthio, HED concludes that the ongoing study (Storage Stability Study 2) will provide the most information about any actual decline of prothioconazole or prothioconazole desthio residues in crop matrices because it includes more than one sampling interval. The results of the other two studies reported in that submission only reflect one sampling interval. The applicant chose the tested matrices in Studies 1 and 2 of that submission to be representative of five diverse crops [an oilseed (canola), a non-oily grain (wheat), a leafy vegetable (mustard greens), a root crop (turnip), and a fruiting vegetable (tomato)] as well as the processed commodities of three crops [an oilseed, a fruiting vegetable, and a non-oily grain]. Even though JAU6476 appears to be slightly unstable in two matrices (tomato paste, wheat bran), the overall impact on the crop residues will not be significant. However, based on OPPTS 860.1380, the Agency will consider corrections on a case-by-case basis, taking into account factors such as the absolute (ppm) and relative (% ROC) residue levels of the component that is unstable in storage. Therefore, correction for dissipation of prothioconazole-derived residues during freezer storage will not be necessary at this time.

Because the applicant has reported that Method No. 00598 is not adequate for determination of weathered residues of prothioconazole, the results of the storage stability study reported in MRID 46246139 will not be used to evaluate the stability of prothioconazole residues in wheat commodities during frozen storage.

Animal commodities

The storage intervals for all matrices from the cattle feeding studies, except fat from the prothioconazole feeding study, were reported to be <30 days. Because samples were stored frozen prior to analysis and analyzed within 30 days of collection, supporting storage stability data are not needed for milk and tissues except fat. Fat samples from the lowest feeding level (0.5-fold) were stored frozen for up to 86 days prior to analysis. For the 1.4-fold and 4.7-fold feeding levels, samples were stored for 43 and 37 days, respectively. A supporting storage stability study indicated that residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy were stable for 27 days (<30% decline). After 89 days in storage, low concurrent recoveries of prothioconazole-4-hydroxy residues were observed at the 0.5-fold feeding level indicating a 33% apparent decline. The 1.4-fold dose group (29.5 ppm) was closest to the anticipated dietary burden (21 ppm).

Conclusions: The applicant will repeat 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. A report will be submitted to EPA. Therefore, correction for dissipation of prothioconazole-derived residues and the prothioconazole4-OH in fat during freezer storage will not be necessary at this time.

860.1400 Water, Fish, and Irrigated Crops

There are no proposed uses that are relevant to this guideline topic.

860.1460 Food Handling

There are no proposed uses that are relevant to this guideline topic.

860.1480 Meat, Milk, Poultry, and Eggs

46246213.der.wpd (Cattle)
46246214.der.wpd (Cattle)

The applicant submitted two cattle feeding studies with the subject petition, one in which cattle were dosed with prothioconazole (MRID 46246213) and one in which cattle were dosed with prothioconazole desthio (MRID 46246214). The second study was considered supplemental. The maximum theoretical dietary burden of prothioconazole to livestock is presented in Table 4.

Table 4. Calculation of Maximum Dietary Burdens of Prothioconazole to Livestock.

				Maximum % of Diet				% of Diet Used				Dietary Burden, ppm			
Crop	Commodity	Residue	%DM	Beef	Dairy	Poultry	Swine	Beef	Dairy	Poultry	Swine	Beef	Dairy	Poultry	Swine
Grain	Aspirated grain fractions	11.025	85	20	20	--	20	20	20	--	20	2.59	2.59	0.00	2.21
Wheat	forage	6.987	25	25	60	--	--	25	60	--	--	6.99	16.77	0.00	0.00
Barley	Hay	6.59	88	25	60	--	--	25	20	--	--	1.87	1.50	0.00	0.00
Peanut	Hay	4.458	85	25	50	--	--	25	0	--	--	1.31	0.00	0.00	0.00
Wheat	Hay	3.571	88	25	60	--	--	5	0	--	--	0.20	0.00	0.00	0.00
Wheat	Straw	1.96	88	10	10	--	--	0	0	--	--	0.00	0.00	0.00	0.00
Barley	Straw	1.871	89	10	10	--	--	0	0	--	--	0.00	0.00	0.00	0.00
Rice	Straw	1.277	90	10	10	--	--	0	0	--	--	0.00	0.00	0.00	0.00
Rice	Hulls	0.8404	90	10	10	15	--	0	0	15	--	0.00	0.00	0.13	0.00
Cowpea	Seed	0.684	88	20	20	10	50	0	0	10	50	0.00	0.00	0.07	0.34
Pea, field	Seed	0.684	90	20	20	20	20	0	0	20	20	0.00	0.00	0.14	0.14
Rice	Bran	0.222	90	15	15	25	15	0	0	25	10	0.00	0.00	0.06	0.02
Rice	Grain	0.222	88	40	40	60	65	0	0	30	0	0.00	0.00	0.07	0.00
Barley	Grain	0.158	88	50	40	75	80	0	0	0	0	0.00	0.00	0.00	0.00
Peanut	Meal	0.158	85	15	15	25	15	0	0	0	0	0.00	0.00	0.00	0.00
Wheat	Milled byproducts	0.108	88	40	50	50	50	0	0	0	0	0.00	0.00	0.00	0.00
Canola	Meal	0.097	88	15	15	15	15	0	0	0	0	0.00	0.00	0.00	0.00
Wheat	Grain	0.061	89	50	40	80	80	0	0	0	0	0.00	0.00	0.00	0.00
							Total	100	100	100	100	12.97	20.86	0.45	2.71

Cattle - MRID 46246213: 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 0.5-fold, 1.4-fold, and 4.7-fold the maximum theoretical dietary burden. 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. Tissue samples (except fat) were extracted with acetonitrile (ACN)/water and aqueous L-cysteine HCl. Fat samples were first extracted with n-hexane, then ACN, L-cysteine HCl and acetone. All samples (including milk and cream) were hydrolyzed with aqueous HCl, then partitioned with methylene chloride and acetone before LC-MS/MS analysis. The method was adequate for data collection based on acceptable concurrent method recovery data. The storage intervals for all matrices except fat were reported to be <30 days; therefore no storage stability data is needed for these matrices. Fat samples from the lowest feeding level (0.5-fold) were stored frozen for up to 86 days prior to analysis. For the 1.4-fold and 4.7-fold feeding levels, samples were stored for 43 and 37 days, respectively. A supporting storage stability study indicated that residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy were stable for 27 days (<30% decline). After 89 days in storage, residues of prothioconazole-4-hydroxy showed a 33% decline. The 1.4-fold dose group (29.5 ppm) was closest to the anticipated dietary burden (21 ppm). Confirmatory data will be

generated to confirm the stability of the prothioconazole-4-hydroxy in fat for a duration of 45 days.

The maximum residues of prothioconazole, prothioconazole desthio, and prothioconazole-4-hydroxy in milk and tissues are listed in Table 5 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 5. 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.

Cattle – MRID 46246214:

Bayer CropScience has submitted a supplemental dairy cattle feeding study with *prothioconazole-desthio, a metabolite of prothioconazole*. Three groups of dairy cattle (3 cows per group) were dosed orally with prothioconazole-desthio at levels equivalent to 5.1, 29, and 125 ppm in the feed. The dosing levels correspond 0.24x, 1.4x, and 6.0x the anticipated dietary burden (Table 4 above). Cattle were dosed once a day for 29 consecutive days. Cows were milked twice daily, and composited daily samples from Study Days 1, 4, 6, 8, 11, 13, 15, 18, 20, 22, 25, 27, 28, and 29 (mid and high dose groups only) were collected for analysis from each cow. Cattle were sacrificed within 17 hours of the last dose, and samples of composite fat (omental and perirenal), liver, kidneys, and composite muscle (loin, elbow and flank) were collected.

Milk and tissues samples were analyzed using an LC/MS/MS method (Method No. 00655 and its modification 00655/M001). This method determines residues of prothioconazole desthio , prothioconazole desthio-3-hydroxy, and prothioconazole desthio-4-hydroxy and compounds that may be converted to these compounds by acid hydrolysis. The validated LOQ was 0.004 ppm for each analyte in milk and 0.010 ppm for each analyte in tissues; the calculated LODs ranged 0.0001-0.0004 ppm. The method is adequate for data collection based on acceptable concurrent method recovery data.

Table 6 summarizes the maximum concentrations of prothioconazole desthio (B), prothioconazole desthio-4-hydroxy (D), and desthio-3-hydroxy (E) found in milk (29 days) and tissues. The total residue appears to have reached a plateau in whole milk by day 10.

Table 6. Maximum Residues of Prothioconazole desthio (B), Prothioconazole desthio-4-hydroxy (D), and Prothioconazole desthio-3-hydroxy (E), as prothioconazole equivalents, by Feeding Level Following Dosing of Dairy Cattle with Prothioconazole desthio for 29 Days.

Matrix	Residues (ppm)								
	5.1 ppm			29.0 ppm			125 ppm		
	B	D	E	B	D	E	B	D	E
Whole Milk (day 29)	--	--	--	<0.004	<0.004	<0.004	<0.004	0.0043	0.0115
Fat	<0.01	<0.01	<0.01	0.011	<0.01	<0.01	0.091	0.024	0.030
Kidney	<0.01	0.019	<0.01	0.033	0.085	0.064	0.237	0.383	0.477
Liver	0.030	<0.01	0.013	0.178	0.037	0.055	1.19	0.171	0.300
Muscle	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.013

[1] Residues of each analyte are expressed as prothioconazole desthio equivalents. The LOQ for each analyte was 0.004 ppm in milk and 0.01 ppm in tissues.

The concentration of prothioconazole desthio (B) at the 29 ppm feeding level is less than or equal to the concentration of prothioconazole from the prothioconazole feeding study at 29 ppm for all commodities except liver. For liver, the concentration of prothioconazole desthio from the 29 ppm prothioconazole desthio feeding study is slightly higher than the combined concentration of prothioconazole and prothioconazole desthio from the 29 ppm prothioconazole feeding study, 0.18 ppm versus 0.13 ppm. The metabolites 4-hydroxy desthio prothiconazole and 3-hydroxy prothioconazole desthio from the prothioconazole desthio feeding study do not contribute significantly to the residue in the prothioconazole desthio feeding study for milk, fat, and muscle. For kidney, these metabolites contribute significantly (0.15 ppm combined versus 0.033 ppm prothioconazole desthio), but the combined residue (0.18 ppm) compares to the 0.18 ppm prothioconazole from the prothioconazole feeding study at 29 ppm. For liver, these metabolites are about 50% of the prothioconazole desthio (from the prothioconazole desthio feeding study at 29 ppm). The combined residue of prothioconazole desthio, 4-hydroxy prothioconazole desthio, and 3-hydroxy prothioconazole (0.27 ppm) is less than the combined residue of prothioconazole, prothioconazole desthio, and 4-hydroxy prothioconazole (0.31 ppm) from the prothioconazole feeding study at 29 ppm.

Conclusions: The submitted cattle study data are adequate to satisfy livestock feeding study data requirements for ruminants.

The feeding study data indicate that tolerances are needed for the combined residues of prothioconazole and prothioconazole desthio in cattle, goat, hog, horse, and sheep commodities. Generally, the prothioconazole and prothioconazole desthio feeding studies will provide similar estimates of the tolerances for livestock commodities.

Using the results of the prothioconazole feeding study and defining the residue for tolerance purposes as the sum of prothioconazole, prothioconazole desthio, and metabolites that can be hydrolyzed to these compounds, calculated as prothioconazole, HED calculates that tolerances should be set at the combined LOQs for milk (0.02 ppm, using LOQs for skim milk and cream); at the combined LOQs for the fat (0.10 ppm) and muscle (0.02 ppm) of cattle, goats, horses, and sheep; at 0.20 ppm for the meat byproducts of cattle, goats, horses, and sheep; and at 0.05 ppm for the meat byproducts of hogs. The available data indicate that a tolerance is not needed for milk fat or the fat and meat of hogs.

Poultry: The applicant did not submit a poultry feeding study with the subject petition but submitted a request for a waiver from the requirements for a poultry feeding study.

The applicant used a value of 0.455 ppm as the maximum theoretical dietary burden for poultry, based on a diet consisting of 15% rice hulls, 60% rice grain, and 25% barley grain (and using "anticipated" tolerance values of 1.5, 0.3, and 0.2 ppm, respectively). This agrees with the 0.45 ppm calculated in Table 4 above, resulting from the feeding of rice and pea commodities. To determine the residues that would be found by the proposed enforcement method for livestock commodities, it can be assumed that residues of JAU6476-glucuronide (N-, S- or O-glucuronides) would be converted to prothioconazole. Under that assumption, the combined residues for prothioconazole and prothioconazole desthio from the metabolism studies (171 ppm and 163 ppm in diet, or about 360X) were: liver, 1.7 and 1.8 ppm; egg, 0.014 and 0.017 ppm; muscle, 0.031 and 0.018 ppm; fat, 0.29 and 0.14 ppm. The residues at a feeding level of 0.455 ppm can be estimated to be: liver, 0.005 ppm; egg, 0.00005 ppm; muscle, 0.00009 ppm; fat, 0.0008 ppm. The enforcement analytical method for livestock commodities has not been validated for poultry items. Assuming that the method has a LOQ of 0.01 ppm for each of the two analytes for poultry commodities (combined LOQ 0.02 ppm, based on an LOQ of 0.01 ppm for each analyte in cattle liver), no residue would be anticipated at the defined feeding level in any of the poultry commodities, except liver. Residues appeared *not* to have obtained a plateau in eggs, as the TRR in the oviduct egg was about 10X that in the eggs. Factoring in a 10X increase in residue in the egg would not lead to a prediction of detectable residues in eggs at a feeding level of 0.45 ppm prothioconazole in the diet

Under the currently proposed uses and defining the residue for tolerance purposes as the sum of prothioconazole, prothioconazole desthio, and metabolites that can be hydrolyzed to these compounds, calculated as prothioconazole, HED *provisionally* concludes that residues are unlikely in poultry commodities except liver and that, therefore, poultry commodity tolerances are not needed, except liver. A conditional tolerance of 0.02 ppm should be proposed for poultry liver, based on the validated LOQ of 0.01 ppm for each of the analytes in cattle liver.

The extreme extrapolation required (360X) and the short interval of the poultry metabolism study (3 days) make 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.

860.1500 Crop Field Trials

46246215.de1.wpd (Canola)
46246216.der.wpd (Rice)
46246217.der.wpd (Peanut)
46246219.der.wpd (Wheat)
46246220.der.wpd (Barley)
46246221.der.wpd (Dried pea and bean)

Table 7. Summary of Residues from the Crop Field Trials with Prothioconazole.

Crop Matrix	Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
BARLEY (proposed use = 0.293 lb ai/A [0.328 kg ai/ha] total application rate, 30-day PHI)									
Total Prothioconazole-Derived Residues									
Barley grain	0.286-0.309 [0.321-0.348]	30-71	49	<0.02	0.158	0.151	0.022	0.040	0.041
Barley hay	0.286-0.309 [0.321-0.348]	12-16	49	0.317	6.59	5.95	1.22	1.72	1.39
Barley straw	0.286-0.309 [0.321-0.348]	30-71	50	<0.05	1.871	1.65	0.304	0.554	0.510
1,2,4-Triazole Residues									
Barley grain	0.286-0.309 [0.321-0.348]	30-71	50	<0.01	<0.01	<0.01	0.005	0.005	0.0
Barley hay	0.286-0.309 [0.321-0.348]	12-16	49	<0.01	<0.01	<0.01	0.005	0.005	0.0
Barley straw	0.286-0.309 [0.321-0.348]	30-71	50	<0.01	<0.01	<0.01	0.005	0.005	0.0
Triazole Conjugate Residues									
Barley grain	0.286-0.309 [0.321-0.348]	30-71	50	<0.10	0.915	0.909	0.239	0.300	0.215
Barley hay	0.286-0.309 [0.321-0.348]	12-16	49	<0.05	0.547	0.445	0.135	0.134	0.104
Barley straw	0.286-0.309 [0.321-0.348]	30-71	50	<0.1	0.385	0.359	0.05	0.090	0.093
CANOLA (proposed use = 0.356 lb ai/A [0.400 kg ai/ha] total application rate, 36-day PHI)									
Total Prothioconazole-Derived Residues									
Canola seed	0.35-0.37 [0.39-0.42]	36-83	44	<0.020	0.097	0.086	0.010	0.015	0.0169
1,2,4-Triazole Residues									

Table 7. Summary of Residues from the Crop Field Trials with Prothioconazole.									
Crop Matrix	Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Canola seed	0.35-0.37 [0.39-0.42]	36-83	44	<0.020	<0.020	<0.020	0.010	0.010	0
Triazole Conjugate Residues									
Canola seed	0.35-0.37 [0.39-0.42]	36-83	44	0.064	0.848	0.716	0.311	0.321	0.124
DRIED PEA AND BEAN (proposed use = 0.534 lb ai/A [0.600 kg ai/ha] total application rate, 7-day PHI)									
Total Prothioconazole-Derived Residues									
Pea, dried shelled	0.530-0.549 [0.595-0.615]	7-8	26	<0.05	0.684	0.661	0.025	0.156	0.219
Bean, dried shelled	0.534-0.580 [0.598-0.650]	7-8	20	<0.05	0.288	0.243	0.025	0.062	0.072
1,2,4-Triazole Residues									
Pea, dried shelled	0.530-0.549 [0.595-0.615]	7-8	26	<0.01	0.011	0.01	0.005	0.005	0.001
Bean, dried shelled	0.534-0.580 [0.598-0.650]	7-8	20	<0.01	<0.01	<0.01	0.005	0.005	0.0
Triazole Conjugate Residues									
Pea, dried shelled	0.530-0.549 [0.595-0.615]	7-8	26	<0.05	0.789	0.775	0.085	0.177	0.213
Bean, dried shelled	0.534-0.580 [0.598-0.650]	7-8	20	<0.02	0.311	0.249	0.045	0.080	0.093
PEANUT (proposed use = 0.713 lb ai/A [0.800 kg ai/ha] total application rate, 14-day PHI)									
Total Prothioconazole-Derived Residues									
Peanut nutmeat	0.707-0.734 [0.792-0.823]	13-15	24	<0.02	<0.02	<0.02	0.01	0.01	0.0
Peanut hay	0.707-0.734 [0.792-0.823]	13-15	24	0.989	4.458	3.630	2.657	2.612	0.884
1,2,4-Triazole Residues									
Peanut nutmeat	0.707-0.734 [0.792-0.823]	13-15	24	<0.02	0.02	<0.02	0.01	0.01	0.0
Peanut hay	0.707-0.734 [0.792-0.823]	13-15	24	<0.02	<0.02	<0.02	0.01	0.01	0.0
Triazole Conjugate Residues									
Peanut nutmeat	0.707-0.734 [0.792-0.823]	13-15	24	0.162	3.903	3.390	0.827	1.158	1.127
Peanut hay	0.707-0.734 [0.792-0.823]	13-15	24	<0.10	1.278	1.244	0.176	0.323	0.361
RICE (proposed use = 0.285 lb ai/A [0.320 kg ai/ha] total application rate, 40-day PHI)									
Total Prothioconazole-Derived Residues									

Table 7. Summary of Residues from the Crop Field Trials with Prothioconazole.									
Crop Matrix	Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Rice, grain	0.34-0.37 [0.38-0.41]	40-67	32	<0.02	0.222	0.191	0.01	0.031	0.048
Rice, straw	0.34-0.37 [0.38-0.41]	40-67	32	<0.05	1.277	1.189	0.432	0.464	0.319
1,2,4-Triazole Residues									
Rice, grain	0.34-0.37 [0.38-0.41]	40-67	32	<0.01	<0.01	<0.01	0.005	0.005	0.0
Rice, straw	0.34-0.37 [0.38-0.41]	40-67	32	<0.01	<0.01	<0.01	0.005	0.005	0.0
Triazole Conjugate Residues									
Rice, grain	0.34-0.37 [0.38-0.41]	40-67	32	<0.05	0.571	0.553	0.025	0.103	0.148
Rice, straw	0.34-0.37 [0.38-0.41]	40-67	32	<0.05	0.506	0.478	0.025	0.088	0.122
WHEAT (proposed use = 0.293 lb ai/A [0.328 kg ai/ha] total application rate, 30-day PHI)									
Total Prothioconazole-derived Residues									
Wheat hay	0.281-0.313 [2] [0.315-0.350]	12-17	66	0.288	3.571	3.543	1.269	1.420	0.970
Wheat grain	0.281-0.313 [2] [0.315-0.350]	10; 30-57	66	<0.02	0.061	0.045	0.010	0.014	0.011
Wheat straw	0.281-0.313 [2] [0.315-0.350]	10; 30-57	64	0.106	1.96	1.899	0.350	0.577	0.471
Wheat forage	0.286-0.299 [0.320-0.336]	7	46	0.061	6.987	5.842	1.352	1.401	1.268
1,2,4-Triazole Residues									
Wheat hay	0.281-0.313 [2] [0.315-0.350]	12-17	66	<0.01	<0.01	<0.01	0.005	0.005	0.0
Wheat grain	0.281-0.313 [2] [0.315-0.350]	10; 30-57	66	<0.01	<0.01	<0.01	0.005	0.005	0.0
Wheat straw	0.281-0.313 [2] [0.315-0.350]	10; 30-57	66	<0.01	<0.01	<0.01	0.005	0.005	0.0
Wheat forage	0.286-0.299 [0.320-0.336]	7	46	<0.01	<0.01	<0.01	0.005	0.005	0.0
Triazole Conjugate Residues									
Wheat hay	0.281-0.313 [2] [0.315-0.350]	12-17	66	0.018	0.665	0.631	0.204	0.220	0.124
Wheat grain	0.281-0.313 [2] [0.315-0.350]	10; 30-57	66	0.098	1.76	1.76	0.460	0.534	0.320
Wheat straw	0.281-0.313 [2] [0.315-0.350]	10; 30-57	64	<0.025	0.495	0.449	0.063	0.095	0.104

Table 7. Summary of Residues from the Crop Field Trials with Prothioconazole.									
Crop Matrix	Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
Wheat forage	0.286-0.299 [0.320-0.336]	7	46	<0.01	0.175	0.173	0.038	0.050	0.042

[1] HAFT = Highest Average Field Trial.
[2] In one field trial, the total application rate was 0.375 lb ai/A (0.420 kg ai/ha); we note that this trial did not include maximum residues for any of the metabolites.

