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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: 06/APR/10

Subject: Pyrimethanil Human Health Risk Assessment for Proposed Uses on Caneberry and Bushberry.

PC Code:	288201	**DP Barcode:**	D360122
Decision No.:	402624	**Registration No.:**	264-xxx
Petition No.:	8F7468	**Regulatory Action:**	Section 3
Risk Assessment Type:	Single Chemical/ Aggregate Assessment	**Case No.:**	None
TXR No.:	None	**CAS No.:**	53112-28-0
MRID No.:	None	**40 CFR**	§180.518

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RIMUERB/RD (7505P)

ARIA/RIMUERB of RD of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. RD of OPP has requested that ARIA evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed and currently registered uses of the active ingredient pyrimethanil.

Bayer Crop Science has as submitted a petition for the use of Fluopyram/Pyrimethanil 500 SC Fungicide (EPA File Symbol 264-xxx), an aqueous suspension-concentrate (SC) formulation containing 375 g/L of pyrimethanil on caneberry and bushberry. The overall risk assessment, dietary risk assessment, and residue chemistry assessment were provided by W. Cutchin, the water exposure assessment by D. Spatz (Environmental Fate and Effects Division (EFED)) and the occupational exposure assessment by M. Dow (ARIA).

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1.0 Executive Summary

Background

Bayer Crop Science has submitted a petition proposing uses for pyrimethanil [4,6-dimethyl-*N*-phenyl-2-pyrimidinamine], formulated as Fluopyram/Pyrimethanil 500 SC Fungicide (EPA File Symbol 264-xxx) an aqueous suspension-concentrate (SC) formulation containing 375 g/L of pyrimethanil, on caneberry and bushberry. The petitioner has proposed the establishment of permanent tolerances for pyrimethanil residues of 12 ppm in/on caneberries subgroup 13-07A and 6.0 ppm in/on bushberries subgroup 13-07B.

Pyrimethanil is an amino acid synthesis inhibitor that inhibits the secretion of fungal enzymes necessary for fungal infection. Pyrimethanil is currently registered in the U.S. for use on almonds, pome fruit, citrus fruit, stone fruit (except cherry), bananas, grapes, onions, pistachios, strawberries, tomatoes and tuberous and corm vegetables. Permanent tolerances have been established for residues of pyrimethanil *per se* in/on plant commodities at levels ranging from 0.05 ppm in/on vegetable, tuberous and corm, subgroup 1C to 150 ppm in/on citrus oil [40 CFR §180.518(a)(1)]. Tolerances have also been established for pyrimethanil residues and its metabolite 4-[4,6-dimethyl-2-pyrimidinyl)amino]phenol in fat (0.01 ppm), kidney (2.5 ppm) and byproducts (except kidney) (0.01 ppm) of cattle, goats, horses and sheep and in milk (0.05 ppm) [40 CFR §180.518(a)(2)].

Proposed Use

Pyrimethanil is proposed as a use on caneberries and bushberries as a foliar application two times at 0.33 – 0.66 lb ai/A with a maximum of 1.33 lb ai/A/season with a preharvest interval (PHI) of 0 days. Since adjuvants were not used in the submitted residue field trials, the label should prohibit such uses on caneberries and bushberries.

Toxicity Profile

Pyrimethanil is of low acute toxicity by oral, dermal, and inhalation routes, a slight eye irritant, not irritating to the skin, and not a dermal sensitizer. A single oral dose of 1000 mg/kg produced a number of acute signs of neurotoxicity, including ataxia, dilated pupils, and decreases in motor activity, hind limb grip strength, and body temperature. However, there was no evidence of neurotoxicity with repeated dosing in a subchronic neurotoxicity study in rats. Exposure to pyrimethanil in oral toxicity studies primarily resulted in decreased body weights and body weight gain, often accompanied by decreases in food consumption. The major target organs of repeated oral exposure were the liver and the thyroid. No reproductive toxicity was observed, and developmental effects (e.g., decreased fetal weight, retarded ossification, extra ribs) were observed only at maternally toxic doses. Special short-term exposure studies demonstrated increased liver UDPGT activity leading to decreases in thyroid hormones (T3, T4) and

compensatory increases in TSH in adult rats. Thyroid adenomas were seen in rats following long-term exposure, and it was concluded that they were mediated via disruption of the thyroid/pituitary axis. There were no concerns for mutagenicity.

