UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

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

MEMORANDUM

DATE: 8/21/2002

SUBJECT: PP#0F06139; HED Dietary Exposure Assessment: Human Dietary Exposure Assessment for First Food Uses of Pyraclostrobin on Many Crops.

DP Barcode:	D284496	PRAT Case:	292946
Submission No.:	S583112	Caswell No.:	None
Chemical No.:	099100	Class:	Fungicide
Trade Name:	Headline™ Fungicide Cabrio™ EG	EPA Reg No.:	7969-RIT 7969-RIA
40 CFR:	Not Registered		
MRID No.:	None		

FROM: William D. Wassell, Chemist
Ghazi Dannan, Toxicologist
William Greear, Toxicologist
Leung Cheng, Chemist
Kelly M. O'Rourke, Biologist
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Stephen C. Dapson, Branch Senior Scientist
RAB3/HED (7509C)
09/04/2002

TO: J. Bazuin/C. Giles-Parker, PM Team 22
Fungicide Branch
Registration Division (7505C)

Note to RD: An occupational exposure assessment will be issued as a separate document.

INTRODUCTION

The Health Effects Division (HED) has conducted an exposure assessment for the new fungicidal active ingredient, pyraclostrobin. BASF Corporation has submitted a petition for the establishment of permanent tolerances for residues of the new foliar fungicide pyraclostrobin

(BAS 500 F) in conjunction with a request for Section 3 registrations for Headline Fungicide, a 20% water dispersible granular formulation (WDG; EPA File Symbol 7969-RIT), and Cabrio™ EG, a 2 lb/gal emulsifiable concentrate formulation (EC; EPA File Symbol 7969-RIA), for use of pyraclostrobin on many food/feed crops. This review was conducted jointly with Pest Management Regulatory Agency (PMRA), Health Canada, Canada, along with participation of California/EPA.

Pyraclostrobin [carbamic acid, [2-[[[1-(4-chlorophenyl)-1*H*-pyrazol-3-yl]oxy]methyl] phenyl]methoxy-, methyl ester] (CAS name) belongs to the strobilurin class of fungicides (β-methoxyacrylate class of compounds). Strobilurins are synthetic analogs of a natural antifungal substance which inhibits spore germination and inhibits mycelial growth and sporulation of the fungus on the leaf surface.

The petitioner is proposing the establishment of tolerances for the combined residues of pyraclostrobin and its desmethoxy metabolite, methyl 2-[[[1-(4-chlorophenyl)-1*H*-pyrazol-3-yl]oxy]methyl]phenylcarbamate, expressed as the parent compound, in/on the following commodities at the indicated levels:

Almond, hulls	1.6 ppm
Aspirated grain fractions	2.5 ppm
Banana	0.04 ppm
Barley, grain	0.4 ppm
Barley, hay	25 ppm
Barley, straw	6 ppm
Bean, dry	0.3 ppm
Beet, sugar, root	0.2 ppm
Beet, sugar, tops	8 ppm
Beet, sugar, dried pulp	1 ppm
Berry group	1.3 ppm
Citrus, dry pulp	5.5 ppm
Citrus, oil	4 ppm
Fruit, citrus, group	0.7 ppm
Fruit, stone, group	0.9 ppm
Grape	2 ppm
Grape, raisin	7 ppm
Grass, forage	10 ppm
Grass, hay	4.5 ppm
Grass, seed screenings	27 ppm
Grass, straw	14 ppm
Nut, tree, group	0.04 ppm
Peanut, nutmeat	0.05 ppm
Peanut, refined oil	0.1 ppm
Pistachio	0.7 ppm

Radish, tops	16 ppm
Rye, grain	0.04 ppm
Rye, straw	0.5 ppm
Strawberry	0.4 ppm
Vegetable, bulb, group	0.9 ppm
Vegetable, cucurbit, group	0.5 ppm
Vegetable, fruiting, group	1.4 ppm
Vegetable, root, except sugar beet, subgroup	0.4 ppm
Vegetable, tuberous and corm, subgroup	0.04 ppm
Wheat, grain	0.2 ppm
Wheat, hay	6 ppm
Wheat, straw	8.5 ppm

Additionally, the petitioner has proposed the establishment of tolerances for the combined residues of pyraclostrobin and its metabolites convertible to 1-(4-chlorophenyl)-1*H*-pyrazol-3-ol and 1-(4-chloro-2-hydroxyphenyl)-1*H*-pyrazol-3-ol, expressed as the parent compound, in/on the following commodities at the indicated levels:

Cattle*, fat	0.1 ppm
Cattle*, liver	1.5 ppm
Cattle*, meat	0.1 ppm
Cattle*, meat byproducts, except liver	0.2 ppm
Milk	0.1 ppm

* also to include goats, hogs, horses, and sheep

Hazard Profile:

The following is a list of the documents that summarize the hazard profile:

References:
Pyraclostrobin - Report of the Hazard Identification Assessment Review Committee, G. Dannan, 9/13/2001, HED Doc No. 014669.
Pyraclostrobin - 2nd Report of the Hazard Identification Assessment Review Committee, G. Dannan, 7/22/2002, TXR No. 0050932.
Pyraclostrobin: Report of the FQPA Safety Factor Committee, B. Tarplee, 10/10/2001, HED Doc. No. 014695.
Cancer Assessment Document - Evaluation of the Carcinogenic Potential of Pyraclostrobin, 12/26/2001, TXR No. 0050363.

