



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: August 18, 2006

MEMORANDUM

SUBJECT: Prothioconazole: Occupational Exposure and Risk Assessment for Proposed Uses on Barley, Oilseed (except Sunflower and Safflower) Crop Group, Dried Shelled Pea and Bean (except Soybean) Subgroup, Peanut, Rice and Wheat. PC Code: 113961, DP Barcode: D303579.

Regulatory Action: Section 3 Registration, New AI

FROM: Sarah Winfield, Biologist *swinfield*
Registration Action Branch 3
Health Effects Division (7509P)

THROUGH: Jack Arthur, ORE Assessment Team Leader *Jack Arthur*
and
Stephen Dapson, Ph.D., Branch Senior Scientist *Stephen Dapson*
Registration Action Branch 3
Health Effects Division (7509P)

TO: Barry O'Keefe, Risk Assessor
Registration Action Branch 3
Health Effects Division (7509P)
and
Cynthia Giles-Parker, Product Manager
Fungicide Branch
RD/SRRD (7505P)

Introduction

Bayer CropScience is applying to register a new active ingredient, prothioconazole, for use on barley, oilseed (except sunflower and safflower) crop group, dried shelled pea and bean (except soybean) crop subgroup, peanut, rice, and wheat crops. This Section 3 registration action involves registering technical grade prothioconazole and its end-use product, PROLINE® 480 SC Fungicide, as well as establishing tolerances for the raw agricultural commodities derived from the requested use sites. This document addresses occupational exposures and risks resulting from the proposed uses. 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, listed below, have been determined to require a review of their ethical conduct. They are also subject to review by the Human Studies Review Board. The listed studies have received the appropriate review.

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.

Study Review for Determination of Exposure to JAU 6476 (prothioconazole) and JAU 6476-desithio (SXX 0665) During Mixing/Loading and Application of JAU 6476 in Cereals, (MRID#: 46246447; TAF# 4-1-23), Teri Schaeffer/Karie Riley (Versar), 10/4/04. [REDACTED]

Table of Contents

1.0	Executive Summary	3
2.0	Ingredient Profile	4
	2.1 Summary of Proposed Uses	5
	2.2 Physical and Chemical Properties	8
3.0	Hazard Characterization/Assessment	9
4.0	Residential (Non-Occupational) Exposure/Risk Characterization	11
5.0	Occupational Exposure/Risk Pathway	12
	5.1 Short-/Intermediate-Term Handler Risk	13
	5.2 Short-/Intermediate-Term Postapplication Risk	17
6.0	Data Needs and Label Requirements	19
	References	19

1.0 Executive Summary

Bayer CropScience is applying to register a new active ingredient (ai), prothioconazole, for agricultural use as a systemic, broad spectrum fungicide in the liquid formulation PROLINE® 480 SC (soluble concentrate, 41% ai). There are no proposed residential uses, and therefore residential exposure and risk are not assessed in this document.

Prothioconazole is in the triazolinthione chemical class and is a de-methylation-inhibitor (DMI-type) fungicide. The petitioner is currently proposing food/feed uses on grain crops, oilseed crops, peas and beans, lentils, peanuts and rice. The PROLINE® 480 SC Fungicide label indicates prothioconazole will be applied on these crops 2 – 4 times per season, at rates ranging from 0.0875 to 0.178 lb ai/A (5- to 21- day re-treatment intervals) with overall maximum seasonal application rates ranging from 0.269 to 0.713 lb ai/A. Pre-harvest intervals (PHIs) range from 7 to 40 days depending on the crop. The label also indicates prothioconazole can be applied with both aerial and ground equipment, 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 desthio-prothioconazole, 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 desthio-prothioconazole 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 (14th 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 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 an 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 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 Margins of Exposure (MOEs) range from 870 to 5,000. One exposure scenario (closed M/L for aerial application to wheat) did not reach the LOC of an MOE of 1000 with engineering controls. M/L for aerial application for crops other than wheat also required applying the engineering control of a closed M/L system, in order to result in MOEs of 1000 or greater. 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 exposure scenarios reach MOEs of 1000 with baseline clothing and no gloves.

