DATE OUT: 07/OCT/2004

SUBJECT: **PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]**
DP BARCODE No.:D303318 **REG./File Symbol No.:** 264-IEL
PRODUCT NAME: Proline 480SC Fungicide
PCC:113961**; Decision No.:** 341717 ; **FOOD USE [X]**
INTEGRATED FORMULATION: Yes [ ] NO [X]

FROM: Shyam Mathur,
Product Chemistry Team Leader
Technical Review Branch/RD (7505C)

TO: James Tomerlin / Cynthia Giles-Parker, RM 22
Fungicide Branch/RD(7505C)

INTRODUCTION:

The Bayer CropScience has submitted an application for the registration of the new active ingredient Prothioconazole Technical and the end-use product "Proline 480SC Fungicide" in USA and also in Canada. In a letter dated March 31, 2004, the Bayer CropScience has requested that the submission be considered as a negotiated Joint Review with Pest Management Regulatory Agency (PMRA) of Canada and EPA, and has allowed the sharing of study reviews between EPA and PMRA. The crops proposed for the joint review include barley, oil seed (except sunflower and safflower) crop group, dried shelled pea and bean (except soybean) subgroup, and wheat. For the US label, the use on rice and peanuts has also been proposed. The product chemistry data on the new AI have been submitted under MRID No. 462460-01, 462460-02 & 462460-03 along with the CSF for basic formulation dated 02-16 -04. These data were reviewed by PMRA and secondary review was conducted by TRB (see PCR dated 10-05-04; D 303308). The product chemistry data on the end use product Proline 480SC Fungicide have been submitted under MRID No. 462460-04. The registrant also submitted a CSF for basic formulation (dated 02-15-04) and a CSF for alternate formulation (dated 02-16-04) to support the registration application of the end use product. The PMRA has conducted the primary review. The report for the PMRA submission #2004-0844 was written on July 12, 2004 and Peer reviewed on July 13, 2004. The TRB has been asked to conduct secondary review on the report written by PMRA .

SUMMARY OF FINDINGS

1. The subject product contains Prothioconazole Technical (File Symbol . No. 264-IEU, 97.7%) as the active ingredient with product label claim of 41.0%. The new active ingredient Prothioconazole Technical is undergoing registration process with the Agency.

2. The CSF for basic formulation (dated 02-15-04) is filled out correctly and completely. It is in compliance with PR Notice 91-2 and agree with the label claim nominal concentration. The registrant has proposed expanded certified limits for two of the inert ingredients used in the formulation and provided the justifications. The data submitted corresponding to the guideline reference 830.1550 (product Identity) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.155 and 158.175 respectively.
[MRID No. 462460-04]

3. The CSF for alternate formulation (dated 02-16-04) is filled out correctly and completely. It is in compliance with PR Notice 91-2 & 40CFR§152.43. The nominal concentration of the AI concurs with the label claim nominal concentration. The registrant has proposed expanded certified limits for two of the inert ingredients used in the formulation and provided the justifications. The data submitted corresponding to the guideline reference 830.1550 (product Identity) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.155 and 158.175 respectively. [MRID No. 462460-04]

4. All the food use inert ingredients used in the basic and alternate formulations are cleared by the Agency and have tolerance exemption for food use.

5. The data submitted corresponding to the guideline reference 830.1650(description of formulation process)and 830.1670 (discussion on the formation of impurities) satisfy the data requirements of 40CFR158.165 and 158.167 respectively. [MRID No. 462460-04]

6. The data submitted corresponding to the guideline reference 830.1800 (enforcement of analytical method) satisfy the data requirements of 40CFR§158.180. The HPLC/UV (257 nm) method was used for the determination of the active ingredient Prothioconazole in the end use product. [MRID No. 462460-04]

7. The data submitted corresponding to 830 Series Subgroup B (physical-chemical properties) satisfy the data requirements of 40CFR§158.190. [MRID No. 462460-04]

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for the end-use product "Proline 480SC Fungicide" and has concluded that:

1. The product chemistry data submitted corresponding to guideline reference 830 Series Subgroup A and Subgroup B (physical/chemical properties) satisfy the data requirements of 40CFR§158.150 to 158.190 and are acceptable.