Summaries of the original toxicology DERs are presented in Table 1.

Table 1. Toxicity Profile of Pyraclostrobin Technical **Based on Original DERs**‡			
DER #	**STUDY TYPE - DOSE LEVELS**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**
1	2-YR FEED/CARCINOGENICITY RAT (1999) MRID 45118331, **Acceptable** Dose Levels: 0, 25, 75, 200 ppm: M: 0, 1.2, 3.4, 9.2 mg/kg/day; F: 0, 1.5, 4.7, 12.6 mg/kg/day	75 ppm M/F: 3.4/4.7 mg/kg/day	200 ppm (M/F: 9.2/12.6 mg/kg/day) based on ↓ body wt/ wt gain, and kidney atrophy/tubular casts in both sexes; hepatic necrosis and gross/ microscopic ulcerations/lesions in the glandular and forestomachs in males; hemolymphoreticular tumors in males; and mammary adenocarcinoma in females.
1a	2-YR FEEDING-RAT (1999) MRID 45118329, **Unacceptable** Dose Levels: 0, 25, 75, 200 ppm: M: 0, 1.1, 3.4, 9.0 mg/kg/day; F: 0, 1.5, 4.6, 12.3 mg/kg/day	≥ 200 ppm M/F: 9.0/12.3 mg/kg/day	> 200 ppm (unacceptable because a higher dose could be tolerated)
2	18-MN CARCINOGENICITY MOUSE (1999) MRID 45118330, **Unacceptable** Dose Levels: M: 0, 10, 30, 120 ppm (0, 1.4, 4.1, 17.2 mg/kg/day); F: 0, 10, 30, 120, 180 ppm (0, 1.6, 4.8, 20.5, 32.8 mg/kg/day)	M/F: ≥ 120/180 ppm M/F: 17.2/32.8 mg/kg/day	M/F: > 120/180 ppm (unacceptable because a higher dose could be tolerated).
3	1-YR FEEDING DOG (1999) MRID 45118328, **Acceptable** Dose Levels: 0, 100, 200, 400 ppm M: 0, 2.7, 5.4, 10.8 mg/kg/day F: 0, 2.7, 5.4, 11.2 mg/kg/day	200 ppm M/F: 5.4/5.4 mg/kg/day	400 ppm; M/F: 10.8/11.2 mg/kg/day based on ↑ diarrhea, clinical chem. changes (both sexes), and ↓ body weight gain, and ↓food intake/efficiency in females.
4	2-GEN REPRODUCTION RAT (1999) MRID 45118327, **Unacceptable** Dose Levels: 0, 25, 75, 300 ppm F0M: 0, 2.5, 7.4, 29.0 mg/kg/day F0F: 0, 2.6, 7.8, 30.4 mg/kg/day F1M: 0, 2.8, 8.6, 35.0 mg/kg/day F1F: 0, 3.0, 9.0, 36.0 mg/kg/day	Parental systemic, Reproductive, and Offspring: ≥ 300 ppm M:≥ 29.0-35.0 mg/kg/day F:≥ 30.4-36.0 mg/kg/day	Parental systemic, Reproductive, and Offspring: > 300 ppm M: >29.0-35.0 mg/kg/day F: >30.4-36.0 mg/kg/day
5	DEVELOPMENTAL TOX RAT (1999) MRID 45118325, **Acceptable** Dose Levels: 0, 10, 25, 50 mg/kg/day	Maternal= 10 mg/kg/day Develop = 25 mg/kg/day	Maternal = 25 mg/kg/day based on ↓body wt/ wt gain and ↓food intake/efficiency Develop = 50 mg/kg/day based on ↑ incidences of dilated renal pelvis and cervical ribs with no cartilage.
6	DEVELOPMENTAL TOX RABBIT (1999) MRIDs 45118326 and 45437001, **Acceptable** Dose Levels: 0, 1, 3, 5, 10, 20 mg/kg/day	Maternal 5 mg/kg/day Develop = 5 mg/kg/day	Maternal 10 mg/kg/day based on ↓ body wt gain and ↓food intake/ efficiency Develop = 10 mg/kg/day based on ↑ resorption/post-implantation loss.

Table 1. Toxicity Profile of Pyraclostrobin Technical **Based on Original DERs**‡