Barley: Bayer CropScience has submitted field trial data on barley from field trials conducted in the U.S. and Canada. A total of 25 five trials were conducted in Regions 1 (PA; 1 trial), 5 (ND; 2 trials, ON; 1 trial), 5B (QC; 1 trial), 7 (ND; 3 trials, and SK; 1 trial), 9 (AZ; 1 trial), 10 (AZ; 1 trial), 11 (ID and OR; 2 trials) and 14 (AB; 4 trials, MB; 4 trials, and SK; 4 trials) during the 2000-2001 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, two broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FC) were made to barley at ~0.11-0.18 lb a.i./A (~0.123-0.202 kg a.i./ha) at an average 12-day retreatment interval, for a total seasonal application rate of ~0.29 lb a.i./A (~0.33 kg a.i./ha). Applications were made in ~5-43 gal/A (~45-407 L/ha) of water using ground equipment. An adjuvant was not added to the spray mixture for any applications. Barley hay was cut at 23 test sites, 12-16 days after treatment, and was left in the field for 1-14 days prior to collection of barley hay. Samples of barley grain and straw were harvested at 23 test sites 30-71 days after the last application. At two locations, additional samples were collected to determine residue decline. In the decline trial performed in Region 7 (Northwood, ND), samples were harvested 8, 13, 22, and 28 days after treatment for barley hay and 32, 37, 44, and 47 days after treatment for barley grain and straw. In the decline trial performed in Region 5 (Branchton, ON), samples were harvested 9, 14, 21, and 29 days after treatment for barley hay and 36, 39, 45, and 49 days after treatment for barley grain and straw.

Samples were analyzed for total prothioconazole and the metabolite prothioconazole desthio using LC-MS/MS method RPA JA/03/01. The validated LOQs for the total combined prothioconazole and prothioconazole desthio residues were 0.02 ppm for barley grain and 0.05 ppm for barley hay and straw. The method is adequate for data collection for barley grain, hay and straw based on acceptable concurrent method recovery data and method validation data. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQ for 1*H*-1,2,4-triazole was 0.01 ppm for barley grain, hay and straw, and the validated LOQs for the triazole conjugates were 0.10 ppm for barley grain and straw, and 0.05 ppm for hay. The methods are adequate for data collection for barley matrices based on acceptable concurrent method recovery data.

In barley matrices harvested 30-71 days (12-16 days for hay), total combined prothioconazole and prothioconazole desthio residues were 0.158 ppm, 6.59 ppm and 1.87 ppm, respectively,

in/on barley grain, hay, and straw. Residues of 1*H*-1,2,4-triazole were less than the LOQ (<0.01 ppm) in/on barley grain, hay, and straw; and 0.915 ppm, 0.547 ppm and 0.385 ppm, respectively, in/on barley grain, hay, and straw for the triazole conjugates. Total combined prothioconazole and prothioconazole desthio residues did not increase with increasing sampling intervals in barley grain, hay, and straw, and residues of the triazole conjugates did not increase in grain, but increased slightly with increasing sampling intervals in samples from one trial each for hay and straw.

The maximum storage intervals of crop samples from harvest to analysis for total combined residues of prothioconazole and prothioconazole desthio were 1234 days (40.6 months) for barley grain and 1269 days (41.7 months) for barley hay and straw. The degree of loss of combined prothioconazole and prothioconazole desthio residues (determined as prothioconazole sulfonic acid and prothioconazole desthio) and prothioconazole desthio residues is not expected to exceed 30% after 42 months in barley grain, hay and straw.

Canola: Bayer CropScience has submitted field trial data on canola from field trials conducted in the U.S. and Canada. A total of 22 trials were conducted in Regions 2 (GA; 1 trial), 5 (ND; 1 trial, and ON; 1 trial), 7 (ND; 1 trial, and SK; 1 trial), 11 (ID; 3 trials), and 14 (AB; 4 trials, MB; 5 trials, and SK; 5 trials) during the 2000 growing season. The number and locations of field trials were in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, two broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FC) were made to canola at 0.17-0.19 lb a.i./A (0.19-0.21 kg a.i./ha) at an average 16-day retreatment interval (7-44 days), for a total seasonal application rate of 0.35-0.37 lb a.i./A (0.39-0.42 kg a.i./ha). Applications were made in ~11-42 gal/A (106-395 L/ha) of water using ground equipment. An adjuvant was not added to the spray mixture for any applications. Samples of canola were harvested at 20 test sites, 36-83 days after the last application. Two locations (Ashton, ID and Branchton, ON) were designated for residue decline studies. Samples were harvested 50, 54, 59, and 64 days after treatment in the decline trial performed in ID (region 11). In the ON trial (region 5), all samples were cut inadvertently on day 41. Seed samples from this site were collected on the day of harvest, and 5, 10, and 15 days after harvest.

Samples were analyzed for combined prothioconazole and prothioconazole desthio residues (determined as prothioconazole sulfonic acid and prothioconazole desthio) using LC-MS/MS method RPA JA/03/01. The validated LOQ for combined prothioconazole and prothioconazole desthio residues (designated "total prothioconazole-derived residues" in the method) was 0.02 ppm for canola seed. Samples were analyzed for residues of 1*H*-1,2,4-triazole, and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQs were 0.02 ppm for 1*H*-1,2,4-triazole and 0.025 ppm for the triazole conjugates for canola seed. The methods were adequate for data collection based on acceptable concurrent method recovery data.

The results from the canola field trials indicated that the maximum residues of prothioconazole in/on canola seed harvested 36-83 days following the last of two broadcast foliar applications

were 0.097 ppm for the total combined residues of prothioconazole and prothioconazole desthio, <0.02 ppm for 1*H*-1,2,4-triazole, and 0.848 ppm for the triazole conjugates.

In the residue decline trial conducted in ID, total prothioconazole-derived residues and residues of 1*H*-1,2,4-triazole were less than the LOQ (<0.02 ppm each) at all sampling intervals. Residues of the triazole conjugates did not increase with increasing sampling intervals.

The maximum storage interval of canola seed samples from harvest to analysis for total prothioconazole-derived residues was 1265 days (41.6 months). Prothioconazole-derived residues and prothioconazole desthio residues are stable up to 12.7 months (interim report) in canola matrices. The degree of loss of prothioconazole-derived residues and prothioconazole desthio residues is not expected to exceed 30% after 41.6 months.

Dried shelled pea and bean, group 6C: Bayer CropScience has submitted field trial data on dried peas and beans. A total of 23 field trials were conducted during the 2002 growing season in the U.S. and Canada. Thirteen trials were conducted on dried peas in Regions 5 (MN and ON; 2 trials), 11 (ID; 1 trial, OR; 3 trials, and WA; 1 trial), and 14 (AB; 2 trials, MB; 1 trial, and SK; 3 trials), and 10 trials were conducted on dried beans in Regions 5 (IL, IN, KS, and ON; 4 trials), 7 (ND;1 trial), 7A (AB; 1 trial), 8 (TX; 1 trial), 9 (MT; 1 trial), 10 (CA; 1 trial), and 11 (WA; 1 trial). The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, three broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) were made at ~0.180 lb a.i./A (~ 0.200 kg a.i./ha) at 9- to 15-day retreatment intervals, for a total seasonal application rate of ~0.54 lb a.i./A (~0.60 kg a.i./ha). Applications were made in ~10-33 gal/A of water using ground equipment. A non-ionic surfactant was added to the spray mixture for all applications. An additional plot at each trial was treated with three applications at a target rate of ~0.134 lb a.i./A (~ 0.150 kg a.i./ha); however, the applicant stated that the results from this application were not used because they did not support the desired product label application rate. Samples of dried shelled peas and beans were harvested 7-8 days after the last application from all test sites. It should be noted that in three of the pea field trials and five of the bean field trials, the pea and bean plants were cut and allowed to dry in the field for 2-8 days prior to collection. At two locations for dried peas and one location for dried beans, additional samples were collected to determine residue decline. Samples were harvested, at both locations, 0, 3-4, 7, 14-15, and 21-22 days after treatment for dried peas and 0, 7, 14, and 21 days after treatment for dried beans.

Samples were analyzed for combined prothioconazole and prothioconazole desthio residues (determined as prothioconazole sulfonic acid and prothioconazole desthio and designated "total prothioconazole-derived residues" in the method) using LC-MS/MS method RPA JA/03/01. The validated LOQ for combined prothioconazole and prothioconazole desthio residues was 0.05 ppm for dried peas and dried beans. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQs were 0.01 ppm for 1*H*-1,2,4-triazole for dried peas and beans, 0.02 ppm for the triazole conjugates for dried beans,

and 0.05 ppm for the triazole conjugates for dried peas. The methods are adequate for data collection based on acceptable concurrent method recovery data.

The results from the pea and bean field trials show that the maximum residues of prothioconazole in/on dried peas and beans harvested 7-8 days following the last of three broadcast foliar applications at a total seasonal rate of 0.530-0.580 lb a.i./A (0.595-0.650 kg a.i./ha) were 0.684 ppm in/on dried peas and 0.288 ppm in/on dried beans for the combined residue of prothioconazole and desthio prothioconazle ("total prothioconazole-derived residues"); 0.011 ppm in/on dried peas and less than the LOQ (<0.01 ppm) in/on dried beans for 1*H*-1,2,4-triazole; and 0.789 ppm in/on dried peas and 0.311 ppm in/on dried beans for the triazole conjugates.

In the residue decline trials, residues of 1*H*-1,2,4-triazole were less than the method LOQ (<0.01 ppm) at all sampling intervals in dried peas and beans. The combined residues of prothioconazole and prothioconazole desthio did not increase with increasing sampling intervals in the dried bean trial and in one dried pea trial; in the other dried pea trial, residues increased slightly with increasing sampling intervals (from an average of 0.31 ppm at the 7-day PHI to an average of 0.34 ppm at the 21-day PHI). Residues of the triazole conjugates did not increase with increasing sampling intervals in dried peas, but increased slightly in dried beans with increasing sampling intervals.

The maximum storage interval of crop samples from harvest to analysis for total prothioconazole-derived residues was 542 days (17.8 months) for dried beans and peas. The degree of loss of prothioconazole-derived residues and prothioconazole desthio residues is not expected to exceed 30% after 17.8 months in dried beans and peas.

Peanut: Bayer CropScience has submitted field trial data on peanuts. Twelve trials were conducted in Regions 2 (AL; 1 trial, GA; 3 trials, NC; 3 trials, and VA; 1 trial), 3 (FL; 1 trial), 6 (TX; 2 trials), and 8 (OK; 1 trial) during the 2000 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, four broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) were made to peanuts at ~0.18 lb a.i./A (~0.20 kg a.i./ha) at 12- to 14-day retreatment intervals, for a total seasonal application rate of ~0.72 lb a.i./A (~0.80 kg a.i./ha). Applications were made in ~13-37 gal/A (~119-349 L/ha) of water using ground equipment. An adjuvant was not added to the spray mixture for any applications. Peanut plants were dug up at all test sites 13-15 days after treatment, and were left in the field for 2-8 days prior to collection of peanuts and peanut hay. In one field trial (GA), additional samples were dug up at 7, 14, 21, and 28 days following the last application to evaluate residue decline.

Samples were analyzed for the combined residues of prothioconazole and prothioconazole desthio (determined as prothioconazole sulfonic acid and prothioconazole desthio and designated "total prothioconazole-derived residues" in the analytical method) using LC-MS/MS method RPA JA/03/01. The validated LOQs for total prothioconazole-derived

residues were 0.02 ppm for peanut nutmeat and 0.05 ppm for hay. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQ for 1*H*-1,2,4-triazole was 0.02 ppm for peanut nutmeat and hay, and the validated LOQs for the triazole conjugates were 0.125 ppm for peanut nutmeat and 0.10 ppm for hay. The methods were adequate for data collection based on acceptable concurrent method recovery data.

The results from the peanut field trials indicated that the maximum residues of prothioconazole in/on peanut matrices harvested 13-15 days following the last of four broadcast foliar applications at a total seasonal rate of 0.707-0.734 lb a.i./A (0.792-0.823 kg a.i./ha) were <0.02 ppm in/on nutmeat and 4.458 ppm in/on hay for the combined residue of prothioconazole and prothioconazole desthio; 0.02 ppm in/on nutmeat and less than the LOQ (<0.02 ppm) in/on hay for 1*H*-1,2,4-triazole; and 3.903 ppm in/on nutmeat and 1.278 ppm in/on hay for the triazole conjugates.

In the residue decline trial, residues of 1*H*-1,2,4-triazole were less than the method LOQ (<0.02 ppm) at all sampling intervals for peanut nutmeat and hay, and total prothioconazole-derived residues were less than the method LOQ (<0.02 ppm) at all sampling intervals for nutmeat. The average total combined residue of prothioconazole and prothioconazole desthio in hay increased slightly from the 7-day sampling interval to the 14-day sampling interval and then decreased by the 28-day sampling interval. Residues of the triazole conjugates increased slightly in nutmeat (from an average of 0.868 ppm to an average of 0.964 ppm) with increasing sampling intervals; a greater increase was observed in peanut hay (from an average of 0.117 ppm to an average of 0.355 ppm).

The maximum storage interval of crop samples from harvest to analysis for total prothioconazole-derived residues was 1214 days (39.9 months) for peanut nutmeat and hay. The combined residues of prothioconazole and prothioconazole desthio (determined as prothioconazole sulfonic acid and prothioconazole desthio) and prothioconazole desthio residues are stable up to 12.7 months (interim report). The degree of loss of combined prothioconazole and prothioconazole desthio residues ("prothioconazole-derived residues") and prothioconazole desthio residues is not expected to exceed 30% after 39.9 months.

Rice: Bayer CropScience has submitted field trial data on rice. A total of 16 trials were conducted in Regions 4 (LA; 6 trials, AR; 4 trials, and MS; 1 trial), 5 (MI; 1 trial), 6 (TX; 2 trials), and 10 (CA; 2 trials) during the 2000 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, two broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) were made to rice at ~0.18 lb a.i./A (~0.20 kg a.i./ha) at 13- to 16-day retreatment intervals, for a total seasonal application rate of ~0.36 lb a.i./A (~0.40 kg a.i./ha). Applications were made in ~12-23 gal/A of water using ground equipment. An adjuvant was not added to the spray mixture for any applications. Samples of rice were harvested at 14 test sites 40-67 days after the last application. At two locations, additional samples were collected to determine residue decline. Samples were harvested 49, 55, 58, and 65 days after treatment for the decline trial conducted in Benoit, MS

(Region 4), and 64, 69, 74, and 80 days after treatment for the decline trial conducted in Glen, CA (Region 10).

Samples were analyzed for the combined residue of prothioconazole and prothioconazole desthio (determined as prothioconazole sulfonic acid and desthio prothiocoanzole and designated "total prothioconazole-derived residues" in the method) using LC-MS/MS method RPA JA/03/01. The validated LOQs for the combined residue of prothioconazole and prothioconazole desthio were 0.02 ppm for rice grain and 0.05 ppm for rice straw. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQs were 0.01 ppm for 1*H*-1,2,4-triazole and 0.05 ppm for the triazole conjugates for rice grain and straw. The methods are adequate for data collection based on acceptable concurrent method recovery data.

The results from the rice field trials showed that the combined residue of prothioconazole and prothioconazole desthio (" total prothioconazole-derived residues") in/on rice matrices harvested 40-67 days following the last of two broadcast foliar applications were 0.222 ppm in/on rice grain and 1.277 ppm in/on rice straw. Residues of 1*H*-1,2,4-triazole were less than the LOQ (<0.01 ppm) in/on rice grain and straw. Maximum residues of the triazole conjugates were 0.571 ppm (rice grain) and 0.506 ppm (rice straw).

In the residue decline trials, total combined residues of prothioconazole and prothioconazole desthio in/on rice grain were <LOQ (0.02 ppm) in one trial, and did not increase with increasing sampling intervals in/on rice grain in the other trial. For rice straw, total combined residues of prothioconazole and prothioconazole desthio increased slightly with increasing sampling intervals in one trial. In the other trial, residues in/on straw increased slightly at the middle sampling intervals, and then decreased at the final sampling interval. Residues of the triazole conjugates in/on rice grain were <LOQ (<0.05 ppm) for one trial, and increased slightly in rice grain with increasing sampling intervals in the other trial. For rice straw, residues increased slightly with increasing sampling intervals in one trial, while residues did not increase in the other trial. Residues of 1*H*-1,2,4-triazole in/on rice grain and straw from both trials were less than the method LOQs (<0.02 ppm for total prothioconazole-derived residues, <0.05 ppm for the triazole conjugates, and <0.01 ppm for 1*H*-1,2,4-triazole) at all sampling intervals.

The maximum storage interval of crop samples from harvest to analysis for total prothioconazole-derived residues was 1240 days (40.8 months) for rice grain and straw. The degree of loss of the combined residue of prothioconazole and prothioconazole desthio ("prothioconazole-derived residues") and prothioconazole desthio residues is not expected to exceed 30% after 40.8 months in rice grain and straw.

Wheat: Bayer CropScience has submitted field trial data on wheat from trials conducted in the U.S. and Canada. A total of 54 trials were conducted in Regions 2 (GA and NC; 2 trials), 4 (MS; 2 trials), 5 (IN; 1 trial, KS; 2 trials, NE; 2 trials, and ON; 2 trials), 6 (TX; 2 trials), 7 (AB; 1 trial, ND; 5 trials, SD; 2 trials, and SK; 3 trials), 7A (AB; 2 trials), 8 (OK; 3 trials and TX; 7 trials), 11 (OR; 2 trials), and 14 (AB; 6 trials, MB; 6 trials, and SK; 4 trials) during the 2000

growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500 and Directive 98-02; Section 9.

At each test location, two broadcast foliar applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) were made to wheat. The first application was made at 0.108-0.120 lb a.i./A (0.122-0.135 kg a.i./ha) followed by a second application at 0.170-0.199 lb a.i./A (0.190-0.223 kg a.i./ha) with a 5- to 18-day retreatment interval, for a total seasonal application rate of ~0.29 lb a.i./A (~0.33 kg a.i./ha). In one field trial conducted in IN, the first application was made at 0.185 lb a.i./A (0.207 kg a.i./ha) followed by a second application at 0.190 lb a.i./A (0.213 kg a.i./ha) with a 14-day retreatment interval, for a total seasonal application rate of 0.375 lb a.i./A (0.420 kg a.i./ha). Applications were made in 11-45 gal/A of water using ground equipment. An adjuvant was not added to the spray mixture for any applications.

For 33 trials, including two decline trials, two treatment plots (designated as FORAG and HGRST) were used. The timing of the application varied for the two treatment plots. In the FORAG plot the second application was made 1 day prior to the first cutting of forage and in the HGRST plot the second application was made at full flowering. Wheat forage from the FORAG plots was harvested one day after treatment, but these samples were never analyzed or reported. Wheat hay from the HGRST plots was cut 12-17 days after treatment and was left in the field for 0-14 days prior to collection of wheat hay. Samples of wheat grain and straw from the HGRST plots were harvested at earliest commercial harvest, 30-57 days after the last application, except in one trial in which samples were harvested 10 days after second application.

For 21 trials, one treatment plot (designated as TRTD) was used; the second application was made 7 days prior to the first cutting of the forage. Only wheat forage was harvested from these trials.

