OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: December 31, 2007

MEMORANDUM

SUBJECT: Prothioconazole: Occupational Exposure and Risk Assessment for Proposed Uses on Soybeans and Sugar beets and revised postapplication assessment for: Barley, Oilseed (except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (except Soybean) Subgroup, Peanut and Wheat. PC Code: 113961, DP Barcode: D331662.

Regulatory Action: Section 3 Registration, New uses

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Introduction

Bayer CropScience has submitted tolerance petitions to support the use of prothioconazole on both soybeans and sugar beets. Associated with these petitions are three prothioconazole formulations: PROLINE ® 480 SC Fungicide (a previously registered formulation, modified to include uses on soybeans and sugar beets); PROVOST™ 433 SC Fungicide (a new formulation, proposed for use on peanuts [a previously registered use site on the PROLINE label] and soybeans); and USF 0728 325 SC Fungicide (a new formulation proposed for use on sugar beets).

Additionally, since the last Section 3 action, dislodgeable foliar residue (DFR) data have been submitted, and are considered in the postapplication exposure estimates for the proposed use sites, as well as for previously registered use sites (barley, oilseed crops [except sunflower and

Received in RAC 1/9/2008

safflower], dried shelled pea and bean crops [except soybean], peanuts and wheat crops).

This document addresses occupational exposures and risks resulting from the proposed uses, and includes a modification of previously assessed postapplication exposure and risk estimates, considering the newly submitted DFR data. There are no proposed residential uses, and therefore, residential exposure and risk are not assessed. The aggregate human health risk assessment for all exposure sources (including dietary) are presented in a separate document.

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

> *The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.*

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1.0 Executive Summary

Bayer CropScience has proposed new uses of prothioconazole on both soybeans and sugar beets. Associated with these uses are three prothioconazole formulations: PROLINE ® 480 SC Fungicide (a previously registered formulation, modified to include uses on soybeans and sugar beets); PROVOST™ 433 SC Fungicide (a new formulation, proposed for use on peanuts and soybeans); and USF 0728 325 SC Fungicide (a new formulation proposed for use on sugar beets).

Prothioconazole (generally referred to as an active ingredient or ai) is in the triazolinthione chemical class and is a de-methylation-inhibitor (DMI-type) fungicide. The labels of all formulations, depending on use site, indicate prothioconazole will be applied 2 – 4 times per season, at rates ranging from 0.028 to 0.18 lb ai/A (5- to 30- day re-treatment intervals) with overall maximum seasonal application rates ranging up to 0.71 lb ai/A. Pre-harvest intervals (PHIs) range from 7 to 36 days depending on the crop. The labels also indicate prothioconazole can be applied with both aerial and ground equipment (and banded applications), but not via chemigation. Agricultural workers are expected to have short- and intermediate-term inhalation and dermal exposures based on the proposed use patterns.

Hazard

Prothioconazole breaks down to different compounds in different matrices. Of particular interest is prothioconazole-desthio, a metabolite and degradate that is more toxic than the parent compound (and for which the registrant submitted a nearly complete toxicology database). The prothioconazole risk assessment team selected the most protective quantitative hazard estimates to employ in the prothioconazole risk assessment, resulting in selection of endpoints from the prothioconazole-desthio toxicology database.

The exposure scenarios relevant to this document are short- and intermediate-term dermal and inhalation exposure scenarios. For the short- and intermediate-term dermal exposure scenarios, a quantitative hazard estimate of 30 mg/kg/day (NOAEL) was selected from the dermal developmental toxicity study in the rat, based on an increased incidence of supernumerary rib (14^{th} rib) at the LOAEL (100 mg/kg/day). A dermal absorption factor was not applied because the study was route specific. For the short- and intermediate-term inhalation exposure scenarios, a quantitative hazard estimate of 2 mg/kg/day (NOAEL) was selected from the developmental toxicity study in the rabbit, based on arthrogryposis and multiple malformations at the LOAEL (10 mg/kg/day). Because the developmental study in the rabbit was an oral study, an inhalation absorption factor of 100% was applied to the exposure estimates, because oral and inhalation exposures are assumed to be equivalent. The level of concern (LOC) for all exposure scenarios is a margin of exposure (MOE) of less than 1000, based on the standard uncertainty factors for intraspecies variation (10X) and interspecies extrapolation (10X), and an additional 10X to account for the lack of a NOAEL and a LOAEL from the developmental neurotoxicity study, regarding the neurotoxic endpoint of peripheral nerve lesions and brain morphometrics.