DER #	STUDY TYPE - DOSE LEVELS	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
7	13-WEEK FEEDING RAT (1999) MRID 45118321, **Acceptable** Dose Levels: 0, 50, 150, 500, 1000, 1500 ppm (M: 0, 3.5, 10.7, 34.7, 68.8, 105.8 mg/kg/day; F: 0, 4.2 12.6, 40.8, 79.7,118.9 mg/kg/day)	150 ppm M/F: 10.7/12.6 mg/kg/day	500 ppm (M/F: 34.7/40.8 mg/kg/day) based on ↓body wt/ wt gain in males, ↓food intake (both sexes), ↑ relative liver wt and spleen wt in females and histopathology of duodenum and liver in males, and spleen in both sexes.
8	13-WEEK FEEDING DOG (1999) MRID 45118323, **Acceptable** Dose Levels: 0, 100, 200, 450 ppm M: 0, 2.8, 5.8, 12.9 mg/kg/day F: 0, 3.0, 6.2, 13.6 mg/kg/day	200 ppm M/F: 5.8/6.2 mg/kg/day	450 ppm; M/F: 12.9/13.6 mg/kg/day based on ↑diarrhea, clinical chem. changes, and increased incidence of thickening/mucosal hypertrophy of the duodenum in both sexes; body weight loss, and ↓food intake/efficiency in females.
9	13-WEEK FEEDING MOUSE (1999) MRID 45118320, **Acceptable** Dose Levels: 0, 50, 150, 500, 1000, 1500 ppm M: 0, 9.2, 30.4, 119.4, 274.4, 475.5 mg/kg/day F:0, 12.9, 40.4, 162.0, 374.1, 634.8 mg/kg/day	50 ppm M/F: 9.2/12.9 mg/kg/day	150 ppm; M/F 30.4/40.4 mg/kg/day based on ↓body wt/ wt gain in males, changes in clinical chem (↑urea, ↓triglyceride) in both sexes, and increased incidences among females of lymph node apoptosis, thymus atrophy, and ulcer/erosion in the glandular stomach.
10	ACUTE NEUROTOXICITY RAT (1999) MRID 45118337, **Acceptable** Dose Levels: 0, 100, 300, 1000 mg/kg	Neurotox: 1000 mg/kg Systemic: M/F: 300/1000 mg/kg	Neurotox. >1000 mg/kg Systemic: M/F: 1000/ >1000 mg/kg based on ↓body wt gain in males.
11	90-DAY NEUROTOXICITY RAT (1999) MRID 45118401, **Acceptable** Dose Levels: 0, 50, 250, 750 (M)/1500 (F) ppm M: 0, 3.5, 16.9, 49.9 mg/kg/day F: 0, 4.0, 20.4, 111.9 mg/kg/day	Neurotox: M/F: 750/1500 ppm =49.9/111.9 mg/kg/day Systemic: 250 ppm (M/F: 16.9/20.4 mg/kg/day	Neurotox: M/F: >750/>1500 ppm (>49.9/111.9 mg/kg/day) Systemic: M/F: 750/1500 ppm (49.9/111.9 mg/kg/day) based on ↓ body wt gain, and ↓ food intake/ efficiency.
12	28-DAY DERMAL TOXICITY RAT (1999) MRID 45118324, **Unacceptable** Dose Levels: 0, 40, 100, 250 mg/kg for 5 days/wk	250 mg/kg	> 250 mg/kg (unacceptable because a higher dose could be tolerated and the limit dose is 1000 mg/kg/day).

Table 1. Toxicity Profile of Pyraclostrobin Technical **Based on Original DERs**‡			
DER #	**STUDY TYPE - DOSE LEVELS**	**NOAEL (mg/kg/day)**	**LOAEL (mg/kg/day)**
13	28-DAY FEEDING RAT (1999) MRID 45118322, **Acceptable** Dose Levels: 0, 20, 100, 500, 1500 ppm (M: 0, 1.8, 9.0, 42.3, 120.2 mg/kg/day; F: 0, 2.0 9.6, 46.6, 126.3 mg/kg/day)	100 ppm M/F: 9.0/9.6 mg/kg/day	500 ppm (M/F: 42.3/46.6 mg/kg/day) based on changes in hematology parameters, increased absolute and relative spleen weight, histopathology in spleen and liver, in addition to increased duodenum mucosal hyperplasia in both sexes.

‡Some of the conclusions in original DERs might have been changed in subsequent EPA/HED HIARC and/or CARC Peer Reviews. Also, the PMRA does not necessarily agree with all of the noted effects under the table heading "LOAEL" (see text for details).

FQPA Safety Factor Considerations:

The Health Effects Division (HED) FQPA Safety Factor Committee met on October 1, 2001 to evaluate the available hazard and exposure data for pyraclostrobin and made the recommendation for the FQPA safety factor to be used in human health risk assessments (as required by Food Quality Protection Act of August 3, 1996). This review was conducted jointly with Pest Management Regulatory Agency (PMRA), Health Canada, Canada, along with participation of California/EPA. The committee recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be reduced to 3x in assessing the risk posed by this chemical.

The FQPA SFC concluded that the safety factor is necessary when assessing the risk posed by pyraclostrobin since:

- there is qualitative evidence of increased susceptibility in the prenatal developmental study in rabbits; and
- there is a data gap for a multigeneration reproduction study with pyraclostrobin.

However the safety factor could be **reduced to 3x** for pyraclostrobin because:

- qualitative susceptibility was seen in only one species (rabbits);
- there is no quantitative or qualitative evidence of increased susceptibility; following *in utero* exposure to pyraclostrobin in the prenatal developmental study in rats;
- a developmental neurotoxicity study is not required; and
- the dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposure for infants, children, and/or women of childbearing age.

The safety factor is required for the **Females 13-50 Population Subgroup** when assessing **Acute Dietary and Residential Exposures** to protect against effects seen following *in utero* exposure in the developmental rabbit study.

The safety factor is required for **All Population Subgroups** when assessing **Chronic Dietary and Residential Exposures** due to uncertainty resulting from the data gap for a multigeneration reproduction study (this study will not provide information regarding acute or single-dose exposure).

Dose-Response Assessment:

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. This review was conducted jointly with Pest Management Regulatory Agency (PMRA), Health Canada, Canada, along with participation of California/EPA. The doses and toxicological endpoints selected by the HIARC for various exposure scenarios are summarized in Table 2.

