UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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SCIENTIFIC DATA REVIEWS
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MEMORANDUM

Date: 25 January 2007

Subject: Occupational and Residential Risk Assessment to Support Request for Reduced Restricted Entry Interval (REI) for Corn Detasseling

DP Barcode:	PC Code:	Trade Names:	EPA Reg#s	MRID#	Class
D329421	099100	Headline® Fungicide	7969-186	46788501 46788502	Fungicide

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Introduction

The registrant, BASF Corporation, requests a reconsideration of the restricted entry interval (REI) for the previously-registered use on corn. This memorandum addresses risk from occupational postapplication exposure only; handler risk was evaluated in a previous HED memorandum (D298017).

1.0 Executive Summary

Pyraclostrobin is a fungicidal active ingredient (ai) currently registered for use on a variety of crops (including corn) and turf. In a previous assessment (D298017), it was determined that a restricted entry interval (REI) of 7 days was necessary to yield MOEs greater than 100 for exposure from corn hand harvesting and detasseling activities. This determination was made based on the use of chemical-specific, but not crop-specific dislodgeable foliar reside (DFR) data, and a standard transfer coefficient (TC) value based on data for hand harvesting sweet corn.

The registrant, BASF Corporation, requests a reconsideration of the (REI) for the previously-registered use on corn, and has submitted additional data to support this request: 1) a crop-specific DFR study on corn (MRID# 46788501), and 2) a combined exposure and DFR study (MRID# 46788502) for use in determining an activity-specific transfer coefficient for corn detasseling.

Primary reviews of these studies indicate that data from both are acceptable for the purposes of this assessment. The corn-specific DFR levels were only slightly lower than those previously estimated. However, the activity-specific transfer coefficient estimates for corn detasseling ranged from 260 to 1,500 cm^2/hr, with an arithmetic mean of 710 cm^2/hr; significantly lower than the standard value of 17,000 cm^2/hr (for hand harvesting sweet corn) used in the previous assessment.

The use of these data resulted in a margin of exposure (MOE) of 800 on the day of application for detasseling activities. Because the level of concern for pyraclostrobin is for an MOE less than 100, it is **possible to reduce the REI for corn detasseling** from 7 days **to 12 hours**. In addition, the crop-specific DFR were also used to revise the assessment for **hand harvesting corn**, for which the standard TC of 17,000 cm^2/hr applies. Based on these new data, **5 days is necessary to reach an MOE of 100** for this activity (reduced from 7 days); this is less than the current pre-harvest interval (PHI), and therefore does not create a hardship for harvesting.

[Note: This risk assessment relies in part on data from a study in which adult human subjects were intentionally exposed to a pesticide or other chemical (MRID# 46788502). This study is currently undergoing review to determine its ethical conduct.

2.0 Hazard Profile

On April 5, 2001, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for pyraclostrobin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to pyraclostrobin was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. On October 1, 2001, the FQPA Committee met and confirmed that the safety factor of 3X, applicable to females ages 13 to 50, is appropriate to address the potential for increased susceptibility. However, on December 17, 2002, the HIARC reevaluated the potential for increased susceptibility of infants and children according to the 2002 OPP FQPA 10X Guidance Document, and recommended that the special FQPA factor should be removed [1X] for all potential exposure scenarios to pyraclostrobin because there are no residual uncertainties for pre- and/or postnatal toxicity. The acute toxicity data for the pyraclostrobin technical formulation are presented in Table 1. The doses and toxicological endpoints selected by the HIARC for various exposure scenarios are summarized in Table 2.