Although the registrant submitted prothioconazole-specific handler exposure data (MRID 46246447), these data were only used qualitatively. The first objective of the study aimed to provide unit exposure information on prothioconazole and desthio-prothioconazole. The unit exposure information was determined to be inappropriate for use in exposure estimate calculations (and subsequent risk estimates) because of the small scale of the study, the choice of activity combinations, and the use of Bayer employees as study subjects. The study also investigated the likely range of percent conversion from prothioconazole to desthio-prothioconazole during a typical agricultural workday, and this information is used qualitatively in this document. [REDACTED]

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 15 days following application are required to reach MOEs of 1000. Therefore, the label (which indicates a restricted-entry interval [REI] of 24 hours) should be amended to indicate an REI of 15 days is required to reach acceptable exposure levels.

Additionally, the label should be amended to explicitly state the crops excluded in particular groups (*i.e.*, for the oilseed crop group, sunflower and safflower crops are excluded, and for the dried shelled pea and bean crop subgroup, soybean crops are excluded).

2.0 Ingredient Profile

Prothioconazole is a new 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 D₂, 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/7thArticle022004_EN/$file/07_Dutzmann.pdf);
[http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/ID/8thArticle032004_EN/\\$file/08_Suty-Heinze.pdf](http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/ID/8thArticle032004_EN/$file/08_Suty-Heinze.pdf))

Prothioconazole, formulated as PROLINE ® 480 SC Fungicide (see Table 2), is currently proposed for food/feed uses on the following crops: 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, rice, wheat (spring, durum and winter).

Trade Name	EPA Reg. No.	ai (% of formulation)	Formulation Type	Target Crops	Target Pests	Use Directions and Limitations
PROLINE ® 480 SC Fungicide	264-XXX	41% 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-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, rice 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.

2.1 Summary of Proposed Uses

Table 2.1 provides a summary of the directions provided on the PROLINE ® 480 SC Fungicide label.

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	0.134 - 0.178 [1.3 - 5.7]	2	7 to 14	0.293 [9.37]	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	0.0875 - 0.134 [2.8 - 4.3]	2	7 to 14	0.269 [8.6]	32	Apply as a preventative foliar spray when the earliest disease symptoms appear on the leaves or stems.

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
Canola						
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 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	0.134 -0.178 [4.3 - 5.7]	3	10 to 14	0.534 [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	0.134 -0.178 [4.3 - 5.7]	3	5 to 14	0.534 [17.1]	7	Apply at the first sign of disease. Use higher use rate when conditions are favorable for severe disease pressure and/or when growing less disease resistant varieties.
Lentils						
Broadcast foliar spray; Ground or aerial	0.134 -0.178 [4.3 - 5.7]	3	10 to 14	0.534 [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.

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
Peanut						
Broadcast foliar spray; Ground or aerial	0.156 -0.178 [5.0 - 5.7]	4	14 to 21	0.713 [22.8]	14	Soil Borne disease: Utilize the high use rate. Make four consecutive applications at 14 day intervals. In a typical 7 spray application program beginning 30-40 days after planting, PROLINE 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. PROLINE 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.
Rice						
Broadcast foliar spray; Ground or aerial	0.143 [4.56]	2	Not Specified	0.285 [9.12]	40	Apply at initial sign of disease. Exact timing for rice disease control is dependent on rice growth stage, rice variety, the type of disease to be controlled and disease severity. Applications typically will occur from panicle differentiation to late boot. Consult with local extension personnel or Bayer Crop Science representative to determine if treatment is needed. Under severe disease conditions or when conditions are favorable for continued disease development, a second application of PROLINE may be made as late as 70% panicle emergence from the boot (but no later than 70% panicle emergence from boot).
Wheat (spring, durum and winter) (for Fusarium Head Blight)						
Broadcast foliar spray; Ground or aerial	0.134 -0.178 [4.3 - 5.7]	2	7 to 14	0.293 [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.