Table 2. Summary of Toxicological Doses and Endpoints for Pyraclostrobin for Use in Human Risk Assessment as Determined by HIARC.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13-50)	NOAEL= 5 UF = 100 FQPA SF = 3x	Developmental toxicity findings of increased resorptions/litter and increased total resorptions (i.e., dams with complete litter loss) at 10 mg/kg/day (LOAEL).	Rabbit Prenatal Developmental Toxicity (MRID 45118326/45437001)
	Acute RfD (Females 13-50 years old) = 0.05 mg/kg/day **Acute PAD** (Females 13-50 years old) = Acute RfD/FQPA SF = 0.05/3 = 0.017 mg/kg/day		
Acute Dietary (General Population)	NOAEL= 300 UF = 100 FQPA SF = 1x	The systemic toxicity NOAEL of 300 mg/kg based on decreased body weight gain in males at 1000 mg/kg (LOAEL).	Rat Acute Oral Neurotoxicity (MRID 45118337)
	Acute RfD[1] (General Population) = 3 mg/kg/day **Acute PAD** (General Population) = Acute RfD/FQPA SF = 3/1 = 3 mg/kg/day		

Chronic Dietary	NOAEL = 3.4 UF = 100 FQPA SF = 3x	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).	Rat Oral Carcinogenicity[2] (MRID 45118331)
		Chronic RfD = 0.034 mg/kg/day **Chronic PAD** = Chronic RfD/FQPA SF = 0.034/3 = 0.011 mg/kg/day	
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).[3]	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).[3]	Rat Oral Carcinogenicity[2] (MRID 45118331)
Inhalation, Short- and Intermediate-Term	Oral NOAEL= 5.0	Developmental toxicity findings of increased resorptions at 10.0 mg/kg/day (LOAEL).[4]	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).[4]	Rat Oral Carcinogenicity[2] (MRID 45118331)

[1] The PMRA feels that since the effect was transitory (not seen at 14 days), occured only in the males, and was not seen in the acute oral study at 5,000 mg/kg bw it is not necessary to establish an Acute RfD for the general population.

[2] Subsequent CARC evaluation changed some of the toxicity end-points of the rat carcinogenicity study.

[3] The dermal absorption factor of 14% should be applied to extrapolate from the oral route to the dermal route.

[4] 100% absorption rate (default value) should be used to extrapolate from the oral route to the inhalation route.

Cancer Classification:

The data base for carcinogenicity for pyraclostrobin is considered incomplete. On October 24, 2001, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticides Programs met to evaluate the carcinogenic potential of pyraclostrobin. This review was conducted jointly with Pest Management Regulatory Agency (PMRA), Health Canada, Canada, along with participation of California/EPA. At this meeting, the CARC concluded, that in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), pyraclostrobin should be calssified 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. **The CARC recommended that the studies in female rats and female mice be repeated at adequate dose levels.** The PMRA requests that validation studies be conducted at adequate dose levels for mice and rats in both sexes.

BASF submitted a rebuttal to the CARC's conclusion that the dosages in the cancer studies in rodents were not adequate. BASF concluded that the high dosage in each study was adequate based upon their analyses of the body weight gain and food efficiency data; these data are currently under review at NHEERL.

The NOAELs of 3.4 and 12.6 mg/kg/day are for toxicity and cancer end-points, respectively and both are from the rat oral carcinogenicity study (MRID 45118331). The NOAEL of 3.4 mg/kg/day is based upon chronic toxicity findings at the LOAEL of 9.2 mg/kg/day, as indicated in original DER, including 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. The increased incidences of kidney tubular casts and atrophy observed are commonly found in this strain of rat. These findings were considered by the CARC to be strain and/or age related. The increased incidence of acanthosis and ulcers of the forestomach in both sexes were seen at necropsy late during the study, and were considered to be of equivocal toxicological significance, however, they could not be ruled out as a treatment-related effect. The NOAEL of 12.6 mg/kg/day for a cancer scenario is the highest tested dose in the rat oral carcinogenicity study (MRID 45118331). The CARC considered the highest tested dose of 12.6 mg/kg/day inadequate for assessing carcinogenicity in female rats as a higher dose could be tolerated in female rats. In the absence of actual data at a higher dose, 12.6 mg/kg/day is considered the NOAEL for possible tumor induction in female rats at doses above 12.6 mg/kg/day. The dosing in males at 200 ppm approached an adequate level because there was a minimal decrease of 7% body weight and up to 10% in body weight gain in addition to the slightly increased incidence of erosion/ulceration of the glandular stomach and forestomach. However, "these findings were marginal and are not considered by the PMRA to represent an MTD." Because the PMRA combined the carcinogenicity and chronic rat studies, the incidence of liver necrosis fell within the historical control range. No other liver effects were noted (e.g., weights, enzymes). The PMRA does not consider a 7% decrease in body weight to be toxicologically significant.

The NOAELs (17.2/32.8 mg/kg/day, M/F) in the mouse carcingenicity study are greater than the NOAELs in the rat study.

The NOAEL of 9.6 mg/kg/day is from the 28-day feeding study with rat (MRID 45118322). In this study, incidences of duodenal mucosal hyperplasia were increased in rats of both sexes at 42.3 mg/kg/day (LOAEL) or higher doses (MRID 45118322). This endpoint was also noted in the 90-day rat study with a NOAEL of 10.7 mg/kg bw/day and in the range-finding reproduction study. PMRA selected this study/end-point for cancer risk assessment based on the hypothesis that observed hyperplasia may progress to duodenal neoplasia following long-term exposure.