At two locations (ND and NE), additional samples were collected to determine residue decline. The samples were harvested at both locations 0, 1, 7, and 14 days after treatment for wheat forage at 6 or 7, 14, 20 or 21, and 28 days after treatment for wheat hay, and at 35 or 36, 39 or 40, 44 or 46, and 49 or 50 days after treatment for wheat grain and straw.

Samples were analyzed for total combined residues of prothioconazole and prothioconazole desthio (designated “prothioconazole-derived residues” in the method) using LC-MS/MS method RPA JA/03/01. The validated LOQs for the total prothioconazole-derived residues were 0.02 ppm for wheat grain and 0.05 ppm for wheat forage, hay, and straw. The method is adequate for data collection for wheat grain hay, forage and straw based on acceptable concurrent method recovery data and method validation data. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQ for 1*H*-1,2,4-triazole and triazolylalanine was 0.01 ppm for wheat forage, hay, grain, and straw; and the validated LOQs for triazolylacetic acid were 0.01 ppm for wheat forage, hay, and grain and 0.025 ppm for wheat straw. The method is adequate for data collection in wheat matrices based on acceptable concurrent method recovery data.

The results from the wheat field trials show that in wheat matrices harvested 10-57 days (12-17 days for hay) following the last of two broadcast foliar applications at a total seasonal rate of 0.281-0.375 lb a.i./A (0.315-0.420 kg a.i./ha), the maximum residues of prothioconazole were 0.061 ppm, 1.96 ppm, and 3.571 ppm, respectively, in/on wheat grain, straw, and hay for the combined residue of prothioconazole and prothioconazole desthio; less than the LOQ (<0.01 ppm) in/on wheat grain, straw, and hay for 1*H*-1,2,4-triazole; and 0.495 ppm, 0.665 ppm, and 1.76 ppm, respectively, in/on wheat straw, hay, and grain for the triazole conjugates. In wheat forage harvested 7 days following the last of two broadcast foliar applications at a total seasonal rate of 0.286-0.299 lb a.i./A (0.320-0.336 kg a.i./ha), the maximum residues were 6.987 ppm for the combined residue of prothioconazole and prothioconazole desthio ("total prothioconazole-derived residues"), less than the LOQ (<0.01 ppm) for 1*H*-1,2,4-triazole, and 0.175 ppm for the triazole conjugates.

In the residue decline trials, residues of 1*H*-1,2,4-triazole at all sampling intervals were less than the method LOQ (<0.01 ppm) in/on wheat hay, grain, straw, and forage for both trials (NE and ND). Total prothioconazole-derived residues did not increase in any wheat matrix with increasing sampling intervals, and residues of the triazole conjugates increased slightly in samples of wheat forage from both trials and in wheat straw from one trial but did not increase in wheat hay or grain with increasing sampling intervals.

The maximum storage intervals of crop samples from harvest to analysis for total prothioconazole-derived residues were 469 days (15.4 months) for wheat forage, 1214 days (39.9 months) for wheat grain, 1221 days (40.1 months) for wheat hay, and 1203 days (39.5 months) for wheat straw. The combined residues of prothioconazole and prothioconazole desthio ("prothioconazole-derived residues") are relatively stable up to 1 year (interim report) in wheat matrices. Corrections due to apparent dissipation of combined prothioconazole and prothioconazole desthio residues in samples stored beyond a year are not necessary due to the low absolute (ppm) and % residue levels in wheat matrices. Residues of prothioconazole desthio are stable for up to 1 year and the degree of loss is not expected to exceed 30% after 40.1 months.

Conclusions: The submitted crop field trial residue data are adequate to satisfy data requirements. As stated under Directions for Use (860.1200), the applicant has proposed use on an "Oilseed Crop Subgroup" which consists of the members of the Oilseed Crop Group 20 with the exception of safflower seed and sunflower seed. The representative crops of Crop Group 20 are canola and sunflower. Currently, no crop subgroups have been defined by HED for Crop Group 20. The applicant has submitted crop field trial data for canola but not for sunflower. The available crop field trial data will support use of prothioconazole on the following oilseed commodities: rapeseed, canola, Indian rapeseed, field mustard seed, and crambe.

The submitted crop field trial data support the following tolerances for the combined residues of prothioconazole and its desthio metabolite: barley grain at 0.35ppm; barley hay at 7.0 ppm; barley straw at 4.0 ppm; dried shelled pea and bean, except soybean, subgroup 6C, at 0.90 ppm; peanut at 0.02 ppm; peanut hay at 6.0 ppm, rapeseed seed at 0.15 ppm; rice grain at 0.20

ppm; rice straw at 1.4 ppm; wheat grain at 0.07 ppm; wheat forage at 6.0 ppm; wheat hay at 4.5 ppm; and wheat straw 5.0 ppm. The tolerance values were determined using a statistical calculation with the available field trial data (See Appendix 2).

Residue data for wheat aspirated grain fractions were included with the processing study (see 860.1520). The residue data indicate that total prothioconazole-derived residues concentrate in aspirated grain fractions. Based on a processing factor of 245x and a HAFT residue of 0.045 ppm for wheat grain, the expected residues in wheat aspirated grain fractions following treatment at 1x would be 11.0 ppm. Therefore, a tolerance for aspirated grain fractions is needed to support the proposed uses. Because the applicant is not proposing use of prothioconazole on field corn, sorghum, or soybeans, the residue data from wheat are used to determine the tolerance level for aspirated grain fractions; these data indicate that a tolerance of 11 ppm would be appropriate.

The residue data for aspirated grain fractions indicate that residues of 1,2,4-triazole and the triazole conjugates do not concentrate in wheat aspirated grain fractions.

860.1520 Processed Food and Feed

46246218.der.wpd (Wheat)
46246222.der.wpd (Rice)
46246223.der.wpd (Peanut)
46246224.der.wpd (Canola)

Table 8. Summary of Processing Factors for Prothioconazole.

RAC	Processed Commodity	Average Processing Factor		
		Sum of prothioconazole and prothioconazole desthio	1,2,4-Triazole	Triazole Conjugate Residues
Canola	Meal	<0.7x	NC [1]	2.9x
	Refined oil	<0.7x	NC	<0.02x
Peanut	Meal	>7.9x	>1.9x	1.9x
	Refined oil	NC	NC	<0.01x
	Dry roasted peanuts	NC	>12.5x	0.5x
	Peanut butter	NC	>11.9x	0.6x
Rice	Polished Grain	<0.1x	NC	0.5x
	Bran	0.6x	NC	6.9x
	Hulls	4.4x	NC	0.3x
Wheat	Aspirated grain fractions	245x	NC	0.3x
	Bran	2.4x	NC	3.1x
	Flour	<0.4x	NC	0.5x
	Germ	2.0x	NC	3.6x
	Middlings	0.6x	NC	0.6x
	Shorts	1.0x	NC	1.5x

[1] NC = Not calculated. The processing factor could not be calculated because residues were below the LOQ in both the RAC and the processed fraction.

Canola: Bayer CropScience has submitted a processing study with canola. In a single test conducted in Ontario, Canada during 2000, the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC), was applied to canola plants beginning at the two-leaf stage as two broadcast foliar applications with a 27-day retreatment interval at 0.912-0.919 lb a.i./A/application (1.02-1.03 kg a.i./ha/application), for a total application rate of 1.83 lb a.i./A (2.05 kg a.i./ha; ~5 times the field trial application rate). Canola plants were cut at maturity 47 days after the last treatment and were allowed to dry in the field for 5 days prior to collection of canola seed from treated and control plots. Samples of canola seed were collected, and the remaining bulk samples were processed into meal and refined oil using simulated commercial procedures.

Samples were analyzed for total prothioconazole-derived residues (prothioconazole and the metabolite prothioconazole desthio) using the LC-MS/MS method RPA JA/03/01. The validated LOQ for total prothioconazole-derived residues was 0.02 ppm for canola seed and processed commodities. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method with

modifications. The validated LOQs for 1*H*-1,2,4-triazole were 0.02 ppm for canola seed and meal, and 0.01 ppm for canola oil. The validated LOQs for the triazole conjugates were 0.02 ppm for canola seed and oil, and 0.20 ppm for canola meal. The methods are adequate for data collection based on acceptable concurrent method recovery data.

The maximum storage intervals from collection to analysis for total prothioconazole-derived residues were 1261 days (41 months) for canola seed and 918 days (30 months) for processed canola commodities. Prothioconazole-derived residues and prothioconazole desthio residues are stable up to 1 year (interim report) in canola matrices. The degree of loss of prothioconazole-derived residues and prothioconazole desthio residues is not expected to exceed 30% after 41 months.

Total prothioconazole-derived residues did not concentrate in meal or refined oil (<0.7-fold each). Residues of the triazole conjugates concentrated in canola meal (2.9-fold), but not in refined oil (<0.02-fold). Processing factors could not be calculated for 1*H*-1,2,4-triazole in meal and refined oil, as residues were below the LOQ in these commodities.

Peanut: Bayer CropScience has submitted a processing study with peanut. In a single test conducted in GA during 2000, the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC), was applied to peanut plants during pod development as four broadcast foliar applications with 13- to 15-day re-treatment intervals at 0.899-0.901 lb a.i./A (1.01 kg a.i./ha), for a total application rate of 3.60 lb a.i./A (4.03 kg a.i./ha; ~5 times the field trial application rate). Peanuts were dug up 14 days after the last treatment and were left to dry in the field for 7 days prior to sample collection. Sub-samples of nutmeat were reserved, and the remaining bulk samples were processed into meal, refined oil, dry roasted peanuts, and peanut butter using simulated commercial procedures.

Samples were analyzed for total prothioconazole-derived residues (prothioconazole and the metabolite prothioconazole desthio), 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method. The validated LOQ for total prothioconazole-derived residues was 0.02 ppm for peanuts and processed commodities. The validated LOQs for 1*H*-1,2,4-triazole were 0.01 ppm for peanut nutmeat, meal, and refined oil and 0.05 ppm for dry roasted peanuts and peanut butter. The validated LOQs for the triazole conjugates were 0.01 ppm for refined oil, 0.05 ppm for peanut nutmeat, dry roasted peanuts, and peanut butter, and 1.5 ppm for peanut meal. The methods are adequate for data collection based on acceptable concurrent method recovery data.

The maximum storage intervals from collection to analysis for total prothioconazole-derived residues were 1090 days (36 months) for nutmeat and 911 days (31 months) for processed peanut commodities. Prothioconazole-derived residues and prothioconazole desthio residues are stable up to 12.7 months (interim report). The degree of loss of prothioconazole-derived residues and prothioconazole desthio residues is not expected to exceed 30% after 36 months.

Total prothioconazole-derived residues concentrated >7.9-fold (peanut meal). Processing factors could not be calculated for refined oil, dry roasted peanuts, or peanut butter because residues were below the LOQ in these commodities. Residues of 1*H*-1,2,4-triazole

concentrated >1.9-fold (meal), >12.5-fold (dry roasted peanuts), and >11.9-fold (peanut butter). A processing factor could not be calculated for refined oil because residues were below the LOQ in this commodity. Residues of the triazole conjugates concentrated 1.9-fold (peanut meal), and did not concentrate in refined oil, dry roasted peanuts or peanut butter (<0.01-fold, 0.5-fold and 0.6-fold, respectively).

Rice: Bayer CropScience has submitted a processing study with rice. In a single test conducted in MS during 2000, the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC), was applied to rice plants during panicle formation as two broadcast foliar applications with a 13-day re-treatment interval at 1.07 lb a.i./A (1.20 kg a.i./ha) for the first application and 0.75 lb a.i./A (0.84 kg a.i./ha) for the second application, for a total application rate of 1.82 lb a.i./A (2.04 kg a.i./ha; ~5 times the field trial application rate). Rice grain was harvested at maturity 49 days after the last treatment. Sub-samples of rice grain (RAC) were collected, and the remaining bulk samples were processed into polished grain, bran, and hulls using simulated commercial procedures.

Samples were analyzed for total prothioconazole-derived residues (prothioconazole and the metabolite prothioconazole desthio), 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method. The validated LOQs for prothioconazole-derived residues were 0.02 ppm for rice grain, polished grain, and bran, and 0.01 ppm for rice hulls. The validated LOQ for 1*H*-1,2,4-triazole was 0.01 ppm, and the validated LOQs for the triazole conjugates were 0.05 ppm for rice grain, polished grain, and hulls, and 0.75 ppm for rice bran. The methods are adequate for data collection based on acceptable concurrent method recovery data.

The maximum storage intervals from collection to analysis for total prothioconazole-derived residues were 1222 days (40 months) for rice grain and 902 days (30 months) for processed rice commodities. Prothioconazole-derived residues are stable up to 1 year (interim report) in rice matrices. The degree of loss of prothioconazole-derived residues and prothioconazole desthio residues is not expected to exceed 30% after 40 months in rice and its processed commodities.

Total prothioconazole-derived residues concentrated in rice hulls (4.4-fold) but not in polished grain or bran (<0.1-fold and 0.6-fold, respectively). Residues of the triazole conjugates concentrated in bran (6.9-fold), but did not concentrate in polished rice or hulls (0.5-fold and 0.3-fold, respectively). Residues of 1*H*-1,2,4-triazole were below the LOQ (<0.01 ppm) in polished rice, bran, and hulls. The reported processing factors did not exceed the theoretical concentration factors of 5.0-fold for rice hulls and 7.7-fold for rice bran.

Wheat: Bayer CropScience has submitted a processing study with wheat. In a single test conducted in KS during 2000, the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) was applied to wheat plants during flowering as two broadcast foliar applications with an 11-day retreatment interval at 0.564 lb a.i./A (0.632 kg a.i./ha) for the first application and 0.903 lb a.i./A (1.01 kg a.i./ha) for the second application, for a total application rate of 1.467 lb a.i./A (1.64 kg a.i./ha; ~5.6 times the field trial application rate). Wheat grain was harvested at maturity 47 days after the last treatment. Samples of wheat grain

(RAC) were collected, and the remaining bulk samples were processed into aspirated grain fractions, bran, middlings, shorts, flour, and germ using simulated commercial procedures.

Samples were analyzed for total prothioconazole-derived residues (prothioconazole and the metabolite prothioconazole desthio), 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method. The validated LOQs for prothioconazole-derived residues were 0.02 ppm for wheat grain, bran, flour, middlings, and shorts, and 0.25 ppm for aspirated grain fractions. The validated LOQ for 1*H*-1,2,4-triazole was 0.01 ppm for wheat grain and all processed commodities, and the validated LOQs for the triazole conjugates were 0.01 ppm for wheat grain, 0.20 ppm for aspirated grain fractions and bran, 0.30 ppm for wheat germ and shorts, and 0.25 ppm for middlings. The methods are adequate for data collection based on acceptable method validation and concurrent recovery data.

The maximum storage intervals from collection to analysis for total prothioconazole-derived residues were 1285 days (42 months) for wheat grain and 909 days (30 months) for processed wheat commodities. Prothioconazole-derived residues are relatively stable up to 1 year (interim report) in wheat matrices. Corrections due to apparent dissipation of prothioconazole-derived residues in samples stored beyond a year are not necessary due to the low absolute (ppm) and % residue levels in wheat matrices. Residues of prothioconazole desthio are stable for up to 1 year and the degree of loss is not expected to exceed 30% after 42 months.

Residues of prothioconazole in/on wheat grain (RAC) from the processing study were 0.051 ppm for total prothioconazole-derived residues, less than the LOQ (<0.01 ppm) for 1*H*-1,2,4-triazole, and 1.33 ppm for residues of the triazole conjugates (average of triplicate analyses for each). Total prothioconazole-derived residues concentrated in aspirated grain fractions (245-fold), bran (2.4-fold), and germ (twofold). There was no concentration of residues in flour, middlings, and shorts (<0.4-fold, 0.6-fold, and 1-fold, respectively). Residues of the triazole conjugates concentrated in bran (3.1-fold), germ (3.6-fold), and shorts (1.5-fold), but did not concentrate in aspirated grain fractions, flour, and middlings (0.3-fold, 0.5-fold, and 0.6-fold). Residues of 1*H*-1,2,4-triazole were below the LOQ (<0.01 ppm) in all processed wheat commodities.

The reported processing factors do not exceed the theoretical concentration factors of 7.7-fold for wheat bran, 1.4-fold for wheat flour, and 8.3-fold for wheat shorts.

Conclusions: The submitted processing data for canola, peanut, rice, and wheat are adequate to satisfy data requirements. The processing data indicate that total prothioconazole-derived residues concentrate >7.9x in peanut meal, 4.4x in rice hulls, 2.4x in wheat bran, and 2.0x in wheat germ. Because total prothioconazole-derived residues were below the LOQ in/on all peanut nutmeat samples from the crop field trials, the actual residues observed in peanut meal in the processing study will be used to determine expected residues. Total prothioconazole-derived residues averaged 0.159 ppm in peanut meal in the processing study. When this value is corrected for the exaggeration rate of the study, 5x, expected residues in peanut meal following treatment at 1x are calculated to be 0.032 ppm. Because the tolerance for peanut

nutmeat will be established at the LOQ (0.02 ppm) and because expected residues in peanut meal are less than 2x the LOQ for peanut nutmeat, a tolerance for peanut meal is not needed.

Based on a processing factor of 4.4x for rice hulls and a HAFT residue of 0.191 ppm for rice grain, the expected residues in rice hulls following treatment at 1x would be 0.840 ppm. Because the expected residues are greater than the proposed tolerance of 0.60 ppm for rice grain, a tolerance for rice hulls is needed; a tolerance of 0.90 ppm is appropriate.

Based on processing factors of 2.4x for wheat bran and 2.0x for wheat germ and a HAFT residue of 0.045 ppm for wheat grain, the expected residues in wheat bran and germ following treatment at 1x would be 0.11 and 0.09 ppm, respectively. Because the germ residue is less than the recommended tolerance of 0.10 ppm for wheat grain and because the bran residue is only slightly greater than the recommended tolerance for wheat grain, tolerances are not appropriate for germ and bran.

The HAFT total prothioconazole-derived residues in barley grain are 0.151 ppm. Based on the 2.4x processing factor for wheat bran, the expected residues in barley bran following treatment at 1x would be 0.36 ppm. Because expected residues are not significantly greater than the proposed tolerance of 0.35 ppm for barley grain, a tolerance for barley bran is not needed.

The processing data indicate that residues of 1,2,4-triazole may concentrate in peanut meal (>1.9x), dry roasted peanuts (>12.5x), and peanut butter (>11.9x). Because 1,2,4-triazole residues were below the LOQ in/on all but one peanut nutmeat sample from the crop field trials, the actual residues observed in peanut meal in the processing study should be used to determine expected residues. Residues of 1,2,4-triazole averaged 0.019, 0.125, and 0.119 ppm in peanut meal, dry roasted peanuts, and peanut butter, respectively. When these values are corrected for the exaggeration rate of the study, 5x, expected residues of 1,2,4-triazole in peanut meal, dry roasted peanuts, and peanut butter following treatment at 1x are calculated to be 0.004, 0.025, and 0.024 ppm, respectively.

The processing data indicate that residues of the triazole conjugates may concentrate in canola meal (2.9x), peanut meal (1.9x), rice bran (6.9x), wheat bran (3.1x), wheat germ (3.6x), and wheat shorts (1.5x). The processing factor for canola meal exceeds the theoretical concentration factor of 1.9x; therefore, the theoretical concentration factor will be used to determine expected residues. Based on these processing factors and HAFT residues of 0.716, 3.390, 0.553, and 1.76 ppm for canola seed, peanut, rice grain, and wheat grain, respectively, the expected residues of triazole conjugates in processed commodities following treatment at 1x would be: 1.36 ppm in canola meal; 6.44 ppm in peanut meal; 3.82 ppm in rice bran; 5.46 ppm in wheat bran; 6.34 ppm in wheat germ; and 2.64 ppm in wheat shorts.

860.1650 Submittal of Analytical Reference Standards

As of 3/9/05, an analytical reference standard for prothioconazole is available in the National Pesticide Standards Repository. No standards for the metabolite (prothioconazole desthio) included in the tolerance expression or for the internal standards used in the enforcement method are available. 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:

- prothioconazole desthio [JAU6476-desthio; (2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-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]1H-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:

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

(Note that the mail will be returned if the extended zip code is not used.)

860.1850 Confined Accumulation in Rotational Crops

46246225.der.wpd
46246226.der.wpd

Bayer 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).

MRID 46246225/46246226:
Phenyl-label study
Bayer CropScience has submitted a confined rotational crop study with [phenyl-UL-^{14}C]-prothioconazole (specific activity 3.31 MBq/mg) in rotated crops. The radiolabeled test substance was dissolved in acetonitrile (ACN) and applied to bare sandy loam soil in a single planting container at 0.52 lb a.i./A (582 g a.i./ha). Rotational Swiss chard, turnip, and spring wheat were planted at plantback intervals (PBIs) of 28, 146, and 269 days.