On October 24, 2001, the Cancer Assessment Review Committee (CARC) concluded that pyraclostrobin should be classified into the category "data are inadequate to assess the human carcinogenic potential" because of inadequate dose levels for female rats and mice in the carcinogenicity studies. On September 10, 2003, the CARC reevaluated the carcinogenicity data and reaffirmed the cancer classification based on the determination of inadequate dose levels in the carcinogenicity study for female mice only. The CARC now considers the doses tested in both sexes of the rat carcinogenicity study adequate, and confirmed that the tumor data from the combined results of carcinogenicity and chronic toxicity studies (in rats) showed neither a significant increasing trend nor a significant difference in the pair-wise comparison of the dosed groups with the controls. In the absence of a complete database for carcinogenicity, HED management decided that a Margin of Exposure (MOE) method to assess cancer risk would be appropriate. In an ad hoc meeting with HED senior scientists, which occurred on August 10, 2004, this decision was reaffirmed, along with the conclusion that this approach is applicable to long-term exposure only, for the following reasons: 1) genotoxicity data indicate that pyraclostrobin is not mutagenic; 2) there was no treatment related increase in tumors in male and female rats, or in male mice; and 3) two structural analogs of pyraclostrobin were found "not likely to be carcinogenic to humans".

Table 1. Acute Toxicity Data on Pyraclostrobin Technical

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute Oral	45118302	LD_{50} = > 5000 mg/kg	IV
870.1200	Acute Dermal	45118305	LD_{50} = > 2000 mg/kg	III
870.1300	Acute Inhalation	45118308	0.31< LC_{50} < 1.07 mg/L	II
870.2400	Primary Eye Irritation	45118311	minimal eye irritation; MAS 4.6/110	III
870.2500	Primary Skin Irritation	45118314	moderate skin irritation; MAS 2.2/8.0	III
870.2600	Dermal Sensitization	45118317	not a dermal sensitizer	N/A

Table 2. Summary of Toxicological Doses and Endpoints for Pyraclostrobin for Use in Human Risk Assessment			
Exposure Scenario	**Dose (mg/kg/day)**	**Endpoint**	**Study**
Incidental Oral, Short and Intermediate-Term	NOAEL= 5.8	Increased incidence of diarrhea, clinical chemistry changes, duodenum mucosal hypertrophy, and decreased body weight and food intake/efficiency at 12.9 mg/kg/day (LOAEL).	13-Week Feeding Dog Study (MRID 45118323)
Dermal, Short- and Intermediate-Term	Oral NOAEL= 5.0	Developmental toxicity findings of increased resorptions at 10.0 mg/kg/day (LOAEL).[1]	Rabbit Prenatal Developmental Toxicity (MRID 45118326)
Dermal, Long-Term	Oral NOAEL= 3.4	Decreased body weight/gain, kidney tubular casts and atrophy in both sexes; increased incidence of liver necrosis and erosion/ulceration of the glandular stomach and forestomach in males in addition to hemolymphoreticular tumors in males and mammary adenocarcinoma in females at 9.2 mg/kg/day (LOAEL).[1]	Rat Oral Carcinogenicity (MRID 45118331)
Inhalation, Short- and Intermediate-Term	Oral NOAEL= 5.0	Developmental toxicity findings of increased resorptions at 10.0 mg/kg/day (LOAEL).[2]	Rabbit Prenatal Developmental Toxicity (MRID 45118326)
Inhalation, Long-Term	Oral NOAEL= 3.4	Decreased body weight/gain, kidney tubular casts and atrophy in both sexes; increased incidence of liver necrosis and erosion/ulceration of the glandular stomach and forestomach in males in addition to hemolymphoreticular tumors in males and mammary adenocarcinoma in females at 9.2 mg/kg/day (LOAEL).[2]	Rat Oral Carcinogenicity (MRID 45118331)
Cancer (MOE Approach)	NOAEL = 32.8	Mortality, clinical signs, body weight, body weight gain, food consumption, food efficiency, hematology, organ weights, and gross and microscopic findings for both sexes at all doses were unaffected by treatment. The highest tested dose was 32.8 mg/kg/day in females.[1,2]	Mouse Oral Carcinogenicity (MRID 45118330)

[1] The dermal absorption factor of 14% should be applied to extrapolate from the oral route to the dermal route.
[2] 100% absorption rate (default value) should be used to extrapolate from the oral route to the inhalation route.