Although the inhalation and dermal exposure scenarios employ different quantitative hazard

estimates from different studies for risk calculations – the endpoint/hazard that the quantitative hazard estimates represent is the same. Therefore, the respective risk estimates are combined via the total MOE approach, resulting in a total MOE that reflects risk resulting from exposure via the inhalation and dermal routes, for both short- and intermediate-term exposure durations.

Occupational - handlers

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

Occupational - postapplication

Postapplication dermal MOEs reach 1000 or greater on the day of application for postapplication activities such as scouting in low crops with minimal plant growth, as well as hand weeding; however, for activities such as scouting in crops with fuller foliage plants, irrigating crops and hand harvesting, up to 2 days following application are required to reach MOEs of 1000. Therefore, the labels, which indicate restricted-entry intervals (REIs) of 12 and 24 hours, would need to be amended to indicate an REI of 2 days in order to be protective of the LOC. Additionally, two formulations, PROVOST™ 433 SC Fungicide (for use on peanuts and soybeans) and USF 0728 325 SC Fungicide (for use on sugar beets) include other active ingredients (ais, namely, tebuconazole and trifloxystrobin) – the Registration Division (RD) must ensure that the REI is also protective of these additional ais. Other label amendments are discussed in Section 6.0.

2.0 Ingredient Profile

Prothioconazole is a systemic, broad spectrum fungicide in the triazolinthione chemical class developed by Bayer CropScience. Prothioconazole is a de-methylation-inhibitor (DMI-type) fungicide which works through disruption of ergosterol biosynthesis (ergosterol, a precursor to Vitamin D_2, is an important component of fungal cell walls).
(http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/ID/7thArticle022004_EN/$file/07_Dutzmann.pdf; http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/ID/8thArticle032004_EN/$file/08_Suty-Heinze.pdf)

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

flax, crambe, borage), peanut and wheat (spring, durum and winter); and is proposed for use on soybeans and sugar beets. Additionally, two new prothioconazole formulations – PROVOST™ 433 SC Fungicide (for use on peanuts and soybeans) and USF 0728 325 SC Fungicide (for use on sugar beets) – are being proposed for registration.

Table 2. Prothioconazole End-Use Products.

Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
PROLINE ® 480 SC Fungicide	264-IEL	41% 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3*H*-1,2,4-triazole-3-thione	Soluble concentrate (SC)	Barley, oilseed (except sunflower and safflower) crop group, dried shelled pea and bean (except soybean) subgroup, peanut, sugar beets and wheat.	Broad spectrum systemic fungicide for the control of Ascomycetes, Basidiomycetes, and Deuteromycetes diseases	Applications may be made alone or as a tank mix with other fungicides, insecticides, or herbicides. To optimize disease control, the lowest labeled rate of spray surfactant should be tank-mixed with PROLINE ® 480 SC Fungicide. Application through any type of irrigation system is prohibited. For crops not listed on this label, do not plant back within 30 days of last application. REI – 24 hours
PROVOST™ 433 SC Fungicide	264-IAR	12.9% (also contains 25.8% **tebuconazole**)	SC	Peanuts and soybeans		Provides control or suppression of many important diseases. When reference is made to disease suppression, suppression can mean either erratic control from good to fair or consistent control at a level below that obtained with the best commercial disease control products. For crops not listed on this label, do not plant back within 30 days of last application. REI – 24 hours
USF 0728 325 SC Fungicide	264-XXX	16.0% (also contains 13.7% **trifloxystrobin**)	SC	Sugar beets	Broad spectrum fungicide, that provides control or suppression of several important diseases of sugar beets (*e.g.*, Cercospora Leaf Spot, Powdery Mildew, Rhizoctonia Stem Canker, Crown Rot).	Provides control or suppression of many important diseases. When reference is made to disease suppression, suppression can mean either erratic control from good to fair or consistent control at a level below that obtained with the best commercial disease control products. Contains both Group 11 and Group 3 fungicides. To limit the potential for development of disease resistance: alternate each application with at least one application of a fungicide from a different fungicide group. REI – 12 Hours

2.1 Summary of Proposed Uses

Table 2.1 provides a summary of the directions indicated on the PROLINE ® 480 SC Fungicide, PROVOST™ 433 SC Fungicide and USF 0728 325 SC Fungicide labels.