Dose-response and FQPA Assessment

The toxicity data base for pyrimethanil is adequate for risk assessment and tolerance setting. Appropriate endpoints were identified for exposures to pyrimethanil. The identified endpoints for pyrimethanil are as follows:

> The acute dietary no-observable adverse-effect level (NOAEL) for the general population is 100 mg/kg/day. The lowest-observable adverse-effect level (LOAEL) is 1000 mg/kg/day based on an acute neurotoxicity (rat) study.
>
> The acute dietary NOAEL for females 13-49 years is 45 mg/kg/day. The LOAEL is 300 mg/kg/day based on a developmental toxicity (rabbit) study.
>
> The chronic dietary NOAEL is 17 mg/kg/day. The LOAEL is 221 mg/kg/day based on a chronic toxicity (rat) study.
>
> The short- and intermediate-term incidental oral NOAELs are 23.1 mg/kg/day. The LOAELs are 300-600 mg/kg/day based on a reproductive toxicity (rat) study.
>
> The short- and intermediate-term dermal NOAEL is 23.1 mg/kg/day. The LOAEL is 294 mg/kg/day based on a reproductive toxicity (rat) study. (Dermal absorption = 51%)
>
> The long-term dermal NOAEL is 17 mg/kg/day. The LOAEL is 221 mg/kg/day based on decreased body-weight gains; increased serum cholesterol and gamma-glutamyl transferase (GGT), increased relative liver/body-weight ratios, necropsy and histopathological findings in the liver and thyroid. (Dermal absorption = 51%)
>
> The inhalation (short-, intermediate-term) NOAEL is 23.1 mg/kg/day. The LOAEL is 294 mg/kg/day based on a reproductive toxicity (rat) study. (Inhalation absorption = 100% assumed)
>
> The long-term inhalation NOAEL is 17 mg/kg/day. The LOAEL is 221 mg/kg/day based on a reproductive toxicity (rat) study. (Inhalation absorption = 100% assumed)

The pyrimethanil risk assessment team has evaluated the quality of the hazard and exposure data; and, based on these data, recommended that the Food Quality Protection Act (FQPA) safety factor (SF) be reduced to 1x. The recommendation is based on the following:

- There is no evidence of qualitative or quantitative increased susceptibility following pre-/post-natal exposure to pyrimethanil in the developmental toxicity studies in rats and rabbits or in the two generation reproduction study in rats.
- There are no residual uncertainties concerning pre- and post-natal toxicity.
- The toxicology database for pyrimethanil does not show any evidence of treatment-related effects on the immune system. In a 90-day oral toxicity study with rats, a slight decrease in thymus weight was observed at 529 mg/kg/day (HDT). However, several other non-immune organs were decreased in weight and there was also a decrease in overall body weight, which explains the findings. Therefore, the overall weight of evidence suggests that this chemical does not directly target the immune system. Although an immunotoxicity study is required as a part of new data requirements in the 40 CFR Part 158 for conventional pesticide registration, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD than that currently used for overall risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for lack of this study.
- Evidence of neurotoxicity was observed at a very high dose (the limit dose) in the acute neurotoxicity study in rats. However, the study has a clear NOAEL, which is being utilized as the point of departure for the acute dietary exposure scenario, and there was no evidence of neurotoxicity observed in the subchronic neurotoxicity study in rats.
- A developmental neurotoxicity study is not required. In addition, although decreases in thyroid hormone levels were observed in adult rats in a special 14-day dietary study (due to increased metabolism by the liver), a comparative thyroid assay in young and adult rats is not required. The HIARC (2003) based this decision on the following: the effects seen on the thyroid and the liver in the database, while treatment-related, are not severe in nature; and in each of the studies that show an effect on thyroid hormone levels, as well as in all studies chosen for endpoint selection, there is a wide dose spread (~10-fold difference between NOAELs and LOAELs) which provides a measure of protection for any potential effects linked to decreased thyroid hormone levels in offspring. In addition, the decrease in thyroid hormone in the special 14-day study was relatively mild (≤24%), statistically significant at only one time point, observed at a high dose (379 mg/kg./day), and compensated for by an increase in TSH. Any possible decrease in thyroid hormone levels at the doses chosen for risk assessment would be undetectable. And, there was no indication of any developmental toxicity in offspring, except for decreased body weight, in the 2-gen. reproduction toxicity study.
- Although a repeat mouse carcinogenicity study at adequate doses was requested, an uncertainty factor to account for the lack of the study is not required. A repeat study is not likely to yield a POD lower than the current POD (17 mg/kg/day) selected for the cRfD, since there was no evidence of tumors in the mouse carcinogenicity study up to 254 mg/kg/day.
- There are no residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes tolerance-level residues (established or recommended) and 100% CT for all proposed/established commodities. By using

these assumptions, the acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations which will not likely be exceeded.

- There are no residential uses.

Relating to the carcinogenic potential of pyrimethanil, it is classified as "a Group C carcinogen" based on thyroid follicular cell tumors in both sexes of the 2-year rat study. Since the tumor response had a threshold and was due to disruption of the thyroid/pituitary axis, the Agency has determined that cancer dietary risk concerns due to long-term consumption of pyrimethanil residues are adequately addressed by the chronic dietary exposure analysis using the cRfD; therefore, a separate cancer dietary exposure analysis is not necessary.