3.0 Use Profile

Pyraclostrobin is registered for use on a variety of crops and turf. This specific action involves a reconsideration of the 7-day restricted entry interval (REI) on the label for the end use product Headline® Emulsifiable Concentrate (24% ai, i.e., 2.09 lb ai/gal), for activities associated with corn. The label permits application to corn at a maximum rate of 0.2 lb ai/A up to 6 times per season (no more than 2 sequential applications), with 7- to 14-day intervals.

4.0 Occupational Exposure

4.1 Handler Exposure and Risk

The exposure and risk for handlers involved in the treatment of corn was estimated in a previous assessment: *Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Pyraclostrobin on a Variety of Crops and Residential Turf* (D298017, K. O'Rourke, 8/19/04). Because this current action entails re-evaluation the REI only, handler exposure and risk have not been reconsidered.

4.2 Occupational Postapplication Exposure and Risk

The registrant has requested a reconsideration of the restricted entry interval (REI) for the previously-registered use on corn. In the original assessment for this use (D298017), it was determined that an REI of 7 days was necessary to achieve MOEs greater than 100 for exposure from corn hand harvesting and detasseling activities. This determination was made based on the use of chemical-specific, but not crop-specific dislodgeable foliar reside (DFR) data, and a standard transfer coefficient (TC) value based on data for hand harvesting sweet corn.

The registrant has submitted additional data to support this request: 1) a crop-specific DFR study on corn (MRID# 46788501), and 2) a combined exposure and DFR study (MRID# 46788502) for use in determining an activity-specific transfer coefficient for corn detasseling. The results of these studies are summarized below:

Dislodgeable Foliar Residue (DFR) Study on Corn (MRID# 46788501):

Headline® fungicide, an emulsifiable concentrate containing 23.6% pyraclostrobin, was applied five to six times to corn crops at three test sites (Wisconsin, Michigan, and Idaho) at the maximum label application rate of 0.2 lbs ai/A, with 6- to 7-day application intervals. Triplicate leaf punch samples were collected after each application, before and after the last application, and 1, 2, 3, 4, 7, 10, 14, 21 and 28 days after the final application for each site. The application method and frequency (number and timing) were relevant to the use pattern proposed by the product label. The overall mean field fortification recoveries for the WI, MI and ID sites were 109%, 87.0% and 89.6%, respectively. At the WI site, the residues accumulated with each application to reach their highest level after the sixth application. However, at the MI and ID sites, residues were at their highest immediately after the second application. The corrected mean DFR values occurring immediately after the final application for the Wisconsin, Michigan, and Idaho sites were 0.35 $\mu g/cm^2$, 0.11 $\mu g/cm^2$, and 0.18 $\mu g/cm^2$, respectively. The estimated half-life values were 3.5 days ($r^2 = 0.84$) for corn leaves in WI, 4.3 days ($r^2 = 0.69$) for corn leaves in MI, and 8.1 days ($r^2 = 0.69$) for corn leaves in ID.

Transfer Coefficient (TC) Study for Detasseling Corn (MRID# 46788502):

The purpose of this study was to estimate transfer coefficients for workers detasseling corn by hand. Two applications of Headline® fungicide were made at a rate of 0.2 lb ai per acre 7 days apart to a single plot of corn at a test site in Illinois. The field was machine detasseled at the test location on three occasions prior to the reentry activity. Seven days after the second application of the product, 18 workers reentered the field and were monitored while detasseling the corn by hand. Dermal exposure was assessed by using whole-body dosimetry (inner and outer), hand washes, and face/neck wipes. Though stopped short for rain, the work period was reported to be typical, ranging from 7.5 to 8 hours. In order to calculate transfer coefficients representative of a worker wearing a single layer of clothing, total dermal exposures were based on the sum of the inner dosimeter, face/neck, and handwash residues, and ranged from 13.8 to 82.3 µg/hr. Dislodgeable foliar residue (DFR) samples were also collected from the same plot at several intervals, including the day on which workers reentered the field for exposure monitoring (i.e., 7 days after the last application). The average DFR for this day (0.054 $\mu g/cm^2$) was used to determine dermal transfer coefficients, which were calculated by dividing the dermal exposure (µg/hr) by the average DFR ($\mu g/cm^2$) on the re-entry day. The resulting transfer coefficients ranged from 260 to 1,500 cm^2/hr, with an arithmetic mean of 710 cm2/hr.