2. The CSF's for basic formulation (dated 02-15-04) and for alternate formulation (dated 02-26-04) are acceptable.

3. The justifications provided for proposed expanded certified limits for two inert ingredients are acceptable and the Agency has no objections for the proposed expanded certified limits.

4. The Agency has no deficiencies to report in the product chemistry data submitted for the end use product "Proline 480 SC Fungicide".

5. The registration of the end use product "Proline 480 SC Fungicide" is subject to the approval and registration of Prothioconazole Technical Fungicide (File Symbol No. 264-IEU) with the Agency.

Note to RM: The registrant may be informed to include the chemical name of the active ingredient Prothioconazole in the basic and alternate formulation CSF's. The chemical name of the AI must be consistent with the chemical name of the AI on the product label.

Subgroup A	Data Required Fulfilled	MRID No.
830.1550. Chemical Identity (basic CSF, dated 02-15-04) (Alt. CSF, dated 02-16-04)	A A	462460-04 462460-04
830.1600. Beginning Materials	A	462460-04
830.1650. Formulation Process	A	" " "
830.1670. Discussion of Impurities	A	" " "
830.1700. Preliminary Analysis	NA	
830.1750. Certified Limits (basic CSF, dated 02-15-04) (Alt. CSF, dated 02-16-04)	A A	462460-04 462460-04
830.1800. Enforcement Analytical Method	A	462460-04

Subgroup B	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
830.6302. Color	A	Off white liquid	462460-04
830.6303. Physical State	A	viscous liquid suspension	" " "
830.6304. Odor	A	slight latex paint	" " "
830.6314. Oxidation/Reduction Action	A	None	" " "
830.6315. Flammability	NA		
830.6316. Explodability	NA		
830.6317. Storage stability	A	stable 1 year	462460-04
830.6319. Miscibility	NA		
830.6320. Corrosion Characteristics	A	non-corrosive 2 weeks at 54^0F	462460-04
830.6321. Dielec. Bkd. Vltg.	NA		
830.7000. pH	A	7.0	462460-02
830.7100. Viscosity	A	1146 cps /25^0C	" " "
830.7000. Density/Bulk Density	A	1.17 g/cc @20^0C	" " "

Explanations: A = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

DP BARCODE No.:D303318 **REG./File Symbol No.:** 264-IEL**PRODUCT NAME:** Proline 480SC Fungicide

830.1800. Enforcement analytical method :

The HPLC/UV method was used to determine percent prothioconazole in the TGAI.The percent prothioconazole was determined by comparing the reverse phase HPLC peak areas of the sample and the analytical standard using butyl benzoate as an internal standard.

Parameters & operating conditions:

Liquid chromatograph: HP Model 1050 equipped with a variable wavelength detector and an autoinjector

Column: Du Pont Zorbax Rx-C18, 250 mm x 4.6 mm ID

UV wavelength: 257 nm

Injection volume: 10 μL

Mobile Phase Flow rate: 1.5 ml/min

Mobile Phase**:** Channel A - 55 : 10 : 35 : 0.1(acetonitrile : methanol : water : phosphoric acid)
Channel B - Acetonitrile

Run time (min)	Function	value
Initial	B conc	0
8.99	B conc	0
9.00	B conc	100
12.00	B conc	100
12.01	B conc	0
16.00	Stop	

CONFIDENTIAL APPENDIX
DP BARCODE No.:D303318 **REG./File Symbol No.:** 264-IEL**PRODUCT NAME:** Proline 480SC Fungicide

Names of the inert ingredients for which expanded certified limits have been proposed are:

[redacted]

The PMRA review is attached.

Inert ingredient information may be entitled to confidential treatment

Chemistry data review for the registration of a manufacturing concentrate (MA) or an end-use product (EP).

Product Name: PROLINE 480 SC Fungicide

Submission Number / DP Bar Code: 2004-0844 (This submission is a joint review with the EPA)

Registration Number: Not yet assigned

Source Code(s) / PC Code: PRB-BCZ-1

Applicant's / Registrant's Name and Address:

Bayer Cropscience Inc.
100,3131 - 114th Avenue SE
Calgary, AB T2Z 3X2

Bayer Cropscience Inc., Attn. Todd Denofreo
Carleton Technology & Training Centre
3800-1125 Colonel By Drive, Ottawa, ON K1S 5RI

Formulating Plant's Name and Address:

Bayer Cropscience, Agriculture Division
PO Box 49 13,8400 Hawthorn Rd.
Kansas City, Missouri 64120

TGAI in EP: Prothioconazole technical, Sub. #2004-0843, 97.7% nominal.