Total radioactive residues (TRRs), expressed as JAU6476 equivalents were determined by combustion and/or liquid scintillation counting (LSC). Aliquots of each raw agricultural commodities (RACs) were extracted using acetonitrile (ACN/water; 4:1), containing 1 mg/mL of cysteine HCl, followed by accelerated solvent extraction (ASE) and/or acidic extraction using dioxane/2N HCl (9:1). As needed, extracts were cleaned up by solid phase extraction (SPE) prior to analysis by thin-layer chromatography (TLC) and/or high performance liquid chromatography (HPLC). Metabolites were identified by co-chromatography with authentic

reference compounds as well as by spectroscopic methods (mass spectroscopy or NMR). Samples were stored for a maximum of 57 days between harvest and HPLC analysis.

The TRRs were variable from the first rotation to the second and third rotations, as there was no clear pattern of increasing or decreasing TRRs over time. TRRs from the first rotation to the second and third rotations were as follows: wheat forage (0.021 to 0.062 to 0.040 ppm); wheat hay (0.114 to 0.135 to 0.160 ppm); wheat straw (0.450 to 0.307 to 0.312 ppm); wheat grain (0.007 ppm at 28 days; others not determined); Swiss chard (0.039 to 0.053 to 0.021 ppm); turnip tops (0.046 to 0.028 to 0.036 ppm); and turnip roots (0.043 to 0.031 to 0.015 ppm). Because of the low radioactivity levels in wheat grain, samples from the 146- and 269-day PBIs were not analyzed.

The majority of the TRRs (61-87% of the TRRs) were released from all rotational crop commodities with ACN/water, with the exception of wheat grain. ACN/water released only 23% of the TRRs from wheat grain. Accelerated solvent extraction with ACN/water released an additional 4 to 8% of the TRRs from wheat hay, straw, and grain. Acid hydrolysis with HCl/dioxane released approximately 9 to 21% of the TRRs from wheat hay and straw. Non-extractable residues remaining following extraction/hydrolysis accounted for less than <39% of the TRRs (#0.029 ppm) in rotational crop matrices. Total accountabilities ranged from 99.1-143%.

Total identified residues ranged from 34 to 77% of the TRRs (0.011-0.304 ppm) in rotated crop commodities, except for wheat grain. The highest absolute residues identified were in wheat straw (0.179-0.304 ppm) at all PBIs. Only 5% of the TRRs were identified in wheat grain (0.003 ppm). Prothioconazole was detected at very low levels (<1% of the TRRs; <0.005 ppm) only in samples of 146-day PBI Swiss chard, 28-day PBI turnip root, 146-day PBI turnip top, and 28- and 146-day PBI wheat straw.

JAU6476-desthio was detected in all rotational crop commodities at all PBIs analyzed, and was found to be a major metabolite (present at >10% of the TRRs; 0.003 -0.016 ppm) in the following rotational crop commodities: 28- and 146-day PBI Swiss chard, 28-, 146-, and 269-day PBI turnip root, 28- and 269-day PBI turnip top, 28-day PBI wheat forage, and 28- and 146-day PBI wheat hay. JAU6476 sulfonic acid was found to be a major metabolite in 28-day PBI wheat hay (0.013 ppm) and 269-day PBI wheat straw (0.04 ppm). Glucosides of JAU6476-desthio-dihydroxy-olefin (two isomers) were detected in all rotational crop commodities except 28-day PBI wheat grain, and one or both isomers were found to be major metabolites in 28-day PBI Swiss chard (0.005 ppm), 28-day PBI turnip root (0.005 ppm), all rotations of turnip top (0.004-0.006 ppm), 146- and 269-day PBI wheat forage (<0.01 ppm), all rotations of wheat hay (0.012-0.029 ppm), and 269-day PBI wheat straw (0.033 ppm). Up to three isomers of the glucoside of JAU6476-hydroxy-desthio were also detected in all rotational crop commodities, except 28-day PBI wheat grain and 269-day PBI wheat forage, and at least one of the isomers accounted for significant radioactivity in 146-day PBI Swiss chard (0.006 ppm), 28-day PBI turnip root and top ($\leq$0.006 ppm), and 146-day PBI wheat straw (0.031 ppm).

Additional metabolites identified in rotational crops, each at <10% of the TRRs, were

JAU6476-triazolinone, JAU6476-3-hydroxy-desthio, JAU6476-4-hydroxy-desthio, JAU6476-6-hydroxy-desthio, JAU6476-α-hydroxy-desthio, JAU6476-α-acetoxy-desthio, JAU6476-benzylpropyldiol and its glucoside, and JAU6476-disulfide.

Triazole-label study

Bayer CropScience has submitted a confined rotational crop study with [triazole-3,5-^{14}C]-prothioconazole (specific activity 18.6 mCi/mmole) in rotated crops. The radiolabeled test substance was mixed with formulation blank and applied to bare sandy loam soil in a single planting container as four applications, with a 14-day retreatment interval, at ~0.18 lb a.i./A/application (~204 g a.i./ha), for a total rate of 0.727 lb a.i./A (815 g a.i./ha). Rotational Swiss chard, turnip, and spring wheat were planted at PBIs of 30, 125, and 366 days.

TRRs, expressed as JAU6476 equivalents were determined by combustion and/or LSC. Aliquots of each RAC were extracted using methanol and/or acetonitrile (ACN/water; 4:1), containing 1 mg/mL of cysteine HCl. If 10% or more of the TRRs in a matrix remained unextracted, ASE followed by reflux with MeOH/2N HCl (1:1) and/or dioxane/2N HCl (4:1) was performed. Identification of metabolites was achieved using reverse phase HPLC. Polar residues from sample extracts with retention times between 11 min and 15 min were further separated by ion-pair chromatography into two peaks (TA and THPA/TAA). The THPA and TAA mixture was separated by esterification followed by analysis using a third reverse phase HPLC system. Samples were stored for a maximum of 47 days between harvest and HPLC analysis.

The TRRs were variable from the first rotation to the second and third rotations, as there was no clear pattern of increasing or decreasing TRRs over time. TRRs from the first rotation to the second and third rotations were as follows: wheat forage (0.251 to 0.575 to 0.439 ppm); wheat hay (2.224 to 2.580 to 2.016 ppm); wheat straw (1.695 to 1.361 to 1.597 ppm); wheat grain (3.806 to 4.136 to 5.875 ppm); swiss chard (0.188 to 0.047 to 0.129 ppm); turnip tops (0.131 to 0.507 to 0.084 ppm); and turnip roots (0.059 to 0.442 to 0.061 ppm). TRRs were highest in wheat grain, hay, and straw.

Extraction with ACN/water (Swiss chard and turnip root and top) or ACN/water and MeOH (wheat forage, hay, straw, and grain) released the majority of the TRRs (70-98% of the TRRs). Accelerated solvent extraction with ACN/water at 50°C and 100°C released an additional ~3 to 26% of the TRRs from all wheat matrices, and subsequent ASE with water released ~1 to 5% of the TRRs in wheat hay, straw, and grain. Acid hydrolysis with HCl/dioxane or HCl released ~1 to 5% of the TRRs in wheat hay, straw, and grain. Non-extractable residues remaining following extraction/hydrolysis accounted for <1 to 6% of the TRRs (0.002-0.076 ppm) in rotational crop matrices. Total accountabilities ranged from 97-102%.

Total identified residues ranged from 72 to 99% of the TRRs (0.034-5.43 ppm) in rotated crop commodities. Prothioconazole was not detected in any rotational crop commodity. Triazolylalanine was the major residue identified in Swiss chard, turnip root and top, and wheat forage and grain, at 44 to 93% of the TRRs (0.023-3.9 ppm) at all PBIs. Triazolylalanine accounted for a major portion of the radioactivity in wheat hay and straw, at 15 to 36% of the TRRs (0.197-0.85 ppm). THPA was a major residue in Swiss chard and

wheat forage, hay, and straw, at 18 to 39% of the TRRs (0.008-0.87 ppm). THPA was also found at ≤7% of the TRRs (≤ 0.047 ppm) in rotated turnip root and top and wheat grain from the 30- and 125-day PBIs. THPA was not found in these commodities from the 366-day PBI. Triazolylacetic acid accounted for significant radioactivity in wheat hay, straw, and grain (10-29% of the TRRs; 0.2-1.5 ppm). Triazolylacetic acid was found at ≤6% of the TRRs (≤0.034 ppm) in Swiss chard, turnip root and top, and wheat forage. Additional metabolites identified in rotational crops, each at ≤7% of the TRRs (≤0.063 ppm), were triazolyl-ethanol, triazolyl-ethanol glucoside, JAU6476-desthio, and JAU6476-α-hydroxy-desthio. Free triazole (1*H*-1,2,4-triazole) was not identified in any rotational crop commodity.

Based on the results of the study, it was concluded that the metabolism in rotational crops was qualitatively similar to that in the primary crops peanut, sugar beet and wheat, as the same major metabolites were detected. Additionally, 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.

Conclusions: The submitted confined rotational crop data are adequate to satisfy data requirements. Based on the results of the phenyl-label study, the applicant concluded that metabolism 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. The applicant did not discuss prothioconazole metabolism in soil.

The applicant did not propose a metabolic pathway for [triazole-3,5-^{14}C]-prothioconazole in rotational crops. 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.

860.1900 Field Accumulation in Rotational Crops

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Bayer CropScience has submitted a limited field rotational crop study on the representative crops mustard greens (leafy vegetable), turnip (root vegetable), and wheat (cereal grain). Three trial sites, in GA (Region 2), IN (Region 5), and KS (Region 5), were used for each crop. At each trial site, two spray applications of the 4 lb/gal (480 g/L) suspension concentrate formulation (flowable concentrate; FlC) were made to bare soil at ~0.36 lb a.i./A/application (~0.40 kg a.i./ha), for total application rates of ~0.72 lb a.i./A (0.81 kg a.i./ha); applications

were made with a ~14-day retreatment interval. Mustard, turnip, and wheat were planted at plantback intervals (PBIs) of 1, 4, 8, and 12 months, and samples of mustard greens, turnip roots and tops, and wheat forage, hay, grain, and straw were collected at crop maturity. For winter wheat, the 1-month and 4-month PBI trials were conducted in GA (Region 2), IN (Region 5), and KS (Region 5); the 8- and 12-month PBI trials for spring wheat were conducted in ID (Region 11), ND (Region 7), and OR (Region 12).

Samples were analyzed for the combined residue of prothioconazole and prothioconazole desthio (determined as prothioconazole sulfonic acid and prothioconazole desthio and designated "total prothioconazole-derived residues" in the method) using LC-MS/MS method RPA JA/03/01. The validated LOQs were 0.02 ppm for each analyte in wheat grain and 0.05 ppm for each analyte in mustard greens, turnip root and top, and wheat forage, hay, and straw. Samples were analyzed for residues of 1*H*-1,2,4-triazole and the triazole conjugates triazolylalanine and triazolylacetic acid using an LC-MS/MS method (Bayer Report No. G200598). The validated LOQs for 1*H*-1,2,4-triazole were 0.01 ppm (mustard greens, turnip top, and wheat forage, hay, grain, and straw) and 0.05 ppm (turnip root). The validated LOQs for triazolylalanine were 0.01 ppm (wheat forage, hay, grain, and straw), 0.05 ppm (turnip root and top), and 0.10 ppm (mustard greens). The validated LOQs for triazolylacetic acid were 0.01 ppm (mustard greens and wheat forage, hay, and grain), 0.025 ppm (wheat straw), and 0.05 ppm (turnip root and top). The methods are adequate for data collection based on acceptable concurrent method recovery data.

At the 1-month PBI, total prothioconazole-derived residues were below the LOQ (<0.02 ppm for wheat grain and <0.05 ppm for all other commodities) in mustard greens, turnip root and top, and wheat forage, hay grain, and straw. Because residues of prothioconazole were below the LOQ in all samples from the 1-month PBI, samples from the 4-, 8-, and 12-month PBIs were not analyzed for total prothioconazole-derived residues.

At the 1-month PBI, residues of 1*H*-1,2,4-triazole were below the LOQ (<0.01 ppm) in/on all rotational crop matrices except wheat straw and grain; quantifiable residues of 0.01 ppm were detected in/on two samples each of wheat straw and grain. At the 4-month PBI, residues of 1*H*-1,2,4-triazole were below the LOQ (<0.01 ppm) in/on all rotational crop matrices. Samples from the 8- and 12-month PBIs were not analyzed for 1*H*-1,2,4-triazole residues.

At the 1-month PBI, total residues of triazole conjugates (triazolylalanine and triazolylacetic acid) were 0.102-0.313 ppm (mustard greens), 0.301-0.567 ppm (turnip root), 0.263-0.484 ppm (turnip top), 0.080-1.174 ppm (wheat forage), 0.303-2.025 ppm (wheat hay), 0.710-3.465 ppm (wheat grain), and 0.074-0.719 ppm (wheat straw). At the 4-month PBI, total triazole conjugate residues were 0.081-0.392 ppm (mustard greens), 0.066-0.201 ppm (turnip root), 0.095-0.254 ppm (turnip top), 0.164-0.333 ppm (wheat forage), 0.406-0.763 ppm (wheat hay), 0.615-1.754 ppm (wheat grain), and 0.103-0.278 ppm (wheat straw). The average triazole conjugate residues in each commodity decreased from the 1-month PBI to the 4-month PBI. Samples from the 8- and 12-month PBIs were not analyzed for triazole conjugate residues.

The maximum storage intervals from harvest to analysis for the combined residue of prothioconazole and prothioconazole desthio (designated "total prothioconazole-derived

residues") were 1263 days (41.5 months) for mustard greens, 1243 days (40.8 months) for turnip tops and roots, 1002 days (32.9 months) for wheat forage, 943 days (31.0 months) for wheat hay, 919 days (30.2 months) for wheat grain, and 911 days (29.9 months) for wheat straw. The combined residues of prothioconazole and prothioconazole desthio ("prothioconazole-derived residues") are relatively stable up to 1 year (interim report) in wheat matrices, mustard greens, turnip tops and roots. Corrections due to apparent dissipation of the combined residue of prothioconazole and prothioconazole desthio (designated "prothioconazole-derived residues") in samples stored beyond a year are not necessary due to the low absolute (ppm) and % residue levels in plant matrices. Residues of prothioconazole desthio are stable for up to 1 year and the degree of loss is not expected to exceed 30% after 41.5 months after freezer storage.

Conclusions: The submitted field rotational crop residue data are adequate to satisfy data requirements. The applicant 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 combined residues of prothioconazole and prothioconazole desthio ("prothioconazole-derived residues") in mustard greens, turnip root and top, and wheat forage, hay grain, and straw at the 1-month PBI, are adequate to support the proposed rotational crop restrictions. With these restrictions, tolerances will not be needed for prothioconazole rotated crops, based on a residue definition of the combined residues of prothioconazole and prothioconazole desthio, calculated as prothioconazole. Note that finite residues of triazole conjugates exist at the PBI of one month, and the issue of such residues in rotatational crops was noted in the aggregate exposure assessment of triazole derivatives for human-health risk assessment (D322215, 02/07/2006).

860.1550 Proposed Tolerances

Bayer CropScience has proposed 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 the desthio metabolite in/on raw agricultural and processed commodities, and for residues of prothioconazole, the desthio and 4-hydroxy metabolites, and conjugates that can be converted to these three compounds by acid hydrolysis in/on cattle commodities.

The proposed tolerance expression for plant commodities should be revised to specify that residues of the desthio metabolite are calculated as parent. The tolerance expression for livestock commodities should be revised to residues of prothioconazole, prothioconazole desthio, and conjugates that are converted to these two compounds by acid hydrolysis, calculated as prothioconazole .

There are currently no established Codex or Mexican MRLs for prothioconazole. MRLs in Canada will be established as a result of this Joint Review project. An International Residue Limit Status sheet is attached to this review.

Pending receipt of the required storage stability data, the available crop field trial data will

support tolerances for residues of prothioconazole and the desthio metabolite in/on: barley, grain; barley, hay; barley, straw; barley, bran; grain, aspirated grain fractions; pea and bean, dried shelled, except soybean, subgroup 6C; peanut; peanut, hay; rapeseed, seed; rice, grain; rice, straw; rice, hulls; wheat, grain; wheat, forage; wheat, hay; and wheat, straw.

Tolerance values were determined by application of the NAFTA statistical calculation spreadsheet to the validated field trial data (See Appendix II). In those instances where a substantial quantity of censored data (values $\leq$ LOQ) existed, the recommended value based on a log normal distribution was replaced with the mean plus three standard deviation value. This occurred for pea and bean dried, rapeseed seed, rice grain, and wheat grain

The available data indicate that the proposed tolerance of 0.06 ppm for wheat grain is too low; a revised tolerance of 0.07 ppm should be proposed. The available crop field trial data indicate that the proposed tolerances of 13.0 ppm for aspirated grain fractions , of 7.0 ppm for wheat forage are too high. Revised tolerances of 11 ppm and 6.0 ppm, respectively, should be proposed. The available crop field trial data indicate that the proposed tolerances of 4.0 ppm for wheat hay and 2.3 ppm for wheat straw are too low. Revised tolerances of 4.5 ppm and 5.0 ppm, respectively, should be proposed.

The available crop field trial data indicate that proposed tolerances for barley grain of 0.2 ppm and for barley straw of 2.0 ppm are too low. Revised tolerances of 0.35 ppm and 4.0 ppm, respectively, should be proposed.

The available crop field trial data indicate that proposed tolerance for the pea and bean subgroup, dried, shelled, except soybean, of 0.8 ppm is too low. A revised tolerance of 0.9 ppm should be proposed.

The available crop field trial data indicate that proposed tolerance for peanut hay of 5.0 ppm is too low. A revised tolerance of 6.0 ppm should be proposed.

The available crop field trial data indicate that the proposed tolerance for rice grain of 0.25 ppm is too high. A revised tolerance of 0.20 ppm should be proposed. Likewise, the available field trial data indicate that the proposed tolerance for rice straw of 1.5 ppm is too high. A revised tolerance of 1.4 ppm should be proposed.

Additional crop field trial data are required to support the proposed tolerances for black mustard seed, borage seed, flax seed, and Indian mustard seed.

The proposed tolerances for canola seed, crambe seed, field mustard seed, and Indian rapeseed are not needed. According to 40 CFR §180.1(h), a tolerance for rapeseed will cover these commodities.

The ruminant feeding study will support tolerances for the combined residue of prothioconazole, prothioconazole desthio, and metabolites that are acid hydrolyzed to these two compounds, calculated as prothioconazole , in cattle, goat, hog, horse, and sheep commodities. The applicant must propose tolerances for the fat, meat, and meat byproducts of

goat, horse, and sheep, and must propose tolerances for the meat byproducts of hogs. The values proposed by the applicant are inappropriate as they included the 4-hydroxy prothioconazole metabolite and conjugates thereof that can be acid hydrolyzed to 4-hydroxy prothioconazole. The appropriate levels for the tolerances are listed in Table 9.

A poultry metabolism study will tentatively support tolerances for the combined residue of prothioconazole, prothioconazole desthio, and metabolites that are acid hydrolyzed to these two compounds, calculated as prothioconazole , at the LOQs of the analytical method, for poultry liver. The results of the poultry metabolism study indicate that tolerances are not needed for the remaining poultry commodities. A poultry feeding study must be conducted and the enforcement analytical method must be validated for poultry commodities to sustain these tentative conclusions.

The proposed tolerances should be revised to reflect the correct commodity definitions as specified in Table 9.

Table 9. Tolerance Summary for Prothioconazole.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct commodity definition*
Tolerances for the combined residues of 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]-1H-1,2,4- triazole-1-ethanol], calculated as prothioconazole			
Barley, grain	0.2	0.35	The proposed tolerance is too low.
Barley, hay	7.0	7.0	
Barley, straw	2.0	4.0	The proposed tolerance is too low.
Barley, pearled barley	0.2	Delete, not needed	A separate tolerance is not needed for pearled barley.
Barley, bran	0.4	Delete, not needed	A separate tolerance is not need for barley, bran.
Black mustard, seed	0.1	Delete, not allowed at this time	Additional crop field trial data are needed to support this tolerance.
Borage, seed	0.1	Delete, not allowed at this time	Additional crop field trial data are needed to support this tolerance.
Canola, seed	0.1	Delete, not needed	As specified under 40 CFR §180.1(h), a tolerance for rapeseed applies to canola seed and crambe seed.
Crambe, seed	0.1	Delete, not needed	
Field mustard, seed	0.1	Delete, not needed	Covered under the tolerance for rapeseed.
Flax, seed	0.1	Delete, not allowed at this time	Additional crop field trial data are needed to support this tolerance.
Grain, aspirated fractions	13.	11	The proposed tolerance is too high; *Grain, aspirated grain fractions*
Indian mustard, seed	0.1	Delete, not allowed at this time	Additional crop field trial data are needed to support this tolerance.
Indian rapeseed	0.1	Delete, not needed	Covered under the tolerance for rapeseed.
Pea and bean, dried, shelled, except soybean, subgroup	0.8	0.90	The proposed tolerance is too low. *Pea and bean, dried shelled, except soybean, subgroup 6C*
Peanut, nutmeat	0.02	0.02	*Peanut*
Peanut, hay	5.0	6.0	The proposed tolerance is too low.
Peanut, meal	0.3	Delete, not needed	A separate tolerance is not needed for peanut meal.
Rapeseed, seed	0.1	0.15	The proposed tolerance is too low.
Rice, grain	0.25	0.20	The proposed tolerance is too high.
Rice, straw	1.5	1.4	The proposed tolerance is too high.
Rice, hulls	1.0	0.90	The proposed tolerance is too high.
Wheat, grain	0.06	0.07	The proposed tolerance is too low.