The data from both of these studies are considered acceptable for the purposes of this assessment, however, minor points were noted and are discussed below:

DFR study:

- Residues were at their highest immediately after the second application at the MI and ID sites (ranging from 0.23 to 0.24 $\mu g/cm^2$), rather than after the sixth/final application. However, the values used in this assessment for day 0 are greater than the maximum MI and ID residues, and therefore, are protective.

TC study

- A major rain event occurred between 8-24 hours after the final application, which probably influenced the natural residue decline. In addition, the maximum seasonal application rate of 1.18 lb ai/A was not used. Instead, only 2 applications were made at 0.2 lb ai/A each (0.4 lb ai/A total), which may have resulted in lower than expected residues. These points are of little concern because DFR values from a TC study are only necessary for the day on which activity exposure is measured in order to calculate the transfer coefficients. A separate DFR study was conducted which addresses residue dissipation.

- Because the field was machine detasseled at the test location on three occasions prior to the reentry activity, it was questionable whether this study is representative of typical detasseling activities. Based on personal communication with Larry Olsen, Michigan State University's Interim Extension Agriculture Program Leader, most seed corn is mechanically detasseled, and then 5-7 days later a ground crew enters the field to pull any remaining or late emerging tassels. At the same time, they use a hand-hoe to dig out any off-type plants or weed escapes (an activity called rogueing). This information indicates that the study reflects current detasseling exposure patterns.

As noted previously, the original assessment for this use (D298017) estimated DFR from non crop-specific DFR studies. In this revised assessment, corn DFR data from both MRID#s 46788501 and 46788502 were used. The resulting corn-specific DFR levels were only slightly lower than those previously estimated. The average initial fraction of ai retained on the foliage (previous: 0.18; revised: 0.14) was estimated based on corn DFR data from both MRID#s 46788501 and 46788502. This value was used in estimating all MOEs except for scenarios for which the REI is likely to be less than 1 day; in this case, the maximum measured initial DFR was used, because the predicted DFR was lower for day 0, and a 12-hour REI has been proposed by the registrant. An average fraction of residue that dissipates daily (previous: 0.13; revised: 0.14) was also estimated based on the individual daily dissipation rates from MRID# 46788501. The DFR data from MRID# 46788502 were not considered reliable to estimate dissipation because of a major rain event may have compromised the dissipation kinetics, and the fact that DFR samples were only collected up to 7 days after the last application.

In addition to these residue data, transfer coefficients (TCs) were used to relate the foliage residue values to activity patterns (e.g., detasseling or harvesting) to estimate potential human exposure. The transfer coefficient for detasseling and harvesting used in the previous assessment was from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (policy # 3.1). This value, 17,000 cm^2/hr, is based on an exposure study for hand harvesting sweet corn, and is extrapolated in policy #3.1 to detasseling activities, for which data were not available. For this revised assessment, actual detasseling TCs were calculated from MRID# 46788502. These activity-specific transfer coefficient estimates for corn detasseling ranged from 260 to 1,500 cm^2/hr (with an arithmetic mean of 710 cm^2/hr), and are significantly lower than the standard value used in the previous assessment.