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
Wheat (spring, durum and winter) (for Leaf and Stem Diseases)						
Broadcast foliar spray; Ground or aerial	0.134 -0.156 [4.3 - 5.0]	2	7 to 14	0.293 [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
Vapor pressure (Pa at 20 or 25°C)	<4 x 10 ⁻⁷
Dissociation constant, pK _a	6.9
Octanol/water partition coefficient, Log(K _{ow})	at 20 °C unbuffered: K _{ow} = 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 the Spring and Summer of 2006, the prothioconazole toxicology database was 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 (14th 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 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 exposures to mixers, loaders, and applicators, risk estimates for short- and intermediate-term exposures from both inhalation and dermal routes are added together, because the hazard/endpoint is the same. However, because the MOEs for dermal and inhalation exposures are calculated using different NOAELs, a total MOE approach [$1/(1/\text{MOE}_{\text{dermal}}) + (1/\text{MOE}_{\text{inhalation}})$] 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 ($\text{UF}_A = 10x$ [intraspecies] and $\text{UF}_H = 10x$ [interspecies]) and an additional UF_{DB} (10x, database) for the lack of 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, and therefore, a quantitative cancer assessment is not required.

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

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL=30 mg/kg/day	UF _A =10x UF _H =10x UF _{DB} = 10x	Occupational LOC for MOE = 1000	Dermal developmental study in rats LOAEL = 100 mg/kg/day based on an increased incidence of supernumerary rib (14th rib).
Inhalation Short- and Intermediate-term (1-30 days and 1-6 months)	NOAEL=2.0 mg/kg/day Inhalation absorption are assumed to be 100%	UF _A =10x UF _H =10x UF _{DB} = 10x	Occupational LOC for MOE = 1000	Developmental Toxicity study in rabbits LOAEL = 10 mg/kg/day, based on structural alterations including malformed vertebral body and ribs, arthrogyrosis, 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 (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key data (*i.e.*, lack of a critical study). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

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 limited to use of the proposed formulation PROLINE® 480 SC Fungicide, which is proposed for application on barley, oilseed crops, dried bean and pea crops, peanuts, rice and wheat (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; however, an inhalation absorption factor was applied to the inhalation exposure estimates because the study the endpoint was selected from was not route specific (even though inhalation and oral exposures are considered equivalent [*i.e.*, the inhalation absorption factor used was 100%]). Also, a body weight of 60 kg was used in the exposure estimates, because the endpoints were development (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 1000.

As part of the registration package, the registrant submitted a prothioconazole-specific handler exposure study (MRID 46246447). The first objective of the study aimed to provide unit exposure information on prothioconazole and desthio-prothioconazole. The unit exposure information was determined to be inappropriate for use in exposure estimate calculations (and subsequent risk estimates) because of the small scale of the study, the choice of activity combinations, and the use of Bayer employees as study subjects. The best use of the study was to ascertain the likely range of percent conversion from prothioconazole to desthio-prothioconazole during a typical agricultural workday (the second objective). Only outer dosimeters, which represent workers' clothes, detected both prothioconazole and desthio-

prothioconazole, and therefore offered the most information regarding percent conversion estimates (which ranged from 0.5 to 61%). Although percent conversions were estimated in EPA's secondary review of the study, they are not used quantitatively in this assessment (only qualitatively). Rather than estimate exposure to prothioconazole and desthio-prothioconazole separately (and then estimate separate risks), the risk assessment team decided to estimate exposure based on prothioconazole assuming no conversion (resulting in protective exposure estimates), and compare these estimates to quantitative hazard estimates from the desthio-prothioconazole toxicology database (protective quantitative hazard estimates, because desthio-prothioconazole is generally considered more toxic than prothioconazole). This approach results in a protective risk assessment.

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 PROLINE® 480 SC Fungicide.

Prothioconazole-specific handler exposure data were submitted in support of this action, but as explained above, were used only qualitatively 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.