Table 9. Tolerance Summary for Prothioconazole.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct commodity definition*
Wheat, forage	7.0	6.0	The proposed tolerance is too high.
Wheat, hay	4.0	4.5	The proposed tolerance is too low.
Wheat, straw	2.3	5.0	The proposed tolerance is too low.
Wheat, bran	1.5	Delete, not needed.	Covered under the tolerance for wheat, grain
Wheat, germ	0.15	Delete, not needed.	Covered under the tolerance for wheat, grain.
Tolerances for 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] and conjugates convertible to these two compounds by acid hydrolysis, calculated as prothioconazole			
Milk	0.006	0.02	The proposed tolerance is too low.
Cattle, fat	0.1	0.1	
Cattle, meat	0.01	0.02	The proposed tolerance is too low.
Cattle, meat byproducts	1.2	0.20	The proposed tolerance is too high.
Goat, fat	None	0.1	Extrapolated from cattle.
Goat, meat	None	0.02	Extrapolated from cattle.
Goat, meat byproducts	None	0.20	Extrapolated from cattle.
Hog, meat byproducts	None	0.05	Extrapolated from cattle.
Horse, fat	None	0.1	Extrapolated from cattle.
Horse, meat	None	0.02	Extrapolated from cattle.
Horse, meat byproducts	None	0.20	Extrapolated from cattle.
Sheep, fat	None	0.1	Extrapolated from cattle.
Sheep, meat	None	0.02	Extrapolated from cattle.
Sheep, meat byproducts	None	0.20	Extrapolated from cattle.
Poultry, liver	None	0.02	A tolerance is needed.

Attachments:
International Residue Limit Status sheet
Appendix I - Chemical Names and Structures of Prothioconazole and its Transformation Products

Appendix II - Statistical Calculation of Tolerances

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: 03/09/05

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#4F6830 DP Barcode: D303508 and D314517 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: S.Funk/IO
	Residue definition: combined residues of 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]-1H-1,2,4- triazole-1-ethanol], calculated as prothioconazole (plant commodities); or 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] and conjugates convertible to these two compounds by acid hydrolysis, calculated as prothioconazole (livestock commodities)

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Prothioconazole and the desthio metabolite:	
		Barley, grain	0.35
		Barley, hay	7.0
		Barley, straw	4.0
		Grain, aspirated fractions	11.
		Pea and bean, dried, shelled, except soybean, subgroup	0.90
		Peanut	0.02
		Peanut, hay	6.0
		Rapeseed, seed	0.15
		Rice, grain	0.20
		Rice, straw	1.4
		Rice, hulls	0.90
		Wheat, grain	0.07
		Wheat, forage	6.0
		Wheat, hay	4.5
		Wheat, straw	5.0
		Milk	0.02
		Cattle, fat	0.1

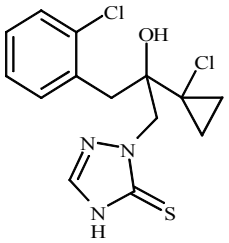
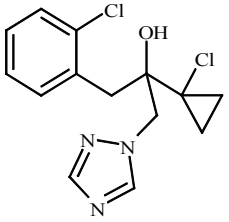
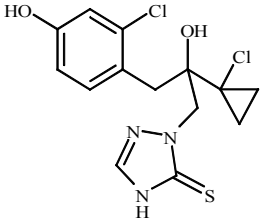
INTERNATIONAL RESIDUE LIMIT STATUS

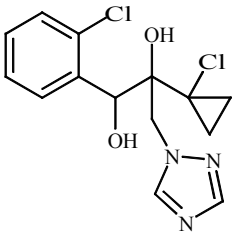
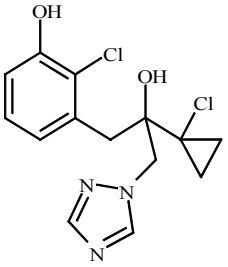
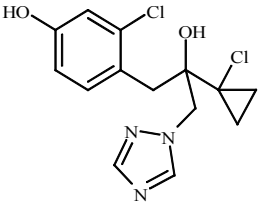
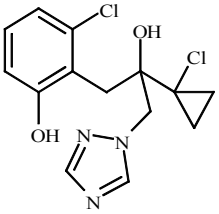
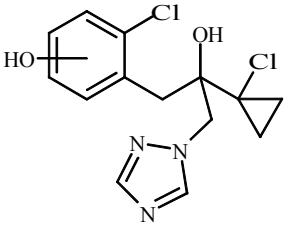
		Cattle, meat	0.02
		Cattle, meat byproducts	0.2
		Goat, fat	0.1
		Goat, meat	0.02
		Goat, meat byproducts	0.2
		Hog, meat byproducts	0.05
		Horse, fat	0.1
		Horse, meat	0.02
		Horse, meat byproducts	0.2
		Sheep, fat	0.1
		Sheep, meat	0.02
		Sheep, meat byproducts	0.2
		Poultry, liver	0.02

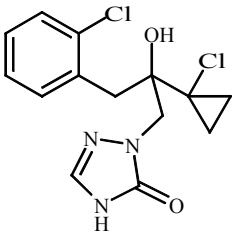
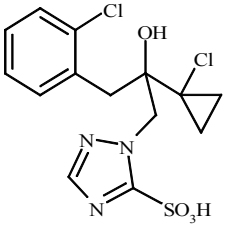
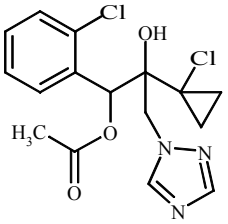
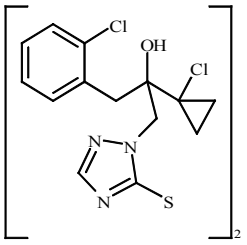
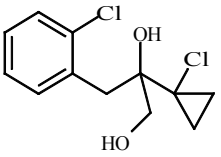
Limits for Canada	Limits for Mexico
□ No Limits □ No Limits for the crops requested Limits to be established under this Joint Review project.	X No Limits □ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

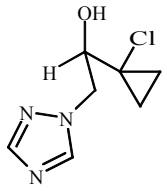
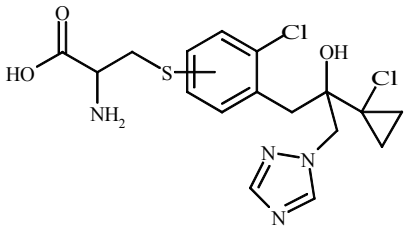
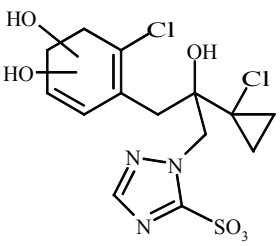
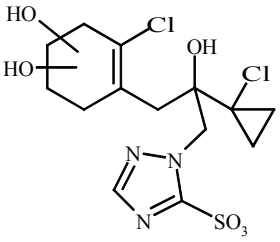
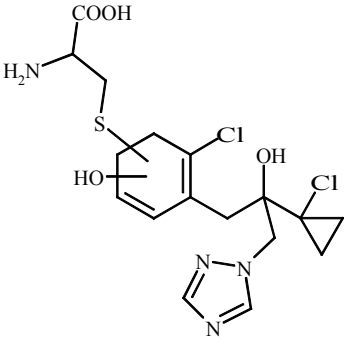
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

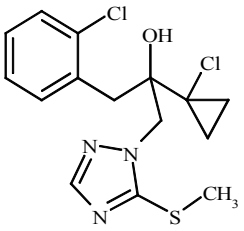
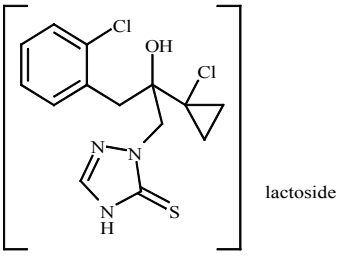
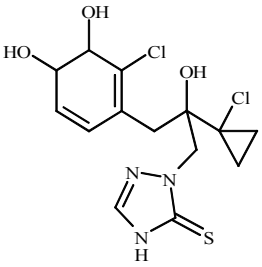
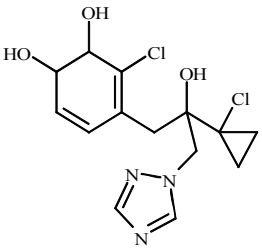
Notes/Special Instructions:S.Funk, 03/17/05

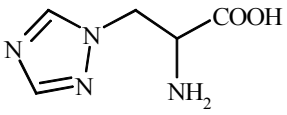
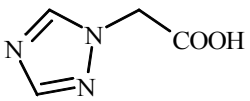
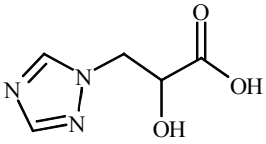
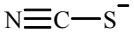
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
Prothioconazole; JAU6476 [Parent] *Wheat forage, hay, straw, and grain* *Peanut hay* *Sugar beet tops* *Rotated Swiss chard, turnip tops and root, and wheat straw* *Goat milk, liver, kidney, muscle, and fat* *Hen egg, liver, muscle, and fat*	2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione	
Prothioconazole desthio; JAU6476-desthio [included in tolerance expression for plant and animal commodities] *Wheat forage, hay, straw, and grain* *Peanut hay and nutmeat* *Sugar beet tops and root* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain* *Goat milk, liver, kidney, muscle, and fat* *Hen egg, liver, muscle, and fat*	α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-1H-1,2,4-triazole-1-ethanol	
Prothioconazole-4-hydroxy; JAU6476-4-hydroxy [included in tolerance expression for animal commodities] *Goat milk, liver, kidney, muscle, and fat* *Hen liver and muscle*	2-[2-(1-chlorocyclopropyl)-3-(2-chloro-4-hydroxyphenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione	

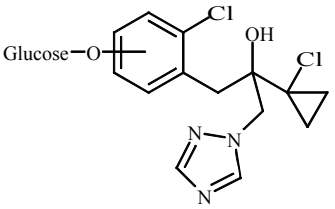
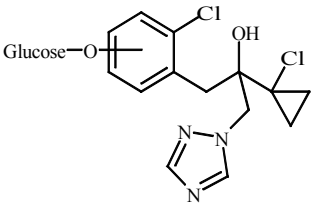
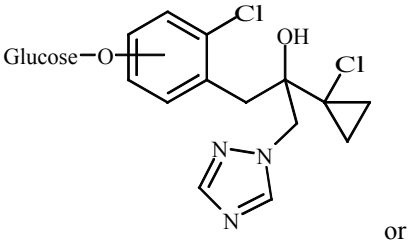
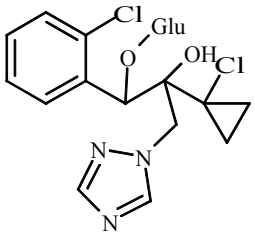
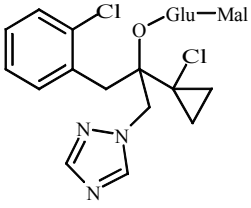
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-α-OH-desthio *Wheat forage, hay, straw, and grain* *Sugar beet tops* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain*	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1,2-propanediol	
JAU6476-3-OH-desthio *Wheat forage, hay, and straw* *Peanut hay* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain* *Goat milk, liver, kidney, muscle, and fat*	α-(1-chlorocyclopropyl)-α-[(2-chloro-3-hydroxyphenyl)-methyl]-1H-1,2,4-triazole-1-ethanol	
JAU6476-4-OH-desthio *Wheat forage, hay, and straw* *Peanut hay* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain* *Goat liver* *Hen egg and liver*	α-(1-chlorocyclopropyl)-α-[(2-chloro-4-hydroxyphenyl)-methyl]-1H-1,2,4-triazole-1-ethanol	
JAU6476-6-OH-desthio *Wheat forage, hay, and straw* *Rotated turnip tops and root and wheat forage and straw*	α-(1-chlorocyclopropyl)-α-[(2-chloro-6-hydroxyphenyl)-methyl]-1H-1,2,4-triazole-1-ethanol	
JAU6476-OH-desthio isomers *Wheat forage and straw* *Sugar beet tops*		

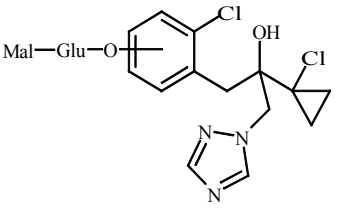
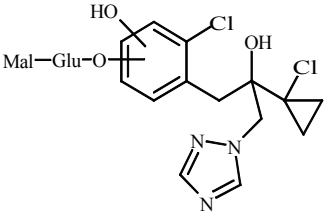
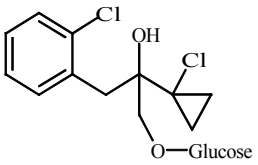
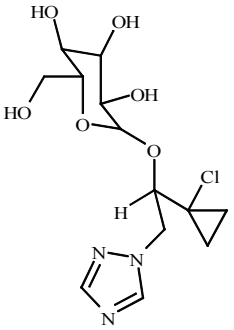
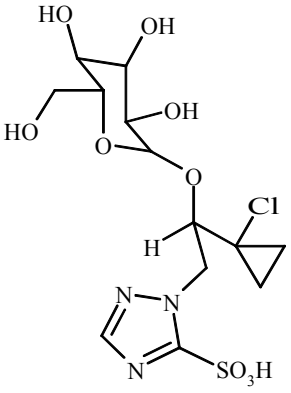
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-triazolinone *Wheat forage, hay, straw, and grain* *Peanut hay* *Sugar beet tops and root* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, and straw*	2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazole-3-one	
JAU6476 sulfonic acid *Wheat forage, hay, and straw* *Peanut hay and nutmeat* *Sugar beet tops* *Rotated Swiss chard, turnip tops, and wheat forage, hay, and straw*	1-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1H-1,2,4-triazole-5-sulfonic acid	
JAU6476-α-acetoxy-desthio *Wheat forage, hay, straw, and grain* *Rotated wheat forage, hay, and straw*	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl acetate	
JAU6476-disulfide *Wheat forage, hay, straw, and grain* *Peanut hay* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, and straw*		
JAU6476-benzylpropyldiol *Wheat straw* *Rotated Swiss chard, turnip tops and root, and wheat straw*	2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)propane-1,2-diol	

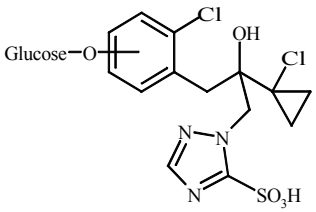
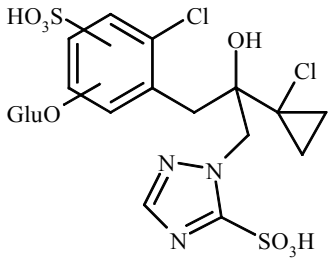
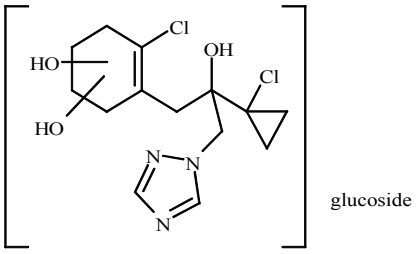
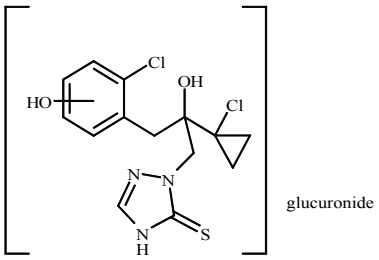
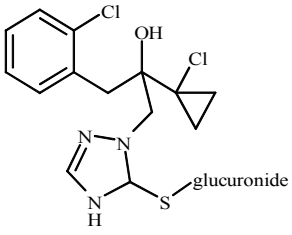
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
Triazolyl-ethanol *Wheat straw* *Peanut hay* *Sugar beet tops* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, and straw* *Hen egg, liver, muscle, and fat*	1-(1-chlorocyclopropyl)-2-(1H-1,2,4-triazol-1-yl)ethanol	
JAU6476-desthio-phenyl-cysteine *Wheat forage* *Peanut hay*		
JAU6476-dihydroxy-diene sulfonic acid *Peanut hay*		
JAU6476-dihydroxyolefin sulfonic acid *Peanut hay*		
JAU6476-desthio-hydroxy-dienyl-cysteine *Peanut hay and nutmeat* *Sugar beet tops and root*		

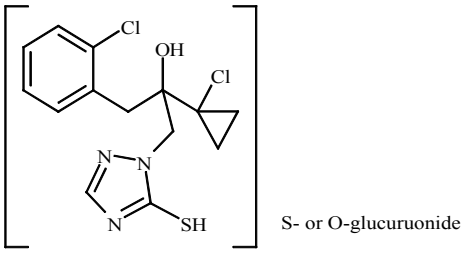
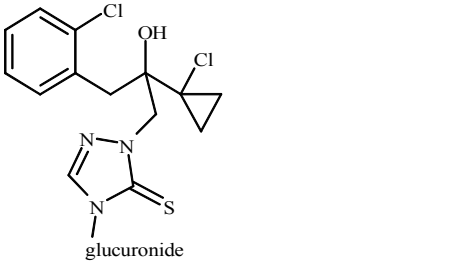
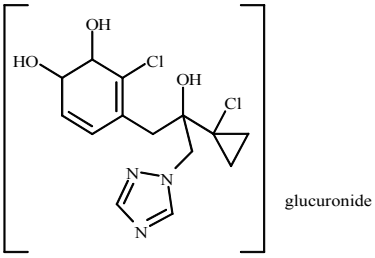
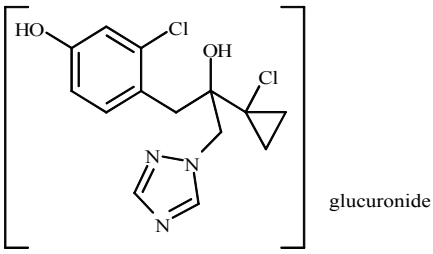
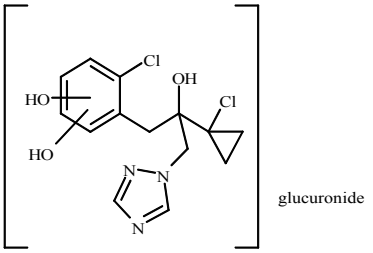
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-S-methyl *Goat liver* *Hen egg, liver, muscle, and fat*	α-(1-chlorocyclopropyl)-α-[(2-chlorophenyl)methyl]-3-(methylthio)-1H-1,2,4-triazole-1-ethanol	
JAU6476-lactoside *Goat milk*		
JAU6476-dihydroxy-diene *Goat milk* *Hen liver and muscle*	2-[2-(1-chlorocyclopropyl)-3-(2-chloro-3,4-dihydroxycyclohexa-1,5-dien-1-yl)-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione [1]	
JAU6476-desthio-dihydroxy-diene *Goat milk and liver*	3-chloro-4-[2-(1-chlorocyclopropyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl]cyclohexa-3,5-diene-1,2-diol [1]	