Table 2.1. Summary of Directions for Use of Prothioconazole

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

Table 2.1. Summary of Directions for Use of Prothioconazole						
Appl. Type, and Equip.	Appl. Rate (lb ai/A) [fl oz/A]	Max. No. Appl. per Season	Retreatment Interval (days)	Max. Seasonal Appl. Rate (lb ai/A) [fl oz/A]	PHI (days)	Use Directions and Limitations
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 – 5.7]	3	10 to 14	0.53 [17.1]	7	Apply at early flower or at the first sign of disease. Use higher use rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Oilseed Crop Subgroup (Rapeseed, Indian rapeseed, Indian mustard, Field mustard, Black mustard, Flax, Crambe and Borage)						
Broadcast foliar spray; Ground or aerial	0.134 -0.178 [4.3 – 5.7]	2	5 to 7	0.356 [11.4]	36	Apply when the crop is 20 to 50% bloom stage (not after the 50% bloom stage). Utilize higher rate for fields with history of heavy disease pressure or for dense crop stands. Good spray coverage is essential.
Peanut						
Broadcast foliar spray; Ground or aerial	0.16 -0.18 [5.0 – 5.7, PROLINE] 0.038-0.10 [4.0 – 10.7, PROVOST]	4	14 to 21	0.71 [22.8, PROLINE] 0.40 [42.8, PROVOST]	14	Soil Borne disease: Utilize the high use rate. Make four consecutive applications at 14 day intervals. In a typical 7 spray application, the formulation should be applied for sprays 3, 4, 5 and 6. For control of soil-borne diseases when using a Leaf Spot Advisory Program schedule, begin in July and continue at 14 day intervals. The formulation must be carried by rainfall or irrigation into the root zone, drought conditions will decrease effectiveness against the root and pod rots. Foliar disease: Apply the specified rate in a preventive spray schedule. Apply up to 4 sprays using a 14 day interval. Use higher rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Soybean						
Broadcast foliar spray; Ground or aerial	0.078-0.094 [2.5-3.0, PROLINE] 0.028 [3.0, PROVOST]	3	10-21	0.28 [9, PROLINE] 0.40 prothio-containing fungicides [PROVOST]	21	Apply as a preventative spray or at first visible symptoms of disease. Repeat applications on a 10-21 day spray interval if environmental conditions are favorable for continued disease development. Use of the higher rate and shorter spray intervals are recommended when disease pressure is severe.
Sugar beets						
Broadcast foliar spray; Ground or aerial, as well as banded-application	0.13-0.18 [4.3-5.7, PROLINE] 0.093-0.13 [8-11, USF 0728]	3	14-30	0.53 [17.1, PROLINE] 0.38 [33, USF 0728; mentions that 0.53 lb ai/A/season is max appl rate for prothioconazole]	7 [PHI of 21 days on USF 0728 label]	Foliar disease: apply at the first sign of disease, and use higher use rate and shorter intervals when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties. Soil-borne disease control: apply either broadcast or in a seven-inch band at the 4-leaf to row closure growth stage.
Wheat (spring, durum and winter) (for Fusarium Head Blight)						

Table 2.1. Summary of Directions for Use of Prothioconazole						
Appl. Type, and Equip.	Appl. Rate (lb ai/A) [fl oz/A]	Max. No. Appl. per Season	Retreatment Interval (days)	Max. Seasonal Appl. Rate (lb ai/A) [fl oz/A]	PHI (days)	Use Directions and Limitations
Broadcast foliar spray; Ground or aerial	0.13 -0.18 [4.3 – 5.7]	2	7 to 14	0.29 [9.37]	30	Apply within the time period from when at least 75% of the wheat heads on the main stem are fully emerged to when 50% of the heads on the main stem are in flower. Optimal timing of application may be at or around 15% flower. Spray equipment must be set up to provide good coverage to wheat heads (using ground application equipment, use forward and backward mounted nozzles or nozzles with a two-directional spray). PROLINE may be applied up to the point where wheat heads are in the full flower growth stage.
Wheat (spring, durum and winter) (for Leaf and Stem Diseases)						
Broadcast foliar spray; Ground or aerial	0.13 -0.16 [4.3 - 5.0]	2	7 to 14	0.29 [9.37]	30	Apply as a preventative foliar spray or when the earliest disease symptoms appear on the leaves or stems. Wheat fields should be observed closely for early disease symptoms, particularly when susceptible varieties are planted and/or under prolonged conditions favorable for disease development. PROLINE may be applied up to the point where wheat heads are in the full flower growth stage.