HED was asked to consider methods to express potential cancer risk based on our assessment of the current data base. A linear (Q_1^*) method to put an upper limit on any possible cancer risk was considered based on mammary tumors in female rats even though, according to the CARC report, "the statistical analyses of the tumor data from the combined results of carcinogenicity and chronic toxicity studies showed neither a significant increasing trend nor a significant difference in the pair-wise comparison of the dosed groups with the controls." HED management consulted with PMRA on this matter and concluded that a Margins of Exposure (MOEs) method would be more appropriate since the genotoxicity data showed that pyraclostrobin is not mutagenic and the highest dosage level in female rats could be interpreted as a NOAEL for cancer. Therefore, HED has calculated MOEs for chronic exposure based upon NOAELs of 3.4 and 12.6 mg/kg/day from the rat oral carcinogencity study and based upon a NOAEL of 9.6 mg/kg/day from the 28-day oral rat study. Additionally, HED Management stated that if a conditional registration is granted for the proposed uses of pyraclostrobin, then requirements for a 2-Generation reproduction toxicity study and a Carcinogenicity study in female rats and mice with higher dose levels should be made a condition of registration. For a complete list of the deficiencies associated with this petition, please see our correspondence of 1/16/2002 (C. Giles-Parker, EPA to C.A. Sanson, Attachment 9), the residue chemistry review (Attachment 5), the HIARC reports (Attachment 1 & 2), and the CARC report (Attachment 4). The PMRA, however, requests the studies be conducted with both sexes.

Dietary Exposure:

Reference: Pyraclostrobin Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration on Various Crops. PP#0F6139, L. Cheng, 7/29/2002, D284524. (Attachment 7)

Acute Dietary Exposure:

HIARC identified acute RfDs for the general population and for females 13 to 50 years old. The acute RfD (3.0 mg/kg/day) for the general population is based on decreased body weight gain in males in the acute neurotoxicity study in rats (NOAEL = 300 mg/kg/day, UF = 100, FQPA Safety Factor = 1x). The acute RfD (0.05 mg/kg/day) for females 13 to 50 years old is based on increased resorptions/litter and increased total resorptions (i.e., dams with complete litter loss) in the developmental toxicity study in rabbits (NOAEL = 50 mg/kg/day, UF = 100, FQPA Safety Factor = 3x). The acute PADs are equal to the acute RfDs divided by the FQPA safety factor.

The acute PAD for the general population is equal to acute RfD for the general population (3.0 mg/kg/day) as the FQPA safety factor for this endpoint is equal to 1x. The acute PAD for females 13 to 50 years old is equal the acute RfD divided by the FQPA safety factor (0.05/3 = 0.017 mg/kg/day). The acute PADs were used to assess acute dietary risk.

HED used Dietary Exposure Evaluation Model (DEEM™, version 7.73) software for conducting an acute dietary (food) exposure analysis **(Attachment 7).** DEEM™ is a dietary exposure analysis system developed by Novigen Sciences, Inc. that is used to estimate exposure to pesticide residues in foods comprising the diets of the US population, including population subgroups. DEEM™ contains food consumption data as reported by respondents in the USDA Continuing Surveys of Food Intake by Individuals conducted in 1989-1992.

A Tier II acute DEEM™ analysis was performed. The assumptions of this Tier I analysis were tolerance-level residues and projected market share estimates. The acute dietary exposure (food only) to pyraclostrobin for some population subgroups are presented in Table 3. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective). Refinements such as use of anticipated residue estimates would yield even lower estimates of acute dietary exposure.

Table 3. Results of Acute Dietary Exposure Analysis for Pyraclostrobin.

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
U.S. Population	3	0.0094	<1.0	0.019	<1.0	0.043	1.5
All Infants (<1 year old)	3	0.014	<1.0	0.030	1.0	0.053	1.8
Children 1-6 years old	3	0.022	<1.0	0.043	1.5	0.12	3.9
Children 7-12 years old	3	0.011	<1.0	0.021	<1.0	0.035	1.2
Females 13-50 years old	0.017	0.0068	41	0.014	81	0.023	140
Males 13-19 years old	3	0.0083	<1.0	0.013	<1.0	0.018	<1.0
Males 20+ years old	3	0.0062	<1.0	0.011	<1.0	0.018	<1.0
Seniors 55+ years old	3	0.0057	<1.0	0.010	<1.0	0.016	<1.0

Chronic Dietary Exposure:

HIARC identified a chronic RfD (0.034 mg/kg/day), based on decreased body weight and body weight gains, increased incidences of kidney tubular casts and atrophy in males and females, and in males, an increased incidence of liver necrosis, gross and microscopic evidence of erosion/ulcer of the glandular stomach and an increased incidence of acanthosis (hyperplasia) and ulcers of the forestomach in the rat carcinogenicity study (NOAEL = 3.4 mg/kg/day, UF = 100,

FQPA safety Factor = 3x). The chronic PAD is equal to the chronic RfD divided by the FQPA Safety Factor (cPAD = 0.034/3 = 0.011 mg/kg/day). The chronic PAD was used to assess chronic risk.