Guarantee: Statement of Product Specification Form (SPF) dated 04/03/15:
Prothioconazole: 2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione.....480 g/L Nominal (Limits: 466 g/L - 494 g/L)

Canadian Label:
Prothioconazole....480 g/L

US Label:
Prothioconazole, 2-[2-(1-Chlorocyclopropyl)-3 -(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione.....41%
Inert Ingredients.....59%
100%

Good Laboratory Practices Compliance Statement:

The studies contained within this report were conducted in accordance with the EPA Good Laboratory Practice Standards as specified in 40 CFR 160.

yes [x] no [ ]

INTRODUCTION:

The purpose of this Cat A submission is to apply for the registration of Proline 480SC Fungicide, a suspension concentrate fungicide formulation. The formulation contains 480 grams per litre (nominal) of Prothioconazole. In support of the registration, an electronic submission containing Part 0-Index, Part 1- label, two Statement of Product Specification Forms dated 04/03/15 for basic and alternate formulations Proline 480 SC Fungicide, and Part 3 Chemistry data were provided.

SUMMARY OF FINDINGS:

Proline 480SC Fungicide is an end use product prepared by a simple blending of the active ingredient and formulation ingredients. The formulation process does not involve any chemical reactions, however, [redacted]. No impurities are expected to be formed as a result of the process.

The product is guaranteed to contain the active ingredient at a nominal concentration of 480 g/L with the lower and upper certified limits of 466 and 494 g/L respectively. The certified limits are within the standard limits. The calculated guarantee is consistent with the guarantee on the label and on the specification form.

The active ingredient was determined by HPLC with UV detection. Full validation data as well as all relevant chromatograms were submitted in support of the method. The method was assessed to be specific and accurate for use as an enforcement analytical method.

Impurities of toxicological concern as identified in section 2.13.4 of DIR 98-04 and TSMP track 1 substances as per Appendix II of DIR 99-03 are not expected to be present in the raw materials or formed as a result of the formulation process. The product does not contain any List 1 or 2 formulants.

Chemical and physical properties were provided where applicable. The product is found to be stable for at least one year in HDPE containers.

The following remains to be addressed:

DACO:	3.3.2
Title:	Statement of Product Specification Form (SPSF)
Deficiencies:	The chemical name is listed as 2-[2-(1-Chlorocyclopropyl)-3-(2-chloropheny1)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione instead of 2-[2-(1-Chlorocyclopropyl).... 2,4-dihydro... in box 12 of SPSF.
Required Data:	**The applicant is required to provide a revised specification form with the correct chemical name of the active ingredient on the SPSF.**

CONCLUSIONS:

Review Status: C1-passed, D&R required

Label Review

1. The active ingredients statement (chemical identities, nominal

concentrations) is consistent with the CSF / SPSF.

yes [x] no [ ]

2. The formulation contains one of the following:

10% or more of a petroleum distillate:	yes	[ ]
	no	[x]
1% or more of methyl alcohol:	yes	[ ]
	no	[x]
sodium nitrite at any level:	yes	[ ]
	no	[x]
a toxic List 1 inert at any level:	yes	[ ]
	no	[x]
arsenic in any form:	yes	[ ]
	no	[x]

3. If yes to any of the above, does the inert ingredients statement contain a footnote indicating this?

yes [ ] no [ ] not applicable [x]

4. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:

yes [ ] no [ ] not applicable [x]

5. The storage and disposal instructions for the pesticide and container are in compliance with PMRA Registration Handbook / PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:

yes [x] no [ ] See DACO 8.4 in EAD review summary [ ]

Chemical and Physical Properties: See Table 1.

1.0 Chemical and Physical Properties

Reference: Fontaine, L.D., (2004) Chemistry Requirements for the Registration of Proline 480 SC Fungicide, Brochure # 2285, pages 169-182.(Data # 1).