2.2 Physical and Chemical Properties

The physical and chemical properties of prothioconazole are summarized in Table 2.2. Regarding inhalation exposure, note that prothioconazole has a low vapor pressure; therefore, after application, although residues are expected to persist on foliage, these residues are not expected to volatilize (rendering postapplication inhalation exposure negligible).

Table 2.2. Physicochemical Properties of the Technical-Grade Prothioconazole.		
Parameter	Value	
Melting point	139.1 – 144.5 °C	
Density (g/ml at 20°C)	1.36 (pure active ingredient)	
	1.17 at 20 °C (end use product)	
Water solubility (g/L)	5.0 pH 4 buffer at 20 °C 0.3 pH 8 buffer at 20 °C 2.0 pH 9 Buffer at 20 °C	
Solvent solubility at 20°C (g/L)	acetone	>250
	acetonitrile	10-100
	dichloromethane	100-250
	dimethylsulfoxide	100-250
	ethyl acetate	<250
	n-heptane	<0.1
	1-octanol	10-100
	Polyethyleneglycol	>250
	2-propanol	10-100
	xylene	1-10

assessment is not required because exposure to prothioconazole was determined to not pose a cancer risk to humans.

Table 3.1 Acute Toxicity of Prothioconazole technical and Desthio-prothioconazole technical					
Guideline	**Study**	**Species**	**Results**	**Tox. Category**	**MRID No.**
Prothioconazole					
870.1100	Acute oral toxicity	Rat	LD_{50} >= 6200 mg/kg (M, F)	IV	46246230
870.1200	Acute dermal toxicity	Rat	LD_{50} >= 2000 mg/kg (M, F)	III	46246244
870.1300	Acute inhalation toxicity	Rat	LC_{50} >= 4.99 mg/L (M, F)	IV	46246246
870.2400	Primary eye irritation	Rabbit	Not an irritant	IV	46246249
870.2500	Primary skin irritation	Rabbit	Not an irritant	IV	46246302
870.2600	Dermal sensitization	Guinea Pig	Not a sensitizer	Negative	46246305
Desthio-prothioconazole					
870.1100	Acute oral toxicity	Rat	LD_{50} = 2806 mg/kg (M, F) (approximate)	III	46246231
870.1100	Acute oral toxicity	Mouse	LD_{50} = 2235 mg/kg (Males) LD_{50} = 3459 mg/kg (Females)	III	46246242
870.1200	Acute dermal toxicity	Rat	LD_{50} >= 5000 mg/kg (M,F)	IV	46246243
870.1300	Acute inhalation toxicity	Rat	LC_{50} >= 5.077 mg/L (M,F)	IV	46246247
870.2400	Primary eye irritation	Rabbit	Slight irritant (iritis, discharge)	III	46246250
870.2500	Primary skin irritation	Rabbit	Not an irritant	IV	46246250
870.2600	Dermal sensitization	Guinea Pig	Not a sensitizer	Negative	46246304

Table 3.2 Summary of Toxicological Doses and Endpoints for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	**NOAEL=30 mg/kg/day**	**UF_A=10x UF_H=10x UF_{DB} = 10x**	**Occupational LOC for MOE ≤ 1000**	Dermal developmental study in rats **(prothioconazole-desthio) LOAEL = 100 mg/kg/day based on an increased incidence of supernumerary rib (14th rib).**
Inhalation Short- and Intermediate-	**NOAEL=2.0 mg/kg/day**	**UF_A=10x UF_H=10x UF_{DB} = 10x**	**Occupational LOC for MOE ≤ 1000**	Developmental Toxicity study in rabbits **(prothioconazole-desthio) LOAEL = 10 mg/kg/day, based on**

Table 2.2. Physicochemical Properties of the Technical-Grade Prothioconazole.	
Parameter	Value
Vapor pressure (Pa at 20 or 25°C)	$<4 \times 10^{-7}$
Dissociation constant, pK_a	6.9
Octanol/water partition coefficient, Log(K_{OW})	at 20 °C unbuffered: Kow = 11300; log K_{ow} = 4.05 pH 4: K_{ow} = 14600; log = 4.16 pH 7: K_{ow} = 6600; log = 3.82 pH 9: K_{ow} = 100; log = 2.00
UV/visible absorption spectrum	Peak maxima at 275 nm. No absorption at >300 nm.