HED used DEEM™, version 7.73, software for conducting a chronic dietary (non-cancer) exposure analysis **(Attachment 7).** A Tier I chronic DEEM™ analysis was performed. The assumptions of this Tier I analysis were the same as outlined above in Section 4.2.2 Acute Dietary. The chronic dietary exposure (food only) to pyraclostrobin for some population subgroups are presented in Table 4. The results of this dietary exposure analysis should be viewed as partial refined and somewhat conservative (health protective). Refinements such as use of anticipated residue estimates would yield even lower estimates of chronic dietary exposure.

Table 4. Results of Chronic Dietary Exposure Analysis for Pyraclostrobin.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.011	0.0030	27
All Infants (< 1 year)	0.011	0.0034	31
Children 1-6 years	0.011	0.0082	74
Children 7-12 years	0.011	0.0045	41
Females 13-50	0.011	0.0022	20
Males 13-19	0.011	0.0027	24
Males 20+ years	0.011	0.0021	19
Seniors 55+	0.011	0.0020	18

Cancer Dietary Exposure:

The data base for carcinogenicity for pyraclostrobin is considered incomplete. On October 24, 2001, the CARC of the Health Effects Division of OPP met to evaluate the carcinogenic potential of pyraclostrobin. This review was conducted jointly with Pest Management Regulatory Agency (PMRA), Health Canada, Canada, along with participation of California/EPA. At this meeting, the CARC concluded that in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified pyraclostrobin 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. **The CARC recommended that the studies in female rats and female mice be repeated at adequate dose levels.**

HED was asked to consider methods to express potential cancer risk based on our assessment of the current data base. A linear (Q_1^*) method to put an upper limit on any possible cancer risk was considered based on mammary tumors in female rats even though, according to the CARC report, "the statistical analyses of the tumor data from the combined results of carcinogenicity and chronic toxicity studies showed neither a significant increasing trend nor a significant difference in the pair-wise comparison of the dosed groups with the controls." HED management consulted with PMRA on this matter and concluded that a Margins of Exposure (MOEs) method would be more appropriate since the genotoxicity data showed that pyraclostrobin is not mutagenic and the highest dosage level in female rats could be interpreted as a NOAEL for cancer. Therefore, HED has calculated MOEs for chronic exposure based upon NOAELs of 3.4 and 12.6 mg/kg/day from the rat oral carcinogencity study and based upon a NOAEL of 9.6 mg/kg/day from the 28-day oral rat study (for details, refer to the "Cancer Classification" section, above). The PMRA, however, requests that validation studies be conducted at adequate dose levels for mice and rats in both sexes.

HED used DEEM™, version 7.73, software for conducting a chronic dietary (cancer) exposure analysis **(Attachment 7).** A Tier I chronic DEEM™ analysis was performed. The assumptions of this Tier I analysis were the same as outlined above in Section 4.2.2 Acute Dietary. The MOEs for chronic (cancer) exposure for the U.S. Population are summarized in Table 5.

Table 5. Margins of Exposure (MOEs) based upon Chronic Exposure (food only) to Pyraclostrobin for the U.S. Population.

NOAEL (mg/kg/day)	Exposure from Food (mg/kg/day)	MOE (food)
3.4	0.0030	1.1×10^3
9.6		3.2×10^3
12.6		4.2×10^3

Note: $MOE = \frac{NOAEL}{Exposure}$

Exposure from Drinking Water:

References:

Drinking Water Assessment for Pyraclostrobin, A. Al-Mudallal, 9/19/2001, D277877. (Attachment 8)

PP#0F06139; Pyraclostrobin. Outcome of the HED Metabolism Assessment Review Committee (MARC) Meeting Held on September 20, 2001. L. Cheng,10/9/2001, D278044. (Attachment 6)

The Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis for pyraclostrobin. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). FIRST (version 1.0) was used to generate EECs for *surface* water and SCI-GROW was used to generate

EECs for ground water. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for determining that pesticides residues (and metabolites) in water are not of concern.

For any given pesticide, the SCI-GROW model generates a single EEC value of pesticide concentration in *ground* water. That EEC is used in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs. The FIRST model generates EECs for acute and chronic exposure scenarios.

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses (if applicable). HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW and FIRST).

HED back-calculates DWLOCs by a two-step process: exposure [food + residential (if applicable)] is subtracted from the PAD to obtain the maximum acceptable exposure allowed in drinking water. DWLOCs are then calculated using that value and default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are less than DWLOCs, HED considers the aggregate risk [from food + water + residential exposures (if applicable)] to be acceptable.

Environmental Profile: The submitted environmental fate data indicate that pyraclostrobin is moderately persistent and practically immobile in soil.

MARC Decision: The HED MARC (Attachment 6) concluded that only pyraclostrobin needs to be included in the drinking water assessment for this active ingredient.

Estimated Environmental Concentrations (EECs): The EECs provided by EFED are based upon the highest proposed application rate for Cabrio EG (6 aerial applications at 0.2 lbs ai/A with 5 days between applications). These use directions are as specified for fruiting vegetables. Tier I (SCI-GROW) modeling estimates that pyraclostrobin residues in ground water, from the proposed use on fruiting vegetables, is 0.009 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for pyraclostrobin residues predicts the peak (acute) EEC is not likely to exceed 20.4 ppb and 0.79 ppb for the annual average (chronic-term) estimate.