Table 1. Chemical & Physical Properties

DACO # / GLN	Title	MRID / Report #	Status[1]	Result[2] or Deficiency

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable. [2] For example, "brown" for 830.6302; "1.021" for 830.7300.				
3.5.1 / 830.6302	Colour	200420-1	A	Off-White Liquid
3.5.2 / 830.6303	Physical State	200420-1	A	Viscous liquid
3.5.3 / 830.6304	Odour	200420-1	A	Slight latex paint odour
3.5.4	Formulation Type	200420-1	A	Suspension concentrate
3.5.5	Container Material and Description	200420-1	A	High density polyethylene (HDPE) bottles.
3.5.6 / 830.7300	Density or Specific Gravity	200420-1	A	1.17 g/mL at 20°C.
3.5.7 / 830.7000	pH	200420-1	A	7.0 for a 10% dilution in distilled water.
3.5.8 / 830.6314	Oxidizing or Reducing Action	BR 2285	A	The formulation does not contain any oxidizing or reducing agents
3.5.9 / 830.7100	Viscosity	200420-1	A	1146 cps using a Brookfield, 25°C.
3.5.10 / 830.6317	Storage Stability Data	200793	A	The product was shown to be stable for at least one year under warehouse conditions.
3.5.11 / 830.6315	Flammability	BR 2285	N/A	The product does not contain a combustible liquid.
3.5.12 / 830.6316	Explodability	BR 2285	N/A	The product does not have any explosive properties
3.5.13 / 830.6319	Miscibility	BR 2285	N/A	The EP is not an emulsifiable liquid and is not to be diluted with petroleum solvents.
3.5.14 / 830.6320	Corrosion Characteristics	200184	A	The product is not expected to be corrosive to the storage container.
3.5.15 / 830.6321	Dielectric Breakdown Voltage	BR 2285	N/A	The EP is not to be used around electrical equipment.

Data Submitted: See Table 2.

Table 2. Data Submitted for Proline 480SC Fungicide

DACO # / GLN	Title	MRID / Report #	Status[1]	Details and/or Deficiency[2]
3.2.1 / 830.1600	Description of Starting Material	BR 2285	A	No deficiencies identified
3.2.2 / 830.1620 830.1650	Production / Formulation Process	BR 2285	A	No deficiencies identified
3.2.3 / 830.1670	Discussion of Impurities	BR 2285	A	No deficiencies identified
3.3.2 / 830.1550	Control Product Specification Form / Confidential Statement of Formula	SPSF dated March 15, 2004	A	No deficiencies identified
3.3.1 / 830.1750	Certification of Limits	BR 2285	A	No deficiencies identified
830.17	Preliminary Analysis	N/A		*For EP containing non-registered TGAI or for EP which is an ISP only.*
3.4.1 / 830.1800	Enforcement Analytical Method	#BR 2285	A	No deficiencies identified

[1] A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not applicable.
[2] Refer to CBI Appendix A for details

ATTACHMENT: CONFIDENTIAL APPENDIX

CONFIDENTIAL APPENDIX A: MANUFACTURING, COMPOSITION AND FORMULANT INFORMATION.