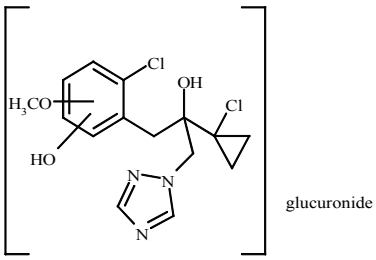
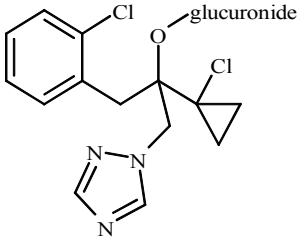
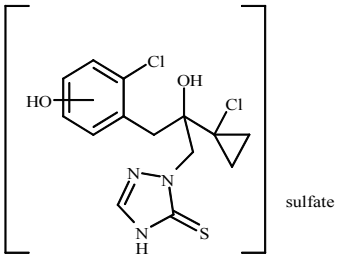
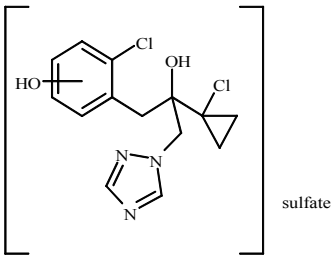
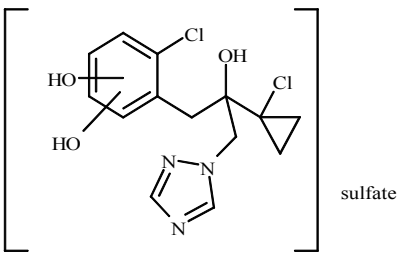
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
Triazole metabolites		
1,2,4-Triazole *Hen egg, liver, muscle, and fat*	1,2,4-triazole	
Triazolylalanine (TA) *Wheat forage, hay, straw, and grain* *Peanut hay and nutmeat* *Sugar beet tops and root* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw and grain*	α-amino-1H-1,2,4-triazole-1-propanoic acid	
Triazolylacetic acid (TAA) *Wheat forage, hay, straw, and grain* *Peanut hay and nutmeat* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain*	1H-1,2,4-triazole-1-acetic acid	
Triazolylhydroxypropionic acid (THPA) *Wheat forage, hay, straw, and grain* *Peanut hay and nutmeat* *Sugar beet tops* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, straw, and grain*	α-hydroxy-1H-1,2,4-triazole-1-propanoic acid	
Thiocyanate *Goat milk, liver, kidney, muscle, and fat* *Hen egg, liver, muscle, and fat*	thiocyanate ion	

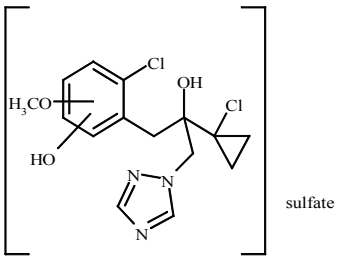
Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
Glucosides		
JAU6476-desthio-glucoside *Wheat hay and straw*		
JAU6476-OH-desthio glucoside isomers [2] *Wheat forage, hay, straw, and grain* *Peanut nutmeat and hay* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, and straw*		
JAU6476-OH-desthio glucoside isomers *Sugar beet tops*		 or 
JAU6476-desthio-malonyl-glucoside *Wheat forage and hay*		

Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-OH-desthio-malonyl-glucoside *Wheat forage, hay, and straw* *Peanut hay*		
JAU6476-dihydroxy-desthio-malonyl-glucoside *Wheat forage*		
JAU6476-benzylpropyldiol glucoside *Wheat hay, straw, and grain* *Rotated turnip tops and root and wheat forage and straw*	2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)propane-1,2-diol glucoside	
Triazolyl-ethanol-glucoside *Wheat forage, hay, and straw* *Peanut hay* *Sugar beet tops* *Rotated turnip tops and root and wheat forage, hay, and straw*		
Triazolyl-sulfonic acid-ethanol-glucoside *Sugar beet tops*		

Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-OH-sulfonic acid-glucoside isomers *Wheat forage and hay* *Sugar beet tops*		
JAU6476-hydroxy-di-sulfonic acid glucoside *Sugar beet tops*		
JAU6476-desthio-dihydroxy-olefin glucosides *Peanut hay and nutmeat* *Rotated Swiss chard, turnip tops and root, and wheat forage, hay, and straw*		
Glucuronides		
JAU6476-hydroxy-glucuronide[2] *Goat milk, liver, kidney, muscle, and fat* *Hen liver*		
JAU6476-S-glucuronide *Goat milk, liver, kidney, muscle, and fat* *Hen egg, liver, muscle, and fat*		

Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-O- or S-glucuronide *Goat milk, liver, kidney, muscle, and fat* *Hen egg, liver, muscle, and fat*		
JAU6476-N-glucuronide *Goat milk, liver, kidney, muscle, and fat* *Hen liver and muscle*		
JAU6476-desthio-3,4-dihydroxy-dienyl-glucuronide *Goat liver* *Hen liver and muscle*		
JAU6476-4-hydroxy-desthio-glucuronide *Goat milk*		
JAU6476-dihydroxy-desthio-glucuronide *Goat milk*		

Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
JAU6476-hydroxy-methoxy-desthio-glucuronide *Goat milk*		
JAU6476-desthio-glucuronide *Goat milk*		
Sulfate conjugates		
Sulfate conjugate of JAU6476-hydroxy *Goat liver*		
Sulfate conjugate of JAU6476-hydroxy-desthio *Hen liver and fat*		
Sulfate conjugate of JAU6476-dihydroxy-desthio *Hen liver, muscle, and fat*		

Appendix I. Chemical Names and Structures of Prothioconazole and its Transformation Products.		
Common Name/Code*Matrix*	Chemical Name	Structure
Sulfate conjugate of JAU6476-hydroxy-methoxy-desthio *Hen liver, muscle, and fat*		

[1] When chemical names were not provided by the petitioner, the chemical naming feature of ISIS/Draw was used to generate the name.
[2] Including 3-hydroxy and/or 4-hydroxy isomers.

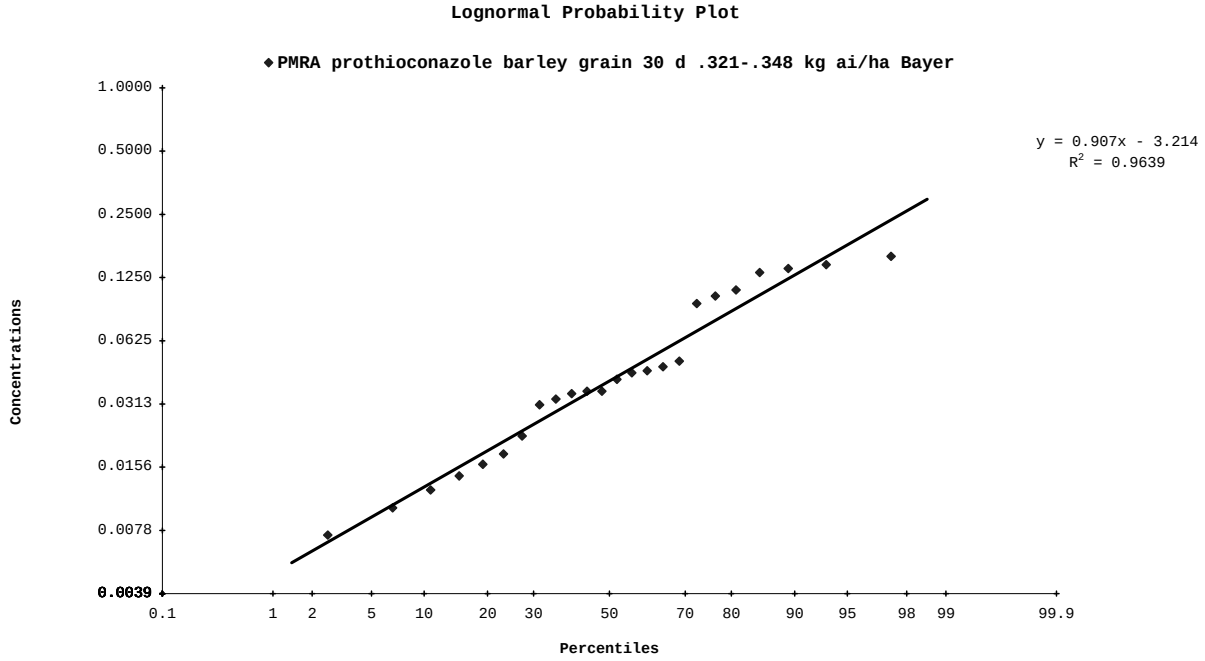
Appendix II – Statistical Calculation of Tolerances

Barley Grain

	Regulator: EPA **Chemical:** prothioconazole **Crop:** barley grain **PHI:** 32 d (30 d Canada) **App. Rate:** .321-.348 kg ai/ha **Submitter:** Bayer **n:** 24 **min:** 0.01 **max:** 0.16 **median;** 0.04 **average:** 0.06		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.15 (0.20)	0.20 (0.25)	0.25 (--)
EU Method I Log Normal	**(0.35)**	**0.35** (0.70)	0.70 (--)
EU Method II Distribution-Free	0.20		
California Method μ + 3σ	**0.25**		
UPLMedian95th	**0.25**		
Approximate Shapiro-Francia Normality Test	0.9639 p-value > 0.05 : Do not reject lognormality assumption		

Residues (LOQ = 0.02)	**LN(Residues)**	**Z-scores**
0.05	-3.00	0.48
0.036	-3.32	-0.16
0.144	-1.94	1.50
0.007419992	-4.90	-1.95
0.010009059	-4.60	-1.50
0.012189445	-4.41	-1.24
0.031	-3.47	-0.48
0.01420563	-4.25	-1.04
0.132	-2.02	1.04
0.102	-2.28	0.73
0.041	-3.19	0.05
0.036	-3.32	-0.05
0.094	-2.36	0.60
0.044	-3.12	0.16
0.158	-1.85	1.95
0.016149969	-4.13	-0.88
0.022	-3.82	-0.60
0.01807106	-4.01	-0.73

0.035	-3.35	-0.26
0.033	-3.41	-0.37
0.138	-1.98	1.24
0.109	-2.22	0.88
0.047	-3.06	0.37
0.045	-3.10	0.26

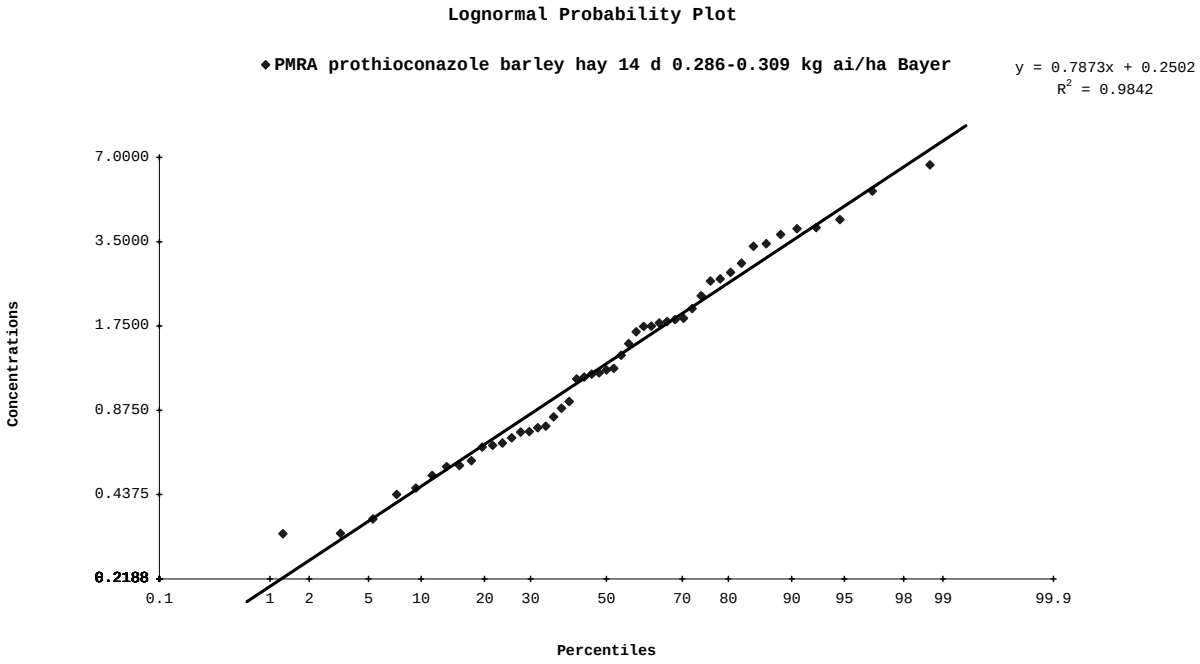


Barley Hay

	Regulator: EPA **Chemical:** prothioconazole **Crop:** barley hay **PHI:** 14 d **App. Rate:** 0.286-0.309 kg ai/ha **Submitter:** Bayer **n:** 49 **min:** 0.32 **max:** 6.59 **median;** 1.22 **average:** 1.72		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	4.5 (5.0)	5.0 (6.0)	7.0 (--)
EU Method I Log Normal	5.0 **(7.0)**	**8.0** (13)	15 (--)
EU Method II Distribution-Free	5.0		
California Method μ + 3σ	**6.0**		
UPLMedian95th	**7.0**		
Approximate Shapiro-Francia Normality Test	0.9842 p-value > 0.05 : Do not reject lognormality assumption		

Residues	LN(Residues)	Z-scores
0.438	-0.83	-1.45
1.133	0.12	-0.21
2.246	0.81	0.65
0.647	-0.44	-0.86
0.318	-1.15	-1.84
0.668	-0.40	-0.72
1.191	0.17	-0.05
5.305	1.67	1.84
1.178	0.16	-0.10
1.151	0.14	-0.15
1.865	0.62	0.53
1.741	0.55	0.26
0.656	-0.42	-0.79
0.551	-0.60	-1.11
0.317	-1.15	-2.24
0.556	-0.59	-1.02
2.933	1.08	0.93
2.718	1.00	0.86
0.512	-0.67	-1.20
1.669	0.51	0.21

3.366	1.21	1.02
0.890	-0.12	-0.31
1.747	0.56	0.31
3.931	1.37	1.45
1.796	0.59	0.36
0.462	-0.77	-1.32
1.220	0.20	0.00
2.534	0.93	0.72
0.731	-0.31	-0.59
0.358	-1.03	-1.61
0.758	-0.28	-0.48
1.235	0.21	0.05
6.590	1.89	2.24
1.375	0.32	0.10
1.514	0.41	0.15
2.021	0.70	0.59
1.814	0.60	0.42
0.829	-0.19	-0.36
0.578	-0.55	-0.93
0.734	-0.31	-0.53
0.767	-0.27	-0.42
3.445	1.24	1.11
0.697	-0.36	-0.65
2.577	0.95	0.79
3.715	1.31	1.20
0.941	-0.06	-0.26
1.843	0.61	0.48
4.197	1.43	1.61
3.895	1.36	1.32

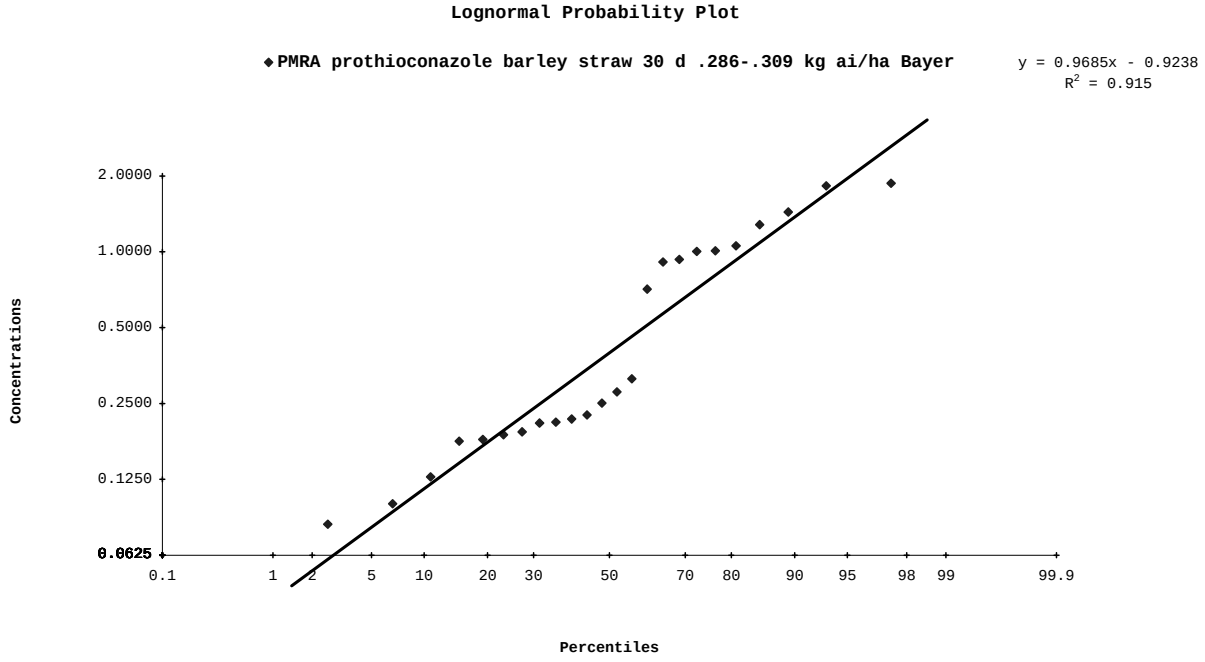

Lognormal Probability Plot
PMRA prothioconazole barley hay 14 d 0.286-0.309 kg ai/ha Bayer
y = 0.7873x + 0.2502
R2 = 0.9842
Concentrations
7.0000
3.5000
1.7500
0.8750
0.4375
0.2188
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles

Barley Straw

	Regulator: EPA **Chemical:** prothioconazole **Crop:** barley straw **PHI:** 30 d **App. Rate:** .286-.309 kg ai/ha **Submitter:** Bayer **n:** 24 **min:** 0.08 **max:** 1.87 **median;** 0.26 **average:** 0.62		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	1.6 (2.0)	2.0 (2.5)	2.5 (--)
EU Method I Log Normal	2.0 **(4.0)**	**4.0** (9.0)	9.0 (--)
EU Method II Distribution-Free		2.5	
California Method μ + 3σ		**2.5**	
UPLMedian95th		**1.6**	
Approximate Shapiro-Francia Normality Test	0.9150 p-value > 0.05 : Do not reject lognormality assumption		

Residues	LN(Residues)	Z-scores
1.003	0.00	0.60
0.180	-1.71	-0.88
1.282	0.25	1.04
0.083	-2.49	-1.95
0.251	-1.38	-0.05
0.911	-0.09	0.37
0.209	-1.57	-0.48
0.128	-2.06	-1.24
0.711	-0.34	0.26
1.439	0.36	1.24
0.188	-1.67	-0.73
0.177	-1.73	-1.04
1.056	0.05	0.88
0.193	-1.65	-0.60
1.828	0.60	1.50
0.100	-2.30	-1.50
0.278	-1.28	0.05
1.008	0.01	0.73
0.313	-1.16	0.16
0.211	-1.56	-0.37
0.932	-0.07	0.48
1.871	0.63	1.95

0.225	-1.49	-0.16
0.217	-1.53	-0.26



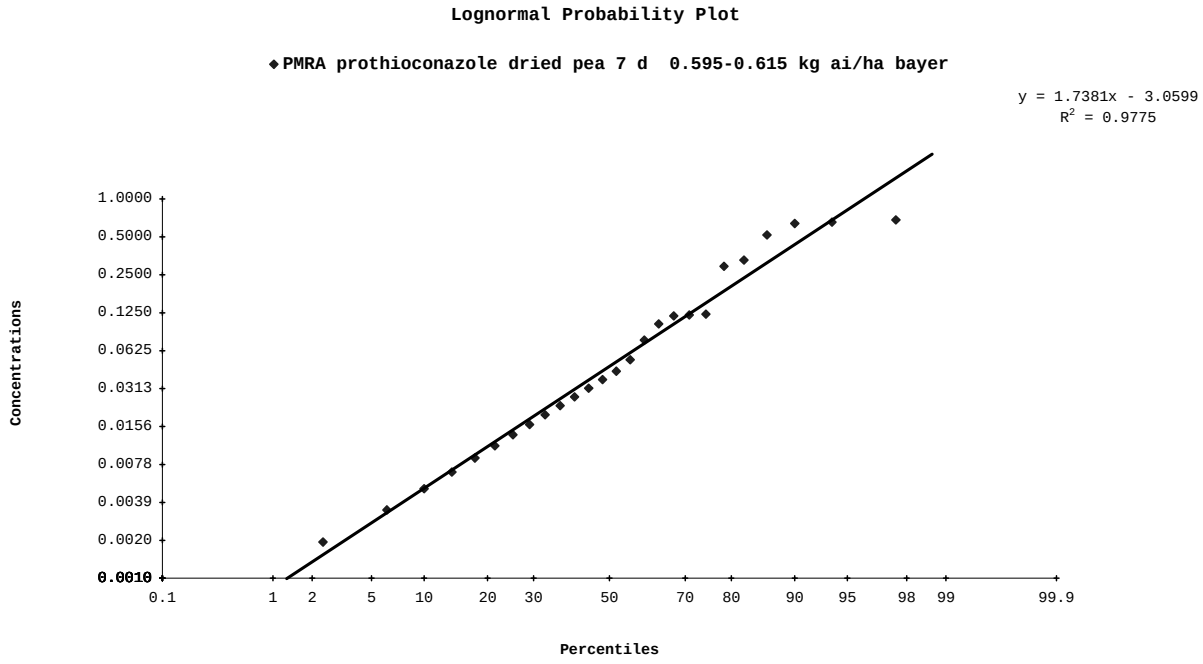
Pea and Bean (dry)