Aggregate Exposure Assessment:

Short-term aggregate risk is made up of the combined exposures from food, water, dermal, inhalation, and incidental oral sources (residential). These exposures are then compared to the appropriate short-term endpoint. Acute aggregate and chronic aggregate risk is made up of the combined dietary exposures from food and water sources.

HIARC did identify acute dietary endpoints for females 13 to 50 years old and for the general population. The acute and chronic aggregate risk assessment was performed using the acute PAD or the chronic PAD, as applicable. Short- and intermediate-term aggregate risk assessment is based on oral, inhalation and dermal exposures which are then compared to relevant NOAELs identified by HIARC. However, since there are no residential uses proposed at this time pyraclostrobin, short- and intermediate-term aggregate risk assessments based on exposure from dermal and inhalation routes of exposure are not required for this fungicide at this time.

Acute Aggregate Exposure:

HIARC identified acute RfDs for the general population and for females 13 to 50 years old. The acute RfD (3.0 mg/kg/day) for the general population is based on decreased body weight gain in males in the acute neurotoxicity study in rats (NOAEL = 300 mg/kg/day, UF = 100, FQPA Safety Factor = 1x). The acute RfD (0.05 mg/kg/day) for females 13 to 50 years old is based on increased resorptions/litter and increased total resorptions (i.e., dams with complete litter loss) in the developmental toxicity study in rabbits (NOAEL = 50 mg/kg/day, UF = 100, FQPA Safety Factor = 3x). The acute PADs are equal to the acute RfDs divided by the FQPA safety factor. The acute PAD for the general population is equal to acute RfD for the general population (3.0 mg/kg/day) as the FQPA safety factor for this endpoint is equal to 1x. The acute PAD for females 13 to 50 years old is equal the acute RfD divided by the FQPA safety factor (0.05/3 = 0.017 mg/kg/day). The acute PADs were used to assess acute dietary risk.

No drinking water monitoring data are available for pyraclostrobin. Models were used to calculate EECs for this fungicide. SCI-GROW (Tier I groundwater) and FIRST (Tier I surface water) models were used. Degradates of concern (as determined by the MARC) are included in the modeled drinking water estimates.

Tier I (SCI-GROW) modeling estimates that pyraclostrobin residues in ground water, from the proposed use on fruiting vegetables, is 0.009 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for pyraclostrobin residues predicts the peak (acute) EEC is not likely to exceed 20.4 ppb and 0.79 ppb for the annual average (chronic-term) estimate.

Acute DWLOC Calculations:

Table 6. Summary of Acute Drinking Water Levels of Comparison for Pyraclostrobin.

Population Subgroup[1]	aPAD mg/kg/day	Food Exposure mg/kg/day (95th percentile)	Maximum Water Exposure (mg/kg/day)[2]	Acute Ground Water EEC[3] (μg/L)	Acute Surface Water EEC[4] (μg/L)	DWLOC (μg/L)[5]
U.S. Population	3.0	0.0094	3.0	0.009	20.4	**1.0×10^5**
All Infants	3.0	0.014	3.0			**3.0×10^4**
Females (13-50 years)	0.05	0.0068	0.043			**1.3×10^5**
Children (1-6 years)	3.0	0.022	3.0			**3.0×10^4**
Males (13-19 years)	3.0	0.0083	3.0			**1.0×10^5**

[1]Population subgroups chosen were the female subgroup with the highest food exposure (60 kg. body weight assumed) the male subgroup with the highest food exposure (70 kg body weight assumed) and infant/child subgroups with the highest food exposure (10 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = PAD (mg/kg/day) - Food Exposure from DEEM (mg/kg/day).
[3]Based upon SCI-GROW modeling results.
[4] Based upon FIRST (version 2) modeling results.
[5] DWLOC(μg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/}\mu\text{g]}}$

Short- and Intermediate-Term Exposure:

As there are no residential uses proposed for this fungicide, short- and intermediate-term aggregate risk assessments based on exposure from oral, inhalation, and dermal routes of exposure were not required for pyraclostrobin.

Chronic Aggregate Exposure:

HIARC identified a chronic RfD (0.034 mg/kg/day), based on decreased body weight and body weight gains, increased incidences of kidney tubular casts and atrophy in males and females, and in males, an increased incidence of liver necrosis, gross and microscopic evidence of erosion/ulcer of the glandular stomach and an increased incidence of acanthosis (hyperplasia) and ulcers of the forestomach in males in the rat carcinogenicity study (NOAEL = 3.4 mg/kg/day, UF = 100, FQPA safety Factor = 3x). The chronic PAD is equal to the chronic RfD divided by the FQPA Safety Factor (cPAD = 0.034/3 = 0.011 mg/kg/day). The chronic PAD was used to assess chronic risk.

No drinking water monitoring data are available for pyraclostrobin. Models were used to calculate EECs for pyraclostrobin. SCI-GROW (Tier I ground water) and FIRST (Tier I surface water) models were used.

The SCI-GROW model estimates that pyraclostrobin residues in ground water, from the proposed use on fruiting vegetables, is 0.009 ppb (µg/L). Additionally, the FIRST model predicts the average annual average (chronic-term) estimate is not likely to exceed 0.79 ppb.

Chronic DWLOC Calculations:

Table 7. Summary of Chronic Drinking Water Levels of Comparison for Pyraclostrobin.