3.0 Hazard Characterization/Assessment

In 2006, the prothioconazole and prothioconazole-desthio toxicology databases were evaluated, and HED senior toxicologists and the RAB3 Toxicology Team established Reference Doses (RfDs) and selected the toxicological endpoints for relevant exposure and risk assessments. Table 3.1 summarizes the hazard posed by acute exposure to prothioconazole (low acute toxicity, categories III and IV), and Table 3.2 presents the toxicological endpoints relevant to this risk assessment.

For the short- and intermediate-term dermal exposure scenarios, a quantitative hazard estimate of 30 mg/kg/day (NOAEL) was selected from the dermal developmental toxicity study in the rat, based on an increased incidence of supernumerary rib (14^{th} rib) at the LOAEL (100 mg/kg/day). A dermal absorption factor was not applied because the study was route specific. For the short- and intermediate-term inhalation exposure scenarios, a quantitative hazard estimate of 2 mg/kg/day (NOAEL) was selected from the developmental toxicity study in the rabbit, based on arthrogryposis and multiple malformations at the LOAEL (10 mg/kg/day). Because the developmental study in the rabbit was an oral study, an inhalation absorption factor of 100% was applied to the exposure estimates, because inhalation and oral exposures are assumed to be equivalent.

For mixers, loaders, and applicators, risk estimates for short- and intermediate-term exposures from both inhalation and dermal routes are combined, because the hazard/endpoint is the same. However, because the MOEs for dermal and inhalation exposures are calculated using different NOAELs, a total MOE approach $1/[(1/MOE_{dermal}) + (1/MOE_{inhalation})]$ is used to combine dermal and inhalation risks. This results in a total MOE that reflects risk from exposure via the inhalation and dermal routes, for both short- and intermediate-term exposure durations.

The LOC for all risk assessments is an MOE of less than 1000. The LOCs are based on the conventional uncertainty factor of 100x (UF_A = 10x [interspecies] and UF_H = 10x [intraspecies]) and an additional UF_{DB} (10x, database) for the lack of a NOAEL and a LOAEL from the developmental neurotoxicity study, regarding the neurotoxic endpoint of peripheral nerve lesions and brain morphometrics. Table 3.3 is a summary of LOCs for occupational risk assessments.

Prothioconazole was classified as "not likely" to be carcinogenic. A quantitative cancer

term (1-30 days and 1-6 months)	**Inhalation absorption are assumed to be 100%**			**structural alterations including malformed vertebral body and ribs, arthrogryposis, and multiple malformations.**
Cancer (oral, dermal, inhalation)	**Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.**			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (*i.e.*, lack of a critical study). MOE = margin of exposure. LOC = level of concern.

Table 3.3 Summary of Levels of Concern for Risk Assessment

Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 – 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	1000	1000	NA
Inhalation	1000	1000	NA

4.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed residential uses, therefore, residential exposure is not expected and residential exposure and risk are not assessed. However, spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from ground equipment application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 Occupational Exposure/Risk Pathway

Occupational exposure to prothioconazole is expected from registered uses on barley, oilseed crops, dried bean and pea crops, peanuts and wheat; as well as proposed uses on soybeans and sugar beets (more detail is provided in Tables 2.1 and 2.2 under Section 2.0). Short- and

intermediate-term dermal and inhalation exposures are expected from handler activities, and short- and intermediate-term dermal exposures are expected from postapplication activities.

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

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

5.1 Short-/Intermediate-Term Handler Risk

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

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

The daily doses presented in this assessment are characterized as mid- to high-end exposure estimates because both upper-percentile and average values were used in the calculations: the unit exposure values from PHED are considered to be central tendency; the areas treated per day values are considered typical-to-high-end; the application rates and other treatment variables used in this assessment are upper-percentile values; and the inhalation absorption factor and body weight values are considered protective. In addition, rather than estimate exposure to

prothioconazole and prothioconazole-desthio separately (and then estimate separate risks), the risk assessment team estimated exposure based on prothioconazole assuming no conversion (resulting in protective exposure estimates), and compared these estimates to quantitative hazard estimates from the prothioconazole-desthio toxicology database (protective quantitative hazard estimates, because prothioconazole-desthio is generally considered more toxic than prothioconazole). This approach results in a protective risk assessment.

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

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

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

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

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

Table 5.1 summarizes the handler exposure estimates and risk resulting from the proposed uses of prothioconazole.