Pea

	PHI: 7 d App. Rate: 0.595-0.615 kg ai/ha Submitter: bayer n: 26 min: 0.00 max: 0.68 median; 0.04 average: 0.15		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.60 (0.70)	0.70 (0.90)	0.90 (--)
EU Method I Log Normal	0.80 **(2.5)**	**2.5** (10)	10 (--)
EU Method II Distribution-Free	0.35		
California Method μ + 3σ	**0.90**		
UPLMedian95th	**0.25**		
Approximate Shapiro-Francia Normality Test	0.9775 p-value > 0.05 : Do not reject lognormality assumption		

Residues (LOQ = 0.05 ppm)	**LN(Residues)**	**Z-scores**
0.12	-2.12	0.55
0.102	-2.28	0.34
0.001895462	-6.27	-1.98
0.003411318	-5.68	-1.54
0.292	-1.23	0.79
0.005030396	-5.29	-1.28
0.006808825	-4.99	-1.09
0.008782788	-4.73	-0.93
0.010986121	-4.51	-0.79
0.013455115	-4.31	-0.67
0.519	-0.66	1.09
0.016231262	-4.12	-0.55
0.639	-0.45	1.28
0.122	-2.10	0.67
0.118	-2.14	0.44
0.019363226	-3.94	-0.44
0.022909197	-3.78	-0.34
0.328	-1.11	0.93
0.026939787	-3.61	-0.24
0.031541633	-3.46	-0.14
0.076	-2.58	0.24

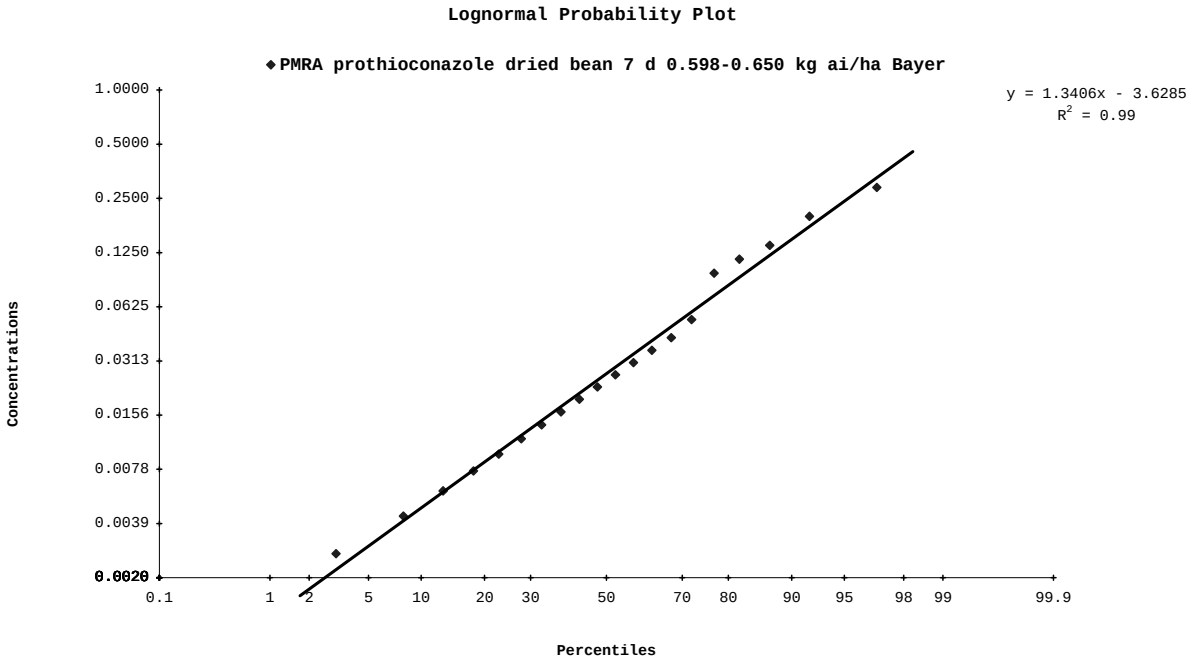
0.036822359	-3.30	-0.05
0.042917445	-3.15	0.05
0.655	-0.42	1.54
0.053	-2.94	0.14
0.684	-0.38	1.98



Bean

	Regulator: EPA **Chemical:** prothioconazole **Crop:** dried bean **PHI:** 7 d **App. Rate:** 0.598-0.650 kg ai/ha **Submitter:** Bayer **n:** 20 **min:** 0.00 **max:** 0.29 **median;** 0.02 **average:** 0.06		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.20 (0.25)	0.25 (0.35)	0.30 (--)
EU Method I Log Normal	0.25 **(0.60)**	**0.60** (2.0)	1.5 (--)
EU Method II Distribution-Free	0.20		
California Method μ + 3σ	**0.30**		
UPLMedian95th	**0.20**		
Approximate Shapiro-Francia Normality Test	0.9900 p-value > 0.05 : Do not reject lognormality assumption		

Residues (LOQ = 0.05 ppm)	**LN(Residues)**	**Z-scores**
0.053	-2.94	0.59
0.002656732	-5.93	-1.87
0.004293274	-5.45	-1.40
0.115	-2.16	0.92
0.005924704	-5.13	-1.13
0.199	-1.61	1.40
0.007642865	-4.87	-0.92
0.009497614	-4.66	-0.74
0.011530548	-4.46	-0.59
0.013784693	-4.28	-0.45
0.096	-2.34	0.74
0.016309357	-4.12	-0.31
0.019164827	-3.95	-0.19
0.137	-1.99	1.13
0.022427309	-3.80	-0.06
0.288	-1.24	1.87
0.026196504	-3.64	0.06
0.030606471	-3.49	0.19
0.0358432	-3.33	0.31
0.042174067	-3.17	0.45


Lognormal Probability Plot
PMRA prothioconazole dried bean 7 d 0.598-0.650 kg ai/ha Bayer
y = 1.3406x - 3.6285
R2 = 0.99
Concentrations
1.0000
0.5000
0.2500
0.1250
0.0625
0.0313
0.0156
0.0078
0.0039
0.0020
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles

Peanut

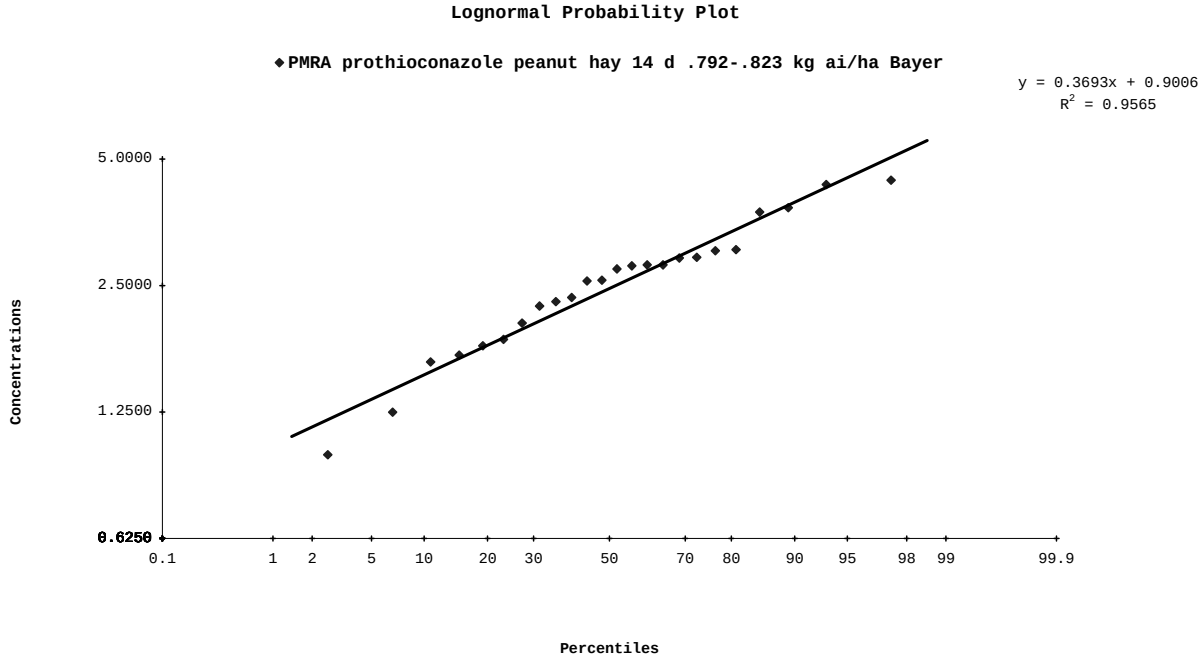
All values were below the limit of quantitation, 0.02 ppm.

Peanut Hay

	Regulator: EPA **Chemical:** prothioconazole **Crop:** peanut hay **PHI:** 14 d **App. Rate:** .792-.823 kg ai/ha **Submitter:** Bayer **n:** 24 **min:** 0.99 **max:** 4.46 **median;** 2.66 **average:** 2.61		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	4.5 (5.0)	5.0 (6.0)	6.0 (--)
EU Method I Log Normal	**(6.0)**	**6.0** (8.0)	8.0 (--)
EU Method II Distribution-Free		6.0	
California Method μ + 3σ		**6.0**	
UPLMedian95th		**16**	
Approximate Shapiro-Francia Normality Test		0.9565 p-value > 0.05 : Do not reject lognormality assumption	

Residues	LN(Residues)	Z-scores
1.645	0.50	-1.24
2.289	0.83	-0.37
2.908	1.07	0.48
2.787	1.02	0.16
2.036	0.71	-0.60
1.709	0.54	-1.04
2.801	1.03	0.37
2.564	0.94	-0.16
0.989	-0.01	-1.95
2.574	0.95	-0.05
1.863	0.62	-0.73
1.797	0.59	-0.88
2.921	1.07	0.60
3.831	1.34	1.24
4.35	1.47	1.50
3.741	1.32	1.04
2.74	1.01	0.05
2.235	0.80	-0.48

4.458	1.49	1.95
3.025	1.11	0.73
1.249	0.22	-1.50
3.044	1.11	0.88
2.342	0.85	-0.26
2.799	1.03	0.26

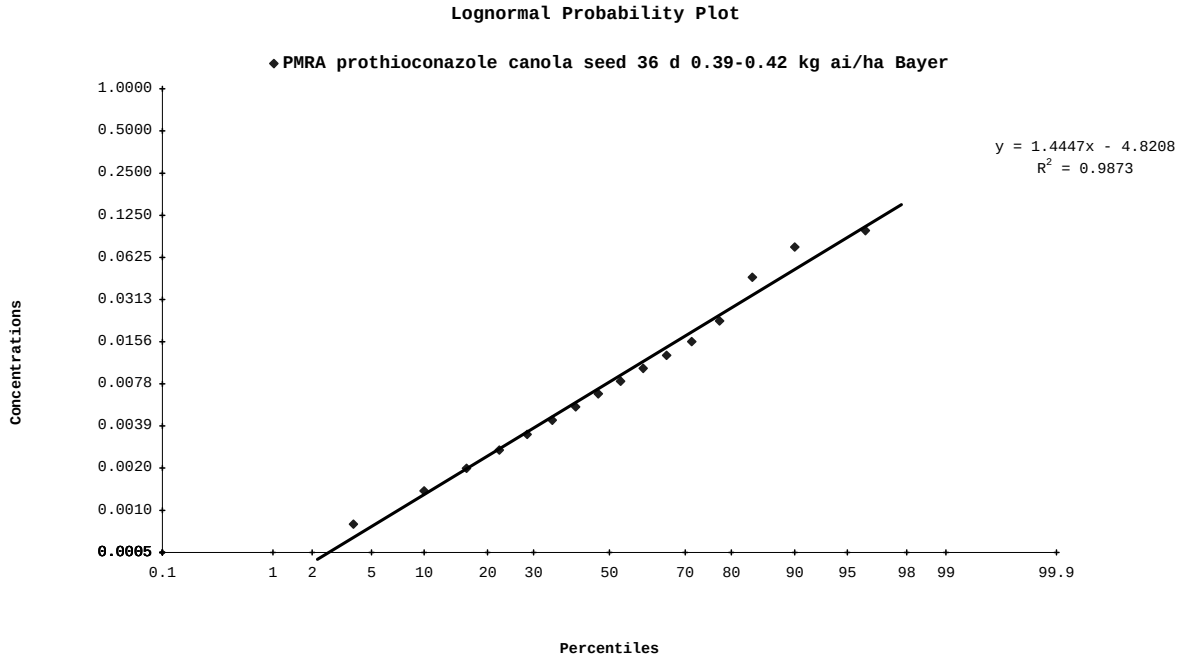


Rapeseed (Canola)

Regulator:	EPA
Chemical:	prothioconazole
Crop:	canola seed
PHI:	36 d
App. Rate:	0.39-0.42 kg ai/ha
Submitter:	Bayer
n:	16
min:	0.00
max:	0.10
median;	0.01
average:	0.02

	95th Percentile	99th Percentile	99.9th Percentile
EU Method I Normal	0.07 (0.10)	0.09 (0.15)	0.15 (--)
EU Method I Log Normal	0.08 **(0.30)**	**0.25** (1.0)	0.60 (--)
EU Method II Distribution-Free	0.05		
California Method μ + 3σ	**0.15**		
UPLMedian95th	**0.05**		
Approximate Shapiro-Francia Normality Test	0.9873 p-value > 0.05 : Do not reject lognormality assumption		

Residues (LOQ = 0.02 ppm)	LN(Residues)	Z-scores
0.022	-3.82	0.76
0.000778668	-7.16	-1.77
0.074	-2.60	1.28
0.001344005	-6.61	-1.28
0.001949138	-6.24	-0.99
0.002626332	-5.94	-0.76
0.003400676	-5.68	-0.57
0.004299853	-5.45	-0.40
0.045	-3.10	0.99
0.005358714	-5.23	-0.23
0.097	-2.33	1.77
0.00662391	-5.02	-0.08
0.008160845	-4.81	0.08
0.010065174	-4.60	0.23
0.012483685	-4.38	0.40
0.015655229	-4.16	0.57

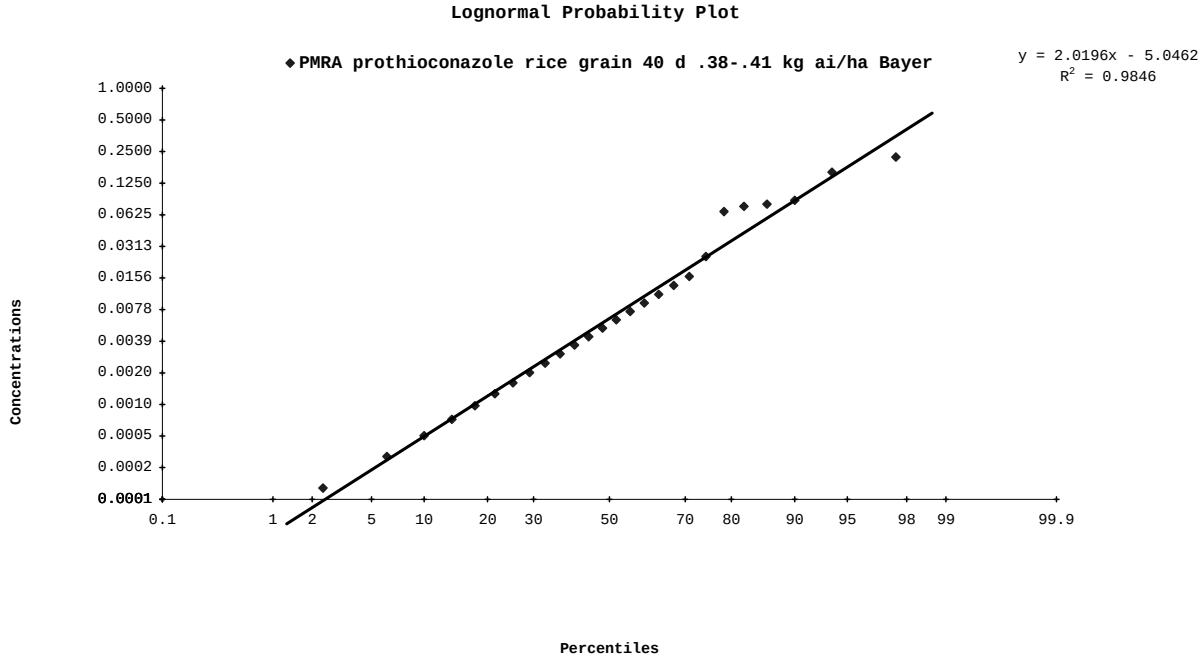

Lognormal Probability Plot
PMRA prothioconazole canola seed 36 d 0.39-0.42 kg ai/ha Bayer
y = 1.4447x - 4.8208
R2 = 0.9873
Concentrations
1.0000
0.5000
0.2500
0.1250
0.0625
0.0313
0.0156
0.0078
0.0039
0.0020
0.0010
0.0005
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles

Rice Grain

	Regulator:	EPA	
	Chemical:	prothioconazole	
	Crop:	rice grain	
	PHI:	40 d	
	App. Rate:	.38-.41 kg ai/ha	
	Submitter:	Bayer	
	n:	26	
	min:	0.00	
	max:	0.22	
	median;	0.01	
	average:	0.03	
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.15 (0.20)	0.20 (0.25)	0.25 (--)
EU Method I Log Normal	**(0.60)**	**0.70** (3.5)	3.0 (--)
EU Method II Distribution-Free		0.08	
California Method μ + 3σ		**0.20**	
UPLMedian95th		**0.04**	
Approximate Shapiro-Francia Normality Test		0.9846 p-value > 0.05 : Do not reject lognormality assumption	

Residues (LOQ = 0.02 ppm)	**LN(Residues)**	**Z-scores**
0.159	-1.84	1.54
0.079	-2.54	1.09
0.00015637	-8.76	-1.98
0.00031169	-8.07	-1.54
0.00049206	-7.62	-1.28
0.00070271	-7.26	-1.09
0.00094866	-6.96	-0.93
0.00123556	-6.70	-0.79
0.00157018	-6.46	-0.67
0.00196068	-6.23	-0.55
0.00241708	-6.03	-0.44
0.00295171	-5.83	-0.34
0.067	-2.70	0.79
0.222	-1.51	1.98
0.086	-2.45	1.28
0.00357997	-5.63	-0.24
0.00432132	-5.44	-0.14
0.00520058	-5.26	-0.05
0.00624988	-5.08	0.05
0.00751159	-4.89	0.14
0.025	-3.69	0.67

0.00904243	-4.71	0.24
0.01092018	-4.52	0.34
0.01325397	-4.32	0.44
0.01620166	-4.12	0.55
0.075	-2.59	0.93

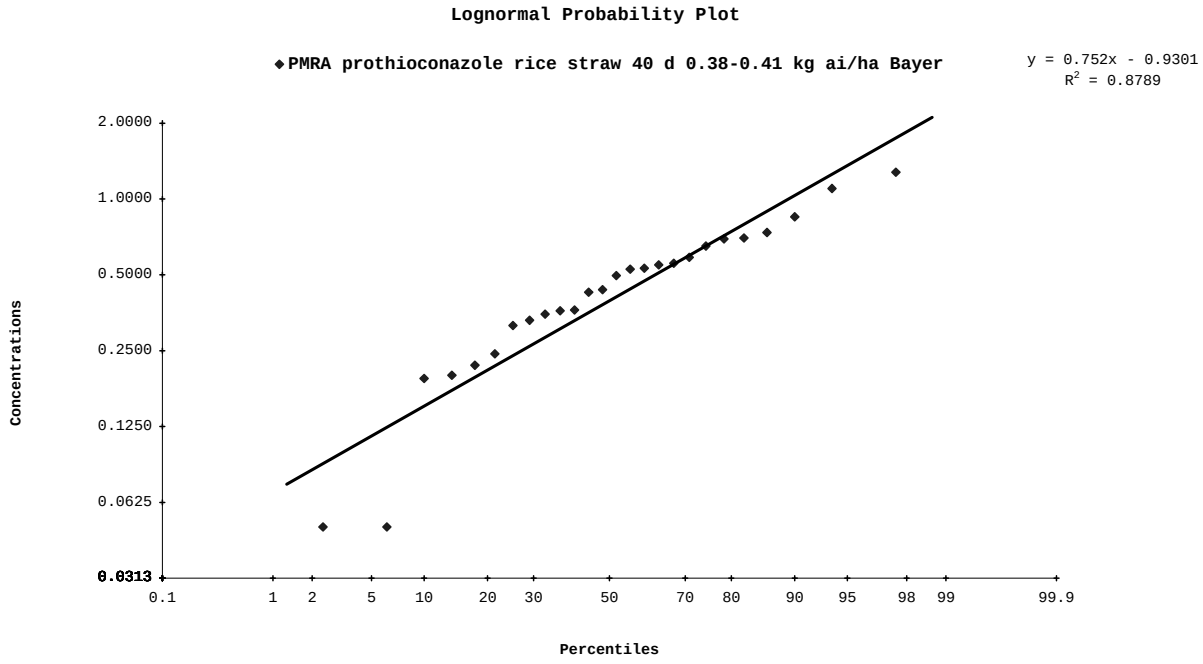


Rice Straw

	Regulator: EPA **Chemical:** prothioconazole **Crop:** rice straw **PHI:** 40 d **App. Rate:** 0.38-0.41 kg ai/ha **Submitter:** Bayer **n:** 26 **min:** 0.05 **max:** 1.28 **median;** 0.47 **average:** 0.49		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	1.0 (1.2)	1.2 (1.5)	1.4 (--)
EU Method I Log Normal	1.5 **(2.5)**	**2.5** (5.0)	4.5 (--)
EU Method II Distribution-Free		1.4	
California Method μ + 3σ		**1.4**	
UPLMedian95th		**3.0**	
Approximate Shapiro-Francia Normality Test	0.8789 p-value <= 0.01: Reject lognormality assumption		