Table 3 presents a summary of the data used in this assessment, as well as a comparison to the assumptions in the previous assessment. The use of these data resulted in a margin of exposure (MOE) of 800 on the day of application for detasseling activities. Because the level of concern for pyraclostrobin is for an MOE less than 100, it is **possible to reduce the REI for corn detasseling** from 7 days **to 12 hours**. In addition, the crop-specific DFR were also used to revise the assessment for **hand harvesting corn**, for which the standard TC of 17,000 cm^2/hr applies. Based on these new data, **5 days is necessary to reach an MOE of 100** for this activity (reduced from 7 days); this is less than the current pre-harvest interval (PHI), and therefore does not create a hardship for harvesting.

Table 3. Estimated REIs, Based on Short-/Intermediate-Term MOEs						
Pyraclostrobin Specific Crops	**Data used to Estimate DFR [1]**	**DAT [2]**	**DFR [3] (µg/cm²)**	**TC [4] (cm²/hr)**	**Activity [4]**	**MOE [5] Short-/ Int-Term**
Previous Assessment (D298017)						
Corn (previous assessment)	Various crops: Average DFR from EC formulation	0	0.40	100	Scouting, weeding immature/low foliage plants	6,600
		0		1,000	Scouting, irrigation, weeding mature/full foliage plants	660
		0		17,000	Sweetcorn hand harvest or detasseling	39
		7	0.13			100
Revised Assessment (data from MRID#s 46788501 and 46788502)						
Corn (revised assessment)	Corn: **Maximum** DFR	0	**0.47**	100	Scouting, weeding immature/low foliage plants	5,700
		0		1,000	Scouting, irrigation, weeding mature/full foliage plants	570
		0		**710**	Detasseling (arithmetic mean from MRID# 46788502)	**800**
	Corn: **Average** DFR	0	**0.31**	17,000	Hand harvest [Note: PHI is 7 days]	51
		4	**0.17**			95
		5	**0.14**			**110**

[1] Previous assessment estimated Dislodgeable Foliar Residue (DFR) from non crop-specific DFR studies. In the revised assessment corn DFR values from MRID#s 46788501 and 46788502 were used - see text for discussion.

[2] DAT = Days after treatment needed to reach MOE > 100; DAT 0 = The day of treatment, after sprays have dried; assumed to be approximately 12 hours.

[3] DFR (ug/cm²) = Application rate (0.2 lb ai/A) x CF (4.54E+8 µg/lb) x CF (2.47E-8 A/cm²) x Average Initial Fraction of ai Retained on the Foliage (previous: 0.18; revised: 0.14) x [(1- Average Fraction of Residue That Dissipates Daily {previous: 0.13; revised: 0.14}) $^{\text{Postapplication day}}$]. Except for scenarios for which the REI is likely to be less than 1 day; in this case, the maximum measured initial DFR was used, because the predicted DFR was lower for day 0, and a 12-hour REI has been proposed by the registrant.

[4] TC (cm²/hr) = transfer coefficients and associated activities from ExpoSAC Policy Memo #003.1 Agricultural Transfer Coefficients@, 8/17/2000. Except for detasseling, for which actual detasseling TCs were taken from MRID# 46788502.

[5] MOE = MOE on the corresponding DAT. MOE = NOAEL / Daily Dose.

Daily Dose = [(DFR x TC x 14% Dermal absorption x 8-hr Exposure Time)] / [(CF: 1000 ug/mg) x 60-kg Body weight

The Short-/Int-term NOAEL is 5 mg/kg/day, The LOC is for an MOE < 100.

5.0 Non-Occupational/Residential/Recreational Exposure

Residential exposure was evaluated in a previous assessment: *Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Pyraclostrobin on a Variety of Crops and Residential Turf* (D298017, K. O'Rourke, 8/19/04).

5.1 Off Target Non-Occupational Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial applications, but, to a lesser extent, could also be a potential source of exposure from ground application methods. Pyraclostrobin is directly applied to residential turf and does not result in exposures of concern. Based on this assessment, HED believes that it is unlikely that there is a higher potential for risk of exposure to spray drift from agricultural uses of this chemical.

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