Formulation Process

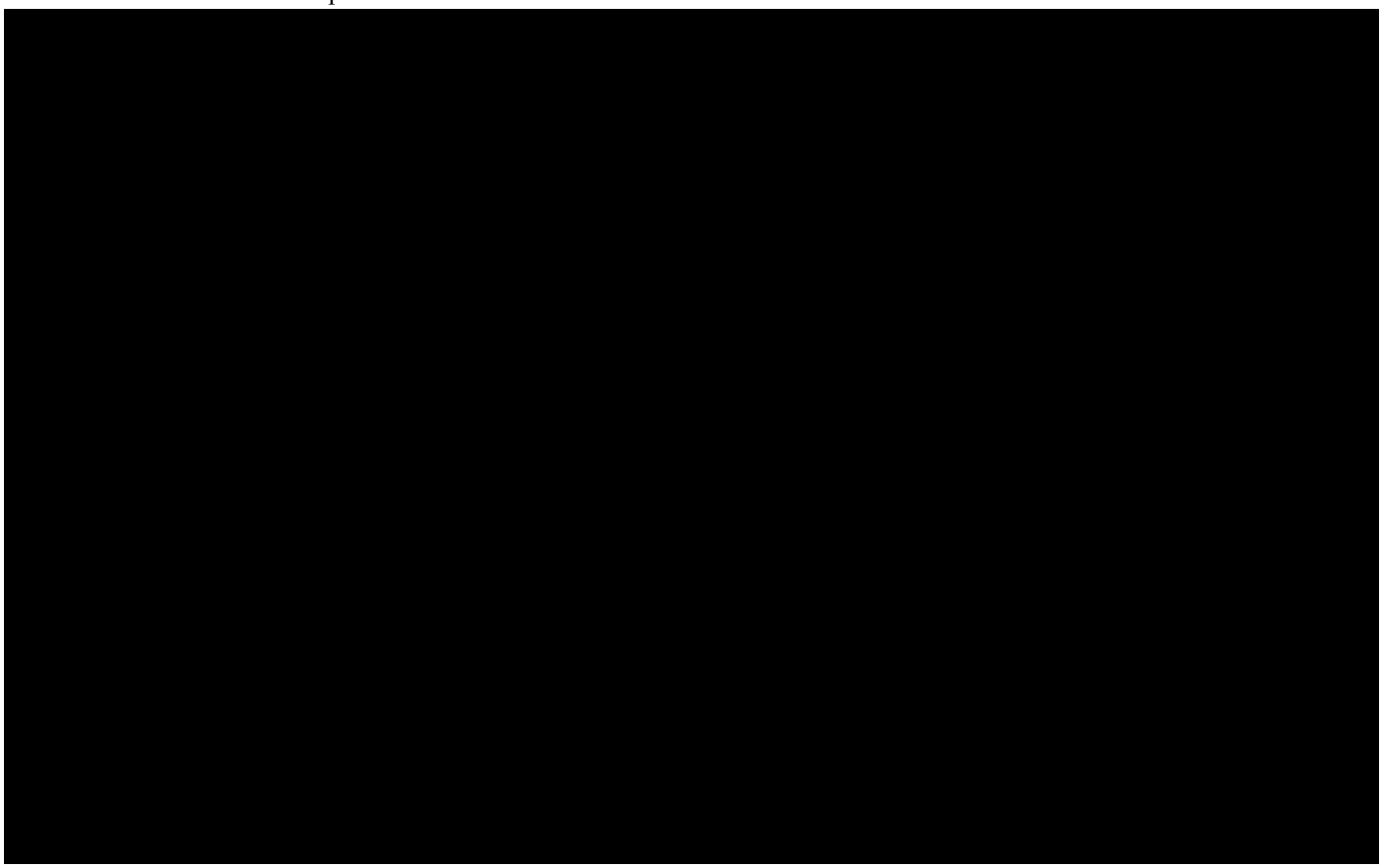
Reference: Fontaine, L.D., (2004) Chemistry Requirements for the Registration of Proline 480 SC Fungicide, Brochure # 2285, page 6-145.

3.2.1 / 830.1600 Description of Starting Materials

A full description of all the starting materials including Material Safety Data Sheets have been provided.

3.2.2 / 830.1650 Description of the Formulation Process

The formulation process is described as follows:



3.2.3 / 830.1670 Discussion of the Formation of Impurities/Impurities of Toxicological Concern

The product is not expected to form any new impurities as a result of the formulation process or any chemical reaction between active ingredient, formulation ingredients or the packaging. Based on the raw materials used, impurities of toxicological concern will not be present during the formulation process.

Conclusion:

Proline 480 SC is an end use product prepared by a simple blending of the active ingredient and formulants. The formulation process does not involve any chemical reactions. None of formulants present in the product are on the inert list 1or 2.

Manufacturing process information may be entitled to confidential treatment

3.3.1 / 830/1750 Certification of Limits

The nominal concentration (NC) of the active ingredient and the upper and lower certified limits (UCL & LCL) are shown in Table 1.