Residues	LN(Residues)	Z-scores
0.694	-0.37	0.79
0.363	-1.01	-0.24
0.05	-3.00	-1.98
0.526	-0.64	0.14
0.7	-0.36	0.93
0.315	-1.16	-0.67
0.427	-0.85	-0.14
1.101	0.10	1.54
0.194	-1.64	-1.28
0.243	-1.41	-0.79
0.2	-1.61	-1.09
0.497	-0.70	0.05
0.531	-0.63	0.24
0.85	-0.16	1.28
0.548	-0.60	0.34
0.05	-3.00	-1.54
0.556	-0.59	0.44
0.736	-0.31	1.09
0.36	-1.02	-0.34
0.437	-0.83	-0.05
1.277	0.24	1.98

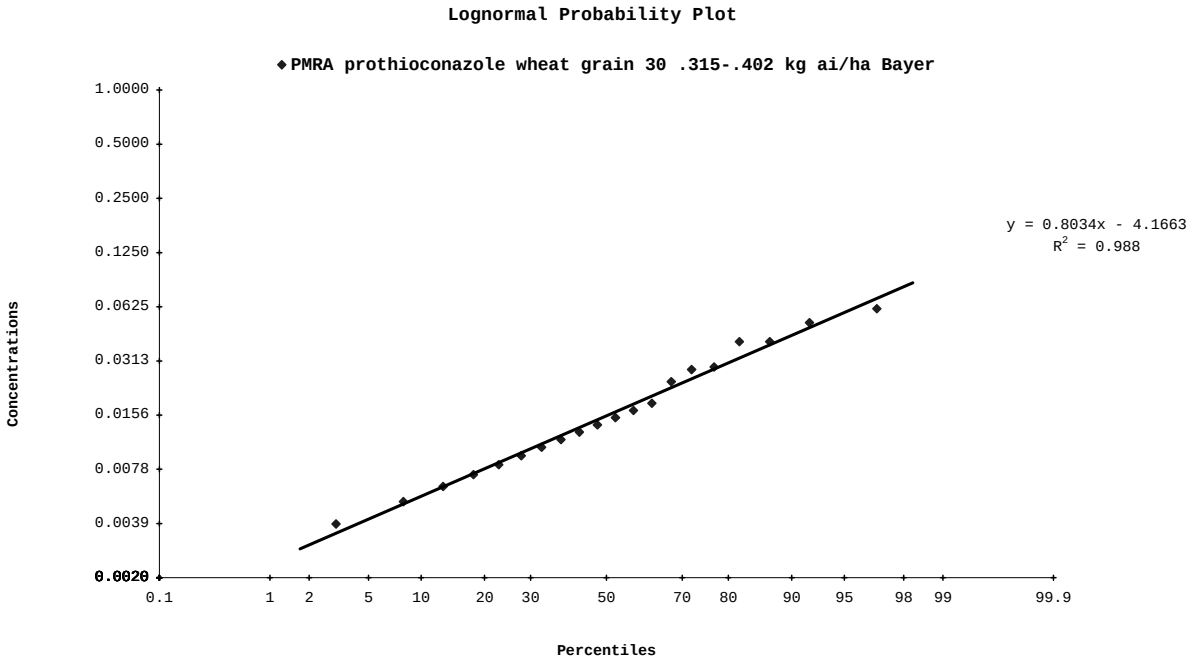
0.33	-1.11	-0.55
0.349	-1.05	-0.44
0.219	-1.52	-0.93
0.587	-0.53	0.55
0.65	-0.43	0.67



Wheat Grain

	Regulator: EPA **Chemical:** prothioconazole **Crop:** wheat grain **PHI:** 30 **App. Rate:** .315-.402 kg ai/ha **Submitter:** Bayer **n:** 20 **min:** 0.00 **max:** 0.06 **median;** 0.01 **average:** 0.02		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.05 (0.06)	0.06 (0.08)	0.08 (--)
EU Method I Log Normal	0.06 **(0.15)**	**0.10** (0.25)	0.20 (--)
EU Method II Distribution-Free		0.06	
California Method μ + 3σ		**0.07**	
UPLMedian95th		**0.09**	
Approximate Shapiro-Francia Normality Test		0.9880 p-value > 0.05 : Do not reject lognormality assumption	

Residues (LOQ = 0.02 ppm)	**LN(Residues)**	**Z-scores**
0.040	-3.22	0.92
0.028	-3.58	0.59
0.029	-3.54	0.74
0.004	-5.55	-1.87
0.005	-5.26	-1.40
0.006	-5.07	-1.13
0.007	-4.92	-0.92
0.008	-4.79	-0.74
0.009	-4.68	-0.59
0.010	-4.57	-0.45
0.051	-2.98	1.40
0.061	-2.80	1.87
0.040	-3.22	1.13
0.011	-4.47	-0.31
0.013	-4.38	-0.19
0.014	-4.28	-0.06
0.015	-4.19	0.06
0.024	-3.73	0.45
0.017	-4.10	0.19
0.018	-4.01	0.31

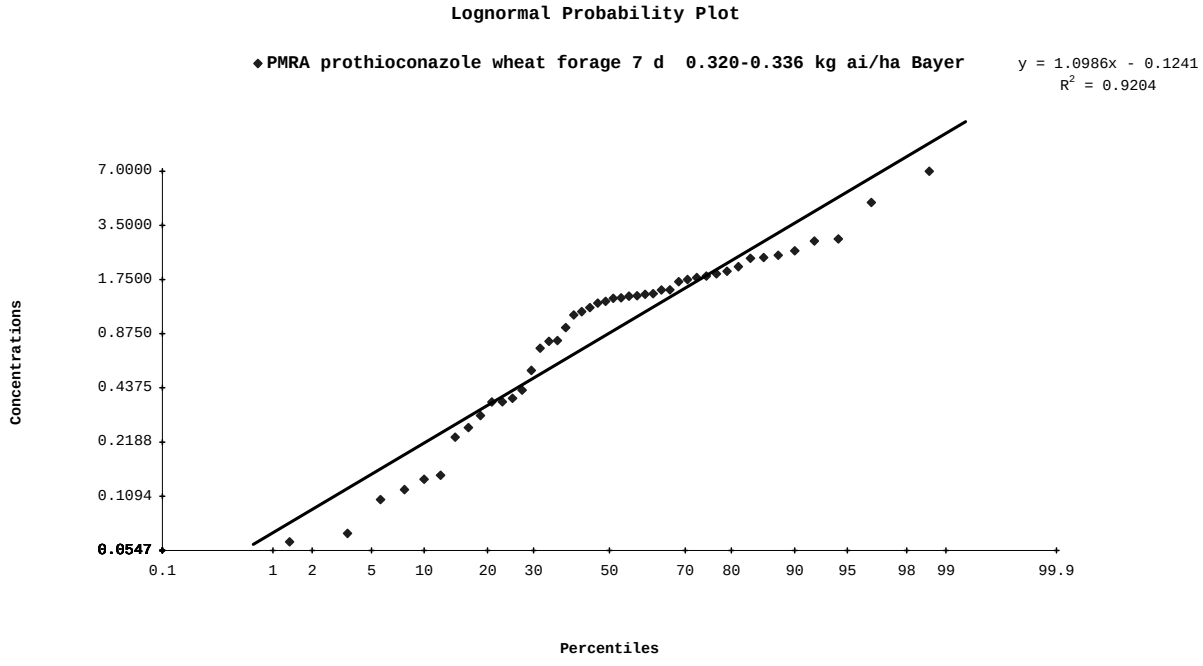

Lognormal Probability Plot
PMRA prothioconazole wheat grain 30 .315-.402 kg ai/ha Bayer
y = 0.8034x - 4.1663
R2 = 0.988
Concentrations
1.0000
0.5000
0.2500
0.1250
0.0625
0.0313
0.0156
0.0078
0.0039
0.0020
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles

Wheat Forage

	Regulator: EPA **Chemical:** prothioconazole **Crop:** wheat forage **PHI:** 7 d **App. Rate:** 0.320-0.336 kg ai/ha **Submitter:** Bayer **n:** 46 **min:** 0.06 **max:** 6.99 **median;** 1.35 **average:** 1.40		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	3.5 (4.5)	4.5 (6.0)	6.0 (--)
EU Method I Log Normal	6.0 **(10)**	**13** (25)	30 (--)
EU Method II Distribution-Free		4.0	
California Method μ + 3σ		**6.0**	
UPLMedian95th		**8.0**	
Approximate Shapiro-Francia Normality Test	0.9204 p-value <= 0.01: Reject lognormality assumption		

Residues	LN(Residues)	Z-scores
1.383	0.32	0.08
0.233	-1.46	-1.07
0.383	-0.96	-0.67
2.528	0.93	1.28
0.307	-1.18	-0.89
1.112	0.11	-0.25
4.696	1.55	1.81
0.365	-1.01	-0.81
0.105	-2.25	-1.58
0.061	-2.80	-2.21
2.388	0.87	1.17
1.413	0.35	0.14
1.461	0.38	0.30
1.325	0.28	-0.03
2.294	0.83	0.97
1.296	0.26	-0.08
0.794	-0.23	-0.42
0.136	-2.00	-1.28
0.727	-0.32	-0.48
1.222	0.20	-0.14
1.378	0.32	0.03
1.532	0.43	0.42
1.702	0.53	0.48

1.827	0.60	0.67
0.263	-1.34	-0.97
0.547	-0.60	-0.54
2.864	1.05	1.42
0.366	-1.01	-0.74
1.161	0.15	-0.19
6.987	1.94	2.21
0.425	-0.86	-0.60
0.119	-2.13	-1.42
0.068	-2.69	-1.81
2.941	1.08	1.58
1.792	0.58	0.60
1.749	0.56	0.54
1.883	0.63	0.74
2.321	0.84	1.07
1.448	0.37	0.25
0.948	-0.05	-0.30
0.143	-1.94	-1.17
0.802	-0.22	-0.36
1.529	0.42	0.36
1.42	0.35	0.19
2.061	0.72	0.89
1.944	0.66	0.81



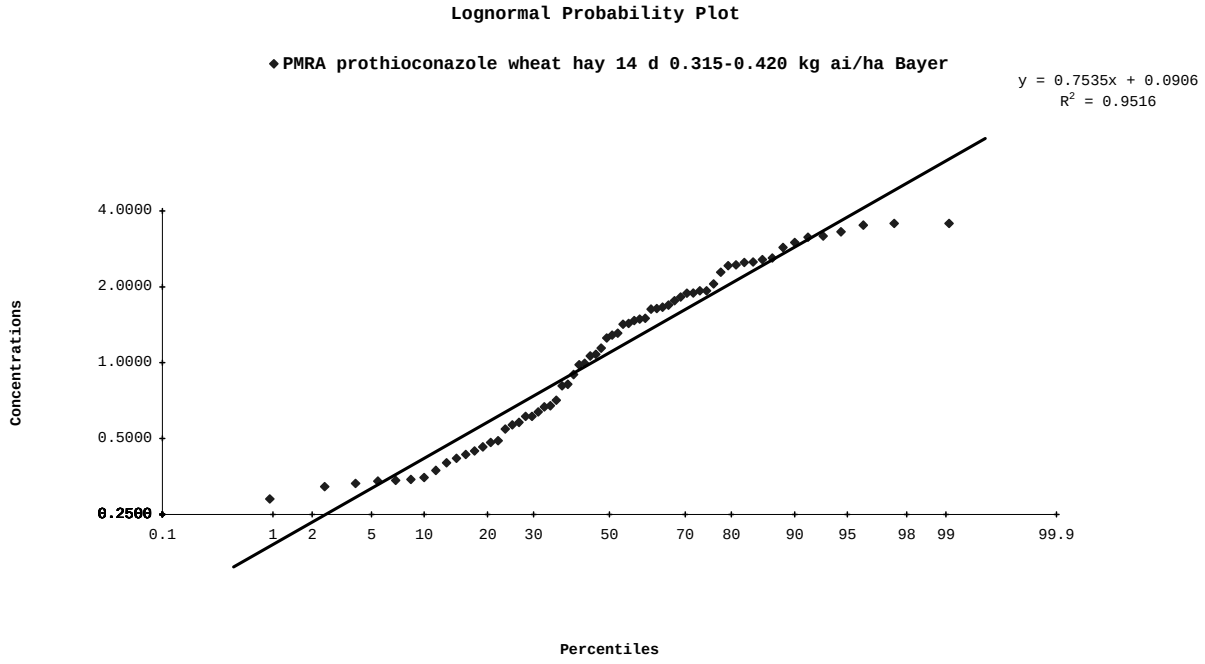
Wheat Hay

	Regulator:	EPA	
	Chemical:	prothioconazole	
	Crop:	wheat hay	
	PHI:	14 d	
	App. Rate:	0.315-0.420 kg ai/ha	
	Submitter:	Bayer	
	n:	66	
	min:	0.29	
	max:	3.57	
	median;	1.27	
	average:	1.42	
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	3.5 (3.5)	4.0 (4.5)	4.5 (--)
EU Method I Log Normal	4.0 **(6.0)**	**7.0** (10)	12 (--)
EU Method II Distribution-Free		4.0	
California Method μ + 3σ		**4.5**	
UPLMedian95th		**7.0**	
Approximate Shapiro-Francia Normality Test	0.9516 0.05 >= p-value > 0.01 : Reject lognormality assumption		

Residues	LN(Residues)	Z-scores
0.545	-0.61	-0.72
0.71	-0.34	-0.37
2.866	1.05	1.20
1.42	0.35	0.09
0.339	-1.08	-1.60
1.889	0.64	0.58
0.322	-1.13	-1.97
2.055	0.72	0.72
2.442	0.89	0.88
1.47	0.39	0.17
0.417	-0.87	-1.06
0.675	-0.39	-0.41
2.998	1.10	1.28
0.612	-0.49	-0.58
1.252	0.22	-0.02
0.432	-0.84	-0.99
0.567	-0.57	-0.67
0.341	-1.08	-1.48
1.822	0.60	0.49
1.928	0.66	0.62
1.489	0.40	0.21
3.515	1.26	1.76

0.809	-0.21	-0.33
2.601	0.96	1.13
1.08	0.08	-0.09
1.308	0.27	0.06
1.286	0.25	0.02
1.641	0.50	0.33
0.821	-0.20	-0.29
1.431	0.36	0.13
0.344	-1.07	-1.37
0.288	-1.24	-2.35
0.447	-0.81	-0.93
0.58	-0.54	-0.62
1.063	0.06	-0.13
3.305	1.20	1.60
1.632	0.49	0.29
0.374	-0.98	-1.20
1.928	0.66	0.67
0.401	-0.91	-1.13
2.568	0.94	1.06
3.569	1.27	1.97
1.761	0.57	0.45
0.482	-0.73	-0.82
0.898	-0.11	-0.25
3.182	1.16	1.48
0.668	-0.40	-0.45
1.66	0.51	0.37
0.49	-0.71	-0.77
0.638	-0.45	-0.49
0.35	-1.05	-1.28
2.509	0.92	0.99
2.501	0.92	0.93
1.5	0.41	0.25
3.571	1.27	2.35
0.981	-0.02	-0.21
3.149	1.15	1.37
1.142	0.13	-0.06
2.287	0.83	0.77
1.886	0.63	0.54
2.428	0.89	0.82
0.995	-0.01	-0.17
1.693	0.53	0.41
0.612	-0.49	-0.54
0.332	-1.10	-1.76

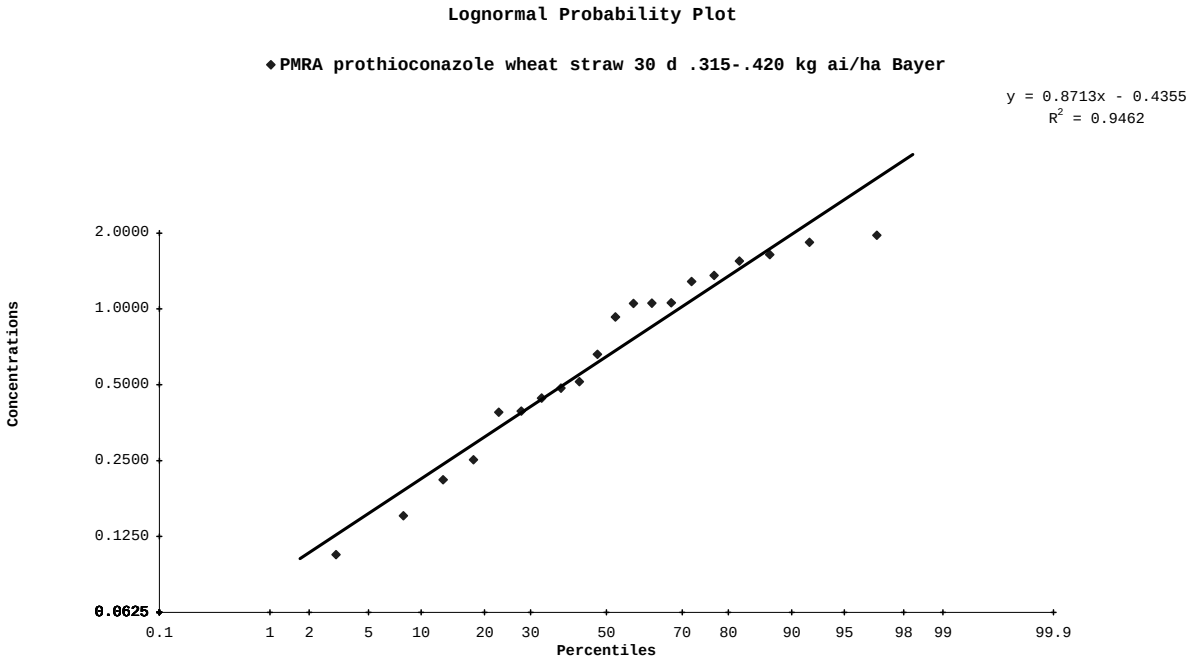
0.463	-0.77	-0.88


Lognormal Probability Plot
PMRA prothioconazole wheat hay 14 d 0.315-0.420 kg ai/ha Bayer
y = 0.7535x + 0.0906
R2 = 0.9516
Concentrations
4.0000
2.0000
1.0000
0.5000
0.2500
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles

Wheat Straw

	Regulator: EPA **Chemical:** prothioconazole **Crop:** wheat straw **PHI:** 30 d **App. Rate:** .315-.420 kg ai/ha **Submitter:** Bayer **n:** 20 **min:** 0.11 **max:** 1.96 **median;** 0.80 **average:** 0.87		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	1.9 (2.5)	2.5 (3.0)	3.0 (--)
EU Method I Log Normal	3.0 **(6.0)**	**5.0** (12)	10 (--)
EU Method II Distribution-Free		3.0	
California Method μ + 3σ		**3.0**	
UPLMedian95th		**5.0**	
Approximate Shapiro-Francia Normality Test	0.9462 p-value > 0.05 : Do not reject lognormality assumption		

Residues	LN(Residues)	Z-scores
0.393	-0.93	-0.59
0.443	-0.81	-0.45
1.838	0.61	1.40
0.93	-0.07	0.06
0.106	-2.24	-1.87
0.21	-1.56	-1.13
1.359	0.31	0.74
1.052	0.05	0.19
0.389	-0.94	-0.74
1.284	0.25	0.59
0.485	-0.72	-0.31
0.515	-0.66	-0.19
1.96	0.67	1.87
1.053	0.05	0.31
0.151	-1.89	-1.40
0.252	-1.38	-0.92
1.643	0.50	1.13
1.058	0.06	0.45
0.661	-0.41	-0.06
1.548	0.44	0.92


Lognormal Probability Plot
PMRA prothioconazole wheat straw 30 d .315-.420 kg ai/ha Bayer
y = 0.8713x - 0.4355
R2 = 0.9462
Concentrations
2.0000
1.0000
0.5000
0.2500
0.1250
0.0625
0.1
1
2
5
10
20
30
50
70
80
90
95
98
99
99.9
Percentiles