Table 5.1. Short- and Intermediate-Term Occupational Exposure and Risk Estimates for Prothioconazole.

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

[1] All estimates are at different mitigation levels (either the lowest at which the LOC is reached, or the highest available if the LOC is not reached) listed below each scenario description.

[2] Acres Treated Per Day from ExpoSAC Policy # 9, 7/5/00

[3] Unit exposure values are given for PPE/Engineering controls listed under Exposure Scenario (column 1) and taken from PHED Version 1.1 as presented in the PHED Surrogate Exposure Guide (8/98);

[4] Daily Dose = [Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure (mg/lb ai handled) x Absorption Factor]/Body Weight. A dermal absorption factor is not applied, since the endpoint chosen is from a dermal toxicity study. An inhalation absorption factor of 100% was used for inhalation risk, since the endpoint chosen is from an oral toxicity study. A body weight of 60 kg used for all calculations because the endpoints are gender-specific. Short-/Intermediate-term Dermal NOAEL=30 mg/kg/day; LOC = 1000. Short-/Intermediate-term Inhalation LOAEL=2.0 mg/kg/day. LOC = 1000

[5] Total MOE = 1/[(1/Dermal MOE) + (1/Inhalation MOE)] (Risk are combined via the total MOE approach because although the endpoints are selected from different studies and conducted with different species, the adverse effects are similar, and therefore merit combination)

[6] Sugar beets: The Total MOE for single layer, gloves M/L for aerial is 200 without a respirator and 230 with a respirator; the Total MOE for double layer, gloves for M/L for aerial is 240 without a respirator and 270 with a respirator. Soybeans: The Total MOE for single layer, gloves M/L for aerial is 390 without a respirator and 430 with a respirator; the Total MOE for double layer, gloves for M/L for aerial is 460 without a respirator and 510 with a respirator

5.2 Short-/Intermediate-Term Postapplication Risk

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

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

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

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

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

logarithm (ln) of the residue values versus the days after the final application. HED-calculated R^2 values ranged from 0.86 to 0.93, and half-lives ranged from 0.49 to 1.8 days for total-prothiconazole (*i.e.*, combined residues of prothiconazole and prothioconazole-desthio converted to prothioconazole-equivalents). Requirements for this type of study are specified by the U.S. EPA OPPT Series 875, Occupational and Residential Exposure Test Guidelines, Group B: Dislodgeable Foliar Residue Dissipation: Agricultural, Guideline 875.2100. The study was reviewed by Versar and by the U.S. EPA.

In the absence of chemical-specific DFR data, HED assumes a default dissipation rate of 10% per day, and that a default fraction of the applied ai is available on the foliage on the day of application (*i.e.*, 20%) when calculating DFR estimates (which in turn are used in postapplication exposure estimates, see footnotes of Table 5.2b). However, the chemical-specific DFR data demonstrated that total prothioconazole (prothioconazole and prothioconazole-desthio combined) dissipate more quickly than 10% per day, and that the fraction of applied ai available on the foliage as a percent of the application rate, can be 2-fold lower than 20%. These DFR data were used to calculate 'fraction of ai applied' and 'dissipation rate' estimates (for use in postapplication exposure estimates) for the crops tested, and were extrapolated to those crops for which no DFR data are available.

In order to estimate DFRs for the crops prothioconazole is registered/proposed for use on, an average percent initial DFR value was calculated from the DFR studies conducted on each crop. Additionally, an average daily dissipation rate was estimated for each of the crops tested (see Table 5.2a). Although uncertainties are introduced into the assessment when crop-specific residues are used to estimate dissipation parameters, it is believed to be more realistic than using default assumptions.

See Table 5.2a for a summary of these values calculated from the DFR study.

Table 5.2a: Results of DFR Study analysis

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

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

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

[3] NA, not applicable

The resulting DFRs, exposure estimates and risks are presented below in Table 5.2b. For some activities and crops, the REIs of 12 and 24 hours on the proposed labels are not adequate to reach

an MOE of 1000. To protect workers conducting all postapplication activities, an REI of 48 hours (2 days) is required (based on scouting barley, canola; and irrigating and scouting beans/peas and sugar beets). [Note: hand harvesting was not evaluated because this practice is being replaced by mechanical harvesting; the label must indicate that hand harvesting is not permitted].