PROLINE® 480 SC is applied aerially and by ground equipment. The following handler scenarios were considered representative of potential exposures expected from use of this product: 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 (for M/L for aerial application to wheat, the LOC was not reached; refer to Table 5.1 for details on the exposure and risk estimates).

- Mixing and Loading for:
 - Aerial: with the engineering controls/PPE (closed system and gloves), all scenarios reached the LOC of an MOE of 1000, except for wheat
 - 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 wheat does not result in an exposure estimate 1000X less than the quantitative hazard estimate (even with engineering controls) this estimate does involve uncertainty regarding hazard and exposure. On the exposure side, prothioconazole exposure estimates are compared to desthio-prothioconazole endpoints (in order to be protective and prevent separating out risks from prothioconazole and desthio-prothioconazole) even though there are data that support desthio exposure estimates being at most about half that of prothioconazole exposure estimates (*i.e.*, conversion estimates of prothioconazole to desthio-prothioconazole ranged from 0.5 to 61%). On the hazard side, an additional 10X has been applied to account for lack of a NOAEL and LOAEL in the DNT study regarding the neurotoxic endpoint of peripheral lesions and brain morphometrics; and had the risk assessment team separated out risk from prothioconazole and desthio-prothioconazole, not only would the desthio-prothioconazole exposure estimates be lower, the prothioconazole quantitative hazard estimate would be about 7X greater than the desthio-prothioconazole quantitative hazard estimate employed in this assessment.

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

Exposure Scenario	Application Rate (lb ai/acre)	Crop	Exposure Route	Acres Treated per Day ¹	PHED Unit Exposure ² (mg/lb ai)	Daily Dose ³ (mg/kg/day)	Route- specific Short-/Inter Term MOE	Total Short- /Inter Term MOE ⁵
Closed M/L Liquids, for Aerial	0.178	Barley, canola, chickpea, dried shelled peas and beans subgroup, lentils, oilseed crop subgroup, peanuts	Dermal	350	0.0086	0.0089	3,400	3,000
			Inhalation		0.000083	0.000086	23,000	
PPE/Engineering control = Closed system + gloves	0.143	Rice	Dermal	1200	0.0086	0.025	1,200	1,000
	0.178	Wheat	Inhalation	1200	0.000083	0.00024	8,300	870
Dermal			0.0086		0.031	970		
Open M/L Liquids, for Groundboom	0.178	Barley, canola, chickpea, dried shelled peas and beans subgroup, lentils, oilseed crop subgroup, peanuts	Inhalation	80	0.000083	0.00030	6,700	3,100
			Dermal		0.023	0.055	5,500	
PPE = single layer + gloves	0.143	Rice	Inhalation	200	0.0012	0.00028	7,100	1,500
			Dermal		0.023	0.011	2,700	
Applying Liquid, with Aerial - fixed wing (enclosed cockpit)	0.178	Wheat	Inhalation	200	0.0012	0.00057	3,500	1,200
			Dermal		0.023	0.014	2,100	
Baseline (no PPE, i.e., single layer, no gloves)	0.178	Barley, canola, chickpea, dried shelled peas and beans subgroup, lentils, oilseed crop subgroup, peanuts	Inhalation	350	0.0012	0.00071	2,800	4,800
			Dermal		0.005	0.052	5,800	
PPE/Engineering control = Closed system + gloves	0.143	Rice	Inhalation	1200	0.000068	0.000071	28,000	1,700
			Dermal		0.005	0.014	2,100	
Applying Liquid, with Aerial - fixed wing (enclosed cockpit)	0.178	Wheat	Inhalation	1200	0.000068	0.00019	11,000	1,400
			Dermal		0.005	0.018	1,700	
Baseline (no PPE, i.e., single layer, no gloves)	0.178	Wheat	Inhalation	1200	0.000068	0.00024	8,300	1,400
			Dermal		0.005	0.014	2,100	