Table 1. Certification of Limits			
Active Ingredient	NC (g/L)	LCL (g/L)	UCL (g/L)
Prothioconazole Technical (97.7% nominal)	480 g/L (41%)	466	494

Conclusion:

1. The calculated NC, based on the pure active ingredient (PAI), is identical to that on the label.

yes [ ] no [ ]

Calculation of active content:

41.97% x 97.7% (nominal) x 1.17 x 10 = 480 g/L

2. The certified limits are within the standard limits as per DACO 3.3.1/40CFR§158.175 or are adequately explained if different.

yes [x] no [ ] not applicable [ ]

3.4.1 / 830.1800 Enforcement Analytical Method

Reference: Fontaine, L.D., (2004) Chemistry Requirements for the Registration of Proline 480 SC
Fungicide, Brochure # 2285, pages 3, 154-168.

Table 2. Details of the analytical method used to determine Prothioconazole in Proline 480SC	
Method ID	TM: C-56.01-00
Sample preparation	Weigh approximately 0.35 g of formulation into a 2 oz bottle. Add 5 mL of water, 20.0 mL of internal standard solution, and 20 mL of acetonitrile.
Instrument	HPLC
Detector	UV detector, variable wavelength at 257 nm
Column	Du Pont Zorbax Rx-C_{18}, 250 mm x 4.6 mm I.D.
Mobile phase (for LC)	Gradient elution consisting of the following solvents: 1. Acetonitrile: MeOH:Water:phosphoric acid, 55:10:35:0.1 and

Table 2. Details of the analytical method used to determine Prothioconazole in Proline 480SC	
	2. Acetonitrile
Quantitation	Internal standard using butyl benzoate
Retention time	Analyte RT (min) Prothioconazole 5.0 min butyl benzoate 7.5 min
Total run time	16 minutes
Chromatograms	Chromatograms of internal standard, formulation blank, reference standard and Proline 480SC formulation sample are provided with the method. The blank chromatograms show no interferences at the retention time of the analytes of interest.

The validation data are shown in Table 3

Table 3. Validation data for Prothioconazole in Proline 480SC					
Method ID	Method type	Linearity	Recovery (%)	RSD (%)	Method
TM: C-56.01-00	HPLC/UV	9.97 -332 mg R^2 = 0.99994	99.4 %	0.61	A

Conclusion: An analytical method was provided for the determination of the active. The method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

Specific Data Reviewed by PMRA

3.3 Specifications:

Reference: Product specification form dated March 15, 2004.(Data # 1).

3.3.2 / 830.1550 Control Product Specification Form / Confidential Statement of Formula

Table 4. Specifications of Proline 480SC				
Component	CAS No.	Purpose	% weight	
			Basic	Alternate
Prothioconazole Technical 2-[2-(1-Chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione, 97.7% nominal	178928-70-6	Active ingredient	41.97	41.97

[redacted]

Inert ingredient information may be entitled to confidential treatment

Table 4. Specifications of Proline 480SC				
Component	CAS No.	Purpose	% weight	
			Basic	Alternate
[redacted]				

Inert ingredient information may be entitled to confidential treatment

Table 4. Specifications of Proline 480SC				
Component	CAS No.	Purpose	% weight	
			Basic	Alternate

[redacted]

3.4.2 Impurities of toxicological concern

Based on the raw materials and manufacturing process, impurities of toxicological concern are not expected to be formed during the formulation of the EP.

Has the manufacturer used the **best available technology** to reduce the amount of impurities to the lowest level?

Inert ingredient information may be entitled to confidential treatment

Yes [ ] no [ ] not stated / applicable [x]

Review History *(for PMRA data tracking purpose only).*

Data Submission and Review History:

Table 5. Correspondence Dates, Data # and Content for Proline 480SC

Data #	Date Received	Content Summary	Reviewer Officer #
1	June 11, 2004	Electronic submission: Part 0-Index, Part 1- label, Statement of Product Specification Forms for Proline 480 SC Fungicide basic and alternate formulations and Part 3 Chemistry.	336

Summary written by: Officer # 336
Date written: July 12, 2004
Peer reviewed by: Officer # 306
Date peer reviewed: July 13, 2004
Last update date:
Review Retrievability: The file was last saved in PMRA database under workbook\2004-0843_LS_3_0_

Review signed off by:

_____ _____

Maria Papiez
Acting Section Head
CES