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

Table 5.2b Summary of Occupational Postapplication Risks for Prothioconazole.								
Crop	**Appl. Rate (lb ai/A)**	**Fraction of ai Retained on Foliage[1]**	**Daily Dissipation Rate[1]**	**Transfer Coefficient (cm^2/hr)[2]**	**Dislodgeable Foliar Residue (ug/cm2)[3]**	**Days After Application (t)**	**Dermal Daily Dose[4] (mg/kg/day)**	**Short-/Inter-Term Dermal MOE[5]**
Barley, Canola (representative oilseed crops)	0.178	0.23[6]	0.48[6]	Low/min: scouting (100)	0.465	0	0.0062	4800
				High or low/full: scouting (1,500)	0.465	0	0.0930	320
					0.240	1	0.0480	630
					0.13	2	0.0248	1200
Dried shelled peas and beans subgroup	0.178	0.23	0.48	Low/min: irrigation and scouting, Low/full or min: hand weeding (100)	0.465	0	0.0062	4800
				Low/full: irrigation and scouting (1,500)	0.465	0	0.0930	320
					0.240	1	0.0480	630
					0.13	2	0.0248	1200
Peanuts	0.178	0.088	0.33	Hand weeding (100)	0.178	0	0.0024	13000
				Low/full: irrigation and scouting (1500)	0.178	0	0.036	840
					0.119	1	0.024	1300
Soybeans	0.0938	0.082	0.47	Hand weeding, Low/full: scouting (100)	0.086	0	0.0012	26000
				Low/full: irrigation and scouting (1500)	0.086	0	0.0173	1700
Sugar beets	0.178	0.17	0.44	Thinning, Hand weeding, Low/full and min: irrigation (100)	0.343	0	0.0046	6600
				Low/full: irrigation and scouting (1500)	0.343	0	0.0686	440
					0.192	1	0.0384	780
					0.108	2	0.0215	1400
Wheat	0.178	0.17[6]	0.44[6]	Low/min: irrigation and scouting (100)	0.343	0	0.0046	6600
				Low/full: irrigation and scouting (1,500)	0.343	0	0.0686	440
					0.192	1	0.0384	780
					0.108	2	0.0215	1400

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

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

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

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

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

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

6.0 Data Needs and Label Recommendations

Data Needs

- **PREVIOUS:** Raw data from field fortifications in MRID 46246447 (in addition to the % conversions reported in the study).
- The registrant indicated prothioconazole-desthio residue measurements were converted to prothioconazole-equivalents, however, they did not specify the method employed to correct the values. HED has assumed the same technique was used in this study, as was used in the applicator study (submitted with a previous petition). That is, to account for prothioconazole-desthio's lower molecular weight, prothioconazole-desthio was converted to "prothioconazole-equivalents" by applying a molar ratio of the two compounds. HED would like confirmation from Bayer that this is indeed the approach used in the DFR study (MRID 470026-01).

Label Recommendations

- USF 0728 325 SC Fungicide, on page 4 of the proposed label, remove the language describing use directions for chemigation. The label states "apply USF 0728 325 SC through irrigation equipment only to crops for which chemigation is specified on this label." There is one crop on the label (sugar beets), and chemigation is not specified in the use directions (whereas aerial and ground application methods are specified).
- USF 0728 325 SC Fungicide specifies a 10-14 day spray interval for soilborne diseases for sugar beets, but the overall restrictions specify a 14-30 day spray interval. The soilborne diseases spray interval should reflect the overall spray interval of 14-30 days.
- USF 0728 325 SC Fungicide should specify a 30-day plant-back interval for crops not on the label.
- **PREVIOUS:** State on the label that sunflower and safflower are excluded from the oilseed crop group.
- Change the REI to 48 hours on all labels.
- Remove all references to rice on the Proline 480 SC label.
- Indicate on the label, that hand-harvesting is prohibited

References

PHED, US EPA (US Environmental Protection Agency). Office of Pesticide Programs. Pesticide Handler Exposure Database (PHED) Version 1.1 Surrogate Exposure Table. August 1998.

Secondary Review for "JAU 480 SC – Dislodgeable Foliar Residue on Various Crops" MRID 470026-01. PC Code 113961. DP Barcode D335477. Sarah Winfield. December 31, 2007.

CC: RAB3 Reading File

13544

R156147

Chemical: Prothioconazole

PC Code:
113961
HED File Code: 11000 Chemistry Reviews
Memo Date: 12/31/2007
File ID: DPD331662
Accession #: 000-00-0124

HED Records Reference Center
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