Table 5.1. Short- and Intermediate-Term Occupational Exposure and Risk Estimates for Prothioconazole. 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. Bolded MOEs are those that do not reach the LOC. The S-T/I-T dermal NOAEL is 30 mg/kg/day. S-T/I-T inhalation NOAEL is 2.0 mg/kg/day.									
Exposure Scenario	Application Rate (lb ai/acre)	Crop	Exposure Route	Acres Treated per Day ¹	PHED Unit Exposure ² (mg/lb ai)	Daily Dose ³ (mg/kg/day)	Route-specific Short-/Inter Term MOE	Total Short-/Inter Term MOE ⁵	
Applying Liquid, with Groundboom (open cab)	0.178	Barley, canola, chickpea, dried shelled peas and beans subgroup, lentils, oilseed crop subgroup, peanuts	Dermal	80	0.014	0.0033	9,100	5,000	
			Inhalation		0.00074	0.00018	11,000		
Baseline (no PPE, i.e., single layer, no gloves)	0.143	Rice	Dermal	200	0.014	0.0067	4,500	2,500	
			Inhalation		0.00074	0.00035	5,700		
Wheat	0.178		Dermal	200	0.014	0.0083	3,600	2,000	
			Inhalation		0.00074	0.00044	4,500		
Flagging for Aerial Operations	0.178	Barley, canola, chickpea, dried shelled peas and beans subgroup, lentils, oilseed crop subgroup, peanuts, wheat	Dermal	350	0.011	0.011	2,700	1,800	
			Inhalation		0.00035	0.00037	5,400		
Baseline (no PPE, i.e., single layer, no gloves)	0.143	Rice	Dermal	350	0.011	0.0092	3,300	2,200	
			Inhalation		0.00035	0.00029	6,900		

¹ Acres Treated Per Day from ExpoSAC Policy # 9, 7/5/00

² Unit exposure values are given for PPE/Engineering controls listed under Exposure Scenario (column 1)

³ 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

⁴ 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)

5.2 Short-/Intermediate-Term Postapplication Risk

Postapplication workers are assumed to have potential short- and intermediate-term dermal exposure (but not inhalation exposure) from the proposed uses of PROLINE® 480 SC Fungicide. All of the proposed uses are for low to medium height row crops and because of this shared feature, the postapplication exposure expected for different crops are similar when similar postapplication activities are conducted. Postapplication activities expected from the proposed uses are scouting, irrigation, hand weeding and hand harvesting. No chemical-specific data relevant to postapplication exposure (*i.e.*, dislodgeable foliar residue [DFR] data) were submitted, therefore, postapplication exposure estimates were calculated using standard HED Exposure SAC assumptions (body weight, exposure duration, fraction of ai retained on foliage and daily dissipation) and policies (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.

The resulting exposure estimates and risks are presented below in Table 5.2. For most activities and crops, the REI of 24 hours on the proposed label is not adequate to protect workers. To protect workers conducting all postapplication activities, an REI of 15 days is required (based on hand harvesting peas and beans); however, an REI of 10 days is adequate to protect workers conducting most postapplication activities. For some postapplication activities, such as irrigation which can often be automated, an REI of 15 (or 10) days may not pose a problem. However, for other postapplication activities, such as harvesting peas and beans (the label indicates a PHI of 7 days), this poses a problem. The estimated REIs were determined using standard values (20% ai initially retained on foliage, 10% daily dissipation). While these assumptions may be overestimating postapplication risk, in the absence of data, further refinement is not feasible. The development of field data would present a more accurate picture of postapplication risk, and therefore, DFR data are required.

Again, it should be pointed out that these estimates involve uncertainty regarding hazard and exposure: an additional 10X has been applied to account for lack of a NOAEL and LOAEL in the DNT study regarding the neurotoxic endpoint of peripheral lesions and brain morphometrics; and for exposure, prothioconazole exposure estimates rely on default assumptions for residues (20% of initial application remains on foliage, and 10% daily dissipation).