Population Subgroup[1]	cPAD mg/kg/day	Food Exposure mg/kg/day	Maximum Water Exposure[2] mg/kg/day	Chronic Ground Water EEC[3] (µg/L)	Chronic Surface Water EEC[4] (µg/L)	DWLOC[5] (µg/L)
U.S. Population	0.011	0.0030	8.0×10^{-3}	0.009	0.79	**2.8×10^{2}**
All Infants	0.011	0.0034	7.6×10^{-3}			**76**
Children (1-6 years)	0.011	0.0082	2.8×10^{-3}			**28**
Females (13-50 years)	0.011	0.0022	8.8×10^{-3}			**2.9×10^{2}**
Males (13 to 19 years)	0.011	0.0028	8.2×10^{-3}			**2.9×10^{2}**

[1]Population subgroups chosen were U.S. population (70 kg. body weight assumed), the female subgroup with the highest food exposure (60 kg. body weight assumed), the male subgroup (70 kg body weight assumed) with the highest food exposure, and infant/child subgroups with the highest food exposure (10 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = PAD (mg/kg/day) - Food Exposure from DEEM (mg/kg/day)
[3]Based upon PRZM/EXAMS Index Reservoir modeling results.
[4] Based upon SCI-GROW modeling results
[5] DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

Aggregate Cancer Exposure Assessment:

The data base for carcinogenicity is considered incomplete. HED was asked to consider methods to express potential cancer risk based on our assessment of the current data base. A linear (Q_1^*) method to put an upper limit on any possible cancer risk was considered based on mammary tumors in female rats even though, according to the CARC report, "the statistical analyses of the tumor data from the combined results of carcinogenicity and chronic toxicity studies showed neither a significant increasing trend nor a significant difference in the pair-wise comparison of the dosed groups with the controls." HED management consulted with PMRA on this matter and concluded that a Margins of Exposure (MOEs) method would be more appropriate since the genotoxicity data showed that pyraclostrobin is not mutagenic and the highest dosage level in

female rats could be interpreted as a NOAEL for cancer. Therefore, HED has calculated MOEs for chronic exposure based upon NOAELs of 3.4 and 12.6 mg/kg/day from the rat oral carcinogencity study and based upon a NOAEL of 9.6 mg/kg/day from the 28-day oral rat study (for details, refer to the "Cancer Classification" section, above).

No drinking water monitoring data are available for pyraclostrobin. HED has calculated aggregate MOEs (food + water exposure) for pyraclostrobin. The SCI-GROW model estimates that pyraclostrobin residues in ground water, from the proposed use on fruiting vegetables, is 0.009 ppb (µg/L). Additionally, the FIRST model predicts the average annual average (chronic-term) estimate is not likely to exceed 0.79 ppb.

Table 8. Margins of Exposure (MOEs) based upon Chronic Aggregate Exposure (food plus water only) to Pyraclostrobin for the U.S. Population.

NOAEL (mg/kg/day)	Exposure from Food (mg/kg/day)	MOE (food)	Exposure from Water (mg/kg/day)	MOE (water)	MOE (food + water)
3.4	0.0030	1.1×10^3	2.3×10^{-5}	1.5×10^5	1.1×10^3
9.6		3.2×10^3		4.2×10^5	3.2×10^3
12.6		4.2×10^3		5.6×10^5	4.2×10^3

Note: $\text{MOE} = \frac{\text{NOAEL}}{\text{Exposure}}$

Attachments:

Attachment 1: Pyraclostrobin - Report of the Hazard Identification Assessment Review Committee, G. Dannan, 9/13/2001, HED Doc No. 014669.

Attachment 2: Pyraclostrobin - 2nd Report of the Hazard Identification Assessment Review Committee, G. Dannan, 7/22/2002, TXR No. 0050932.

Attachment 3: Pyraclostrobin: Report of the FQPA Safety Factor Committee, B. Tarplee, 10/10/2001, HED Doc. No. 014695.

Attachment 4: Cancer Assessment Document - Evaluation of the Carcinogenic Potential of Pyraclostrobin, 12/26/2001, TXR No. 0050363.

Attachment 5: PP#0F06139; Pyraclostrobin on Various Crops. Review of Analytical Methods and Residue Data. L. Cheng, 11/28/2001, D269668.

Attachment 6: PP#0F06139; Pyraclostrobin. Outcome of the HED Metabolism Assessment Review Committee (MARC) Meeting Held on September 20, 2001. L. Cheng,10/9/2001, D278044.

Attachment 7: Pyraclostrobin Acute and Chronic Dietary Exposure Assessments for the Section 3 Registration on Various Crops. PP#0F6139, L. Cheng, 7/29/2002, D284524.

Attachment 8: Drinking Water Assessment for Pyraclostrobin, A. Al-Mudallal, 9/19/2001, D277844.

Attachment 9: Correspondence of 1/16/2002, from C. Giles-Parker to C.A. Sanson.

cc without attachments: W. Wassell, G. Dannan, W. Greear, L. Cheng, K. O'Rourke, RAB3 Reading File.

13544

055592

Chemical:	**Carbamic acid, [2-[[[1-(4-chlorophenyl)-**
PC Code:	**099100**
HED File Code	**14000 Risk Reviews**
Memo Date:	**08/21/2002**
File ID:	**DPD284496**
Accession Number:	**412-03-0019**

HED Records Reference Center
12/10/2002