Table 5.2 Summary of Occupational Postapplication Risks for Prothioconazole. The S-T/I-T dermal NOAEL is 30 mg/kg/day.

Crop	Appl. Rate (lb ai/A)	Fraction of ai Retained on Foliage	Daily Dissipation Rate	Transfer Coefficient (cm ² /hr) ¹	Dislodgeable Foliar Residue (ug/cm ²) ²	Days After Application (t)	Dermal Daily Dose ³ (mg/kg/day)	Short-/Inter-Term Dermal MOE ⁴
Barley, Canola (representative oilseed crops)	0.178			Low/min: scouting (100)	0.399	0	0.0053	5,700
				High or low/full: scouting (1,500)	0.399	0	0.080	380
					0.155	9	0.031	970
Dried shelled peas and beans subgroup	0.178		0.1	Low/min: irrigation and scouting, Low/full or min: hand weeding (100)	0.139	10	0.028	1,100
				Low/full: irrigation and scouting (1,500)	0.399	0	0.0053	5,700
					0.399	0	0.080	380
					0.155	9	0.031	970
					0.139	10	0.028	1,100
Peanuts	0.178		0.1	Low/full: hand harvest (2,500)	0.399	0	0.13	230
					0.139	10	0.046	650
					0.091	14	0.030	990
					0.082	15	0.027	1,000
					0.399	0	0.0053	5,700
Rice	0.143		0.1	Low/full: irrigation and scouting (1,500)	0.399	0	0.080	380
					0.155	9	0.031	970
					0.139	10	0.028	1,100
					0.321	0	0.0043	7,000
					0.321	0	0.064	470
Wheat	0.178			Low/full: scouting (1,500)	0.153	7	0.031	970
					0.138	8	0.028	1,100
					0.399	0	0.0053	5,700
				Low/min: irrigation and scouting (100)	0.399	0	0.080	380
				Low/full: irrigation and scouting (1,500)	0.155	9	0.031	970
					0.139	10	0.028	1,100

¹ Transfer coefficients are taken from the HED Science Advisory Council (SAC) for Exposure SOP 003.1 (August 2000)

² Dislodgeable Foliar Residue $\text{Residue}_{\text{Dislodgeable}} (\text{ug}/\text{cm}^2) = \text{Application rate} (\text{lb ai}/\text{A}) \times \text{Fraction of ai Retained on the Foliage (default assumption)} \times (1 - \text{Fraction of Residue that Dissipates Daily [also default assumption]})$

³ Daily Dose = $[\text{Dislodgeable Foliar Residue} \times 0.001 \text{ mg}/\text{ug} \times \text{Dermal Transfer Coefficient} (\text{cm}^2/\text{hr}) \times \text{Exposure Time (8 hours)}/\text{Body weight (60 kg)}$

⁴ MOE = NOAEL/Daily Dose. Short-/Intermediate-Term Dermal NOAEL = 30 mg/kg/day. LOC = 1000.

6.0 Data Needs and Label Requirements

Data Needs

- Dislodgeable foliar residue data to inform and refine postapplication exposure and risk estimates
- Raw data from field fortifications in MRID 46246447 (in addition to the % conversions reported in the study)

Label Requirements

- State on the label that sunflower and safflower are excluded from the oilseed crop group
- State on the label that soybeans are excluded from the dried peas and beans subgroup
- Change the REI to 15 days

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.

Study Review for Determination of Exposure to JAU 6476 (prothioconazole) and JAU 6476-desthio (SXX 0665) During Mixing/Loading and Application of JAU 6476 in Cereals, (MRID#: 46246447; TAF# 4-1-23), Teri Schaeffer/Karie Riley (Versar), 10/4/04.

CC: RAB3 Reading File



13544



R131999

Chemical: Nitrapyrin

PC Code:
069203

HED File Code: 11100 Other Chemistry Documents

Memo Date: 7/16/1976

File ID: 00000000

Accession #: 000-00-0108

HED Records Reference Center
8/24/2006