Residue Chemistry

The qualitative nature of the pyrimethanil residue in plant commodities is adequately understood based on acceptable metabolism studies in lettuce, grapes, and tomatoes. The HED Metabolism Assessment Review Committee (MARC) has determined that for risk assessment and tolerance expression, parent only is the residue of concern.

There is an adequate residue analytical method of enforcement. A residue analytical method entitled "Analytical Method for the Determination of Residues of ZK 100309 in Vines, Strawberries, and Apples by HPLC" was submitted in conjunction with an earlier pyrimethanil petition for the establishment of a tolerance on imported wine grapes. The method has been subjected to a successful validation by the Analytical Chemistry Branch/ Biological and Economic Analysis Division (ACB/BEAD). This method is adequate for enforcement of the proposed tolerances. The data-collection method used to generate residue data in conjunction with magnitude of the residue studies associated with this petition is a high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) Method DGM C05/98-0. The adequacy of the method for data collection was verified by fortifying control samples of caneberries and bushberries with pyrimethanil that bracketed the measured residue levels. Method recoveries were within the acceptable range of 70-120% for all fortified samples.

There are adequate storage stability data to support the integrity of samples collected from the submitted field studies. There are no storage stability issues or corrections that need to be applied to these residue studies.

The submitted field trial residue data for blackberry, raspberry, and blueberry are adequate. The field trial data reflect the proposed use pattern, an adequate number of trials were conducted in the appropriate geographic regions, and samples were analyzed for the residue of concern using validated data-collection methods. Either blackberries or raspberries can be the representative commodity for caneberries and blueberries are the representative commodity for bushberries. The residue data sets indicate that the

requested tolerances of 12 ppm for caneberries and 6.0 ppm for bushberries are appropriate. ARIA recommends for the requested tolerances. However, a revised Section F is required to correct the commodity definitions to caneberry, crop subgroup 13-07A and bushberry, crop subgroup 13-07B.

There are no processed food items of regulatory interest for caneberries or bushberries. However, the petitioner has submitted a washing and cooking study on blueberries. Washing berries did not significantly change the pyrimethanil residues (washing processing factor of 1.0X). Washing and cooking berries reduced the pyrimethanil residues by a factor of 0.7X. There are no theoretical concentration factors for blueberry processed commodities.

Drinking Water Exposure and Risk

EFED reassessed pyrimethanil for the proposed new uses on small berries (caneberries and bushberries) presented in this memo. Tier I SCI-GROW screening concentration of combined total residues (pyrimethanil + 2-amino-4,6 dimethylpyrimidine) in ground water for uses on are not expected to exceed the estimated drinking water concentration (EDWC) of 4.8 µg/L from the previously estimated use on strawberry in Florida. Tier II PRZM-EXAMS screening drinking water concentrations for combined residues of pyrimethanil (parent + 2-amino-4,6-dimethylpyrimidine) in raw surface source water are not expected to exceed the previously recommended EDWC of 37.8 µg/L for peak (1 in 10 years; acute) based on aerial applications on grapes in New York. For small berries, the annual mean concentration (1-in-10 years, chronic) of 19.25 µg/L and 7.98 µg/L (long-term mean 30-year average; cancer) are higher than any of the previously assessed uses. Therefore, it is recommended that 19.25 µg/L be used for chronic assessments.

Acute Dietary Exposure and Risk

An acute population-adjusted dose (aPAD) is established for females 13 to 50 years old based upon the developmental toxicity study with rabbits. A separate aPAD is established for the general population including infants and children based upon the acute neurotoxicity study with rats. An UF of 100x (10x for inter-species extrapolations, 10x for intra-species variations, and a FQPA SF of 1x) was used to calculate both aPADs. An aPAD of 0.45 mg/kg bw/day was used for the population subgroup females 13-49 years of age. For the general U.S. population and all population subgroups except females 13-49 years of age the aPAD for pyrimethanil is equal to 0.10 mg/kg/day.

The acute dietary analyses assumed Dietary Exposure Evaluation Model (DEEM-FCID™) (ver. 7.81) default processing factors (as necessary), empirical processing factors for orange and apple juice, tolerance-level residues, 100% CT for all commodities and EDWCs (37.8 ppb) for direct and indirect water sources. The resulting acute exposure estimates are below the ARIA's level of concern (<100% aPAD): U.S. general population at 10% aPAD, females 13-49 years of age at 13% aPAD and all other population subgroups with the most highly exposed population subgroup being all infants at 35% aPAD.

Chronic Dietary Exposure and Risk

A cPAD is established based upon the chronic toxicity study with rats. An UF of 100x (10x for inter-species extrapolations, 10x for intra-species variations, and a FQPA SF of 1x) was used to calculate the cPAD. The cPAD for pyrimethanil is equal to 0.17 mg/kg/day.

The chronic dietary analyses assumed DEEM™ (ver. 7.81) default processing factors (as necessary), empirical processing factors for orange and apple juice, tolerance-level residues, 100% CT for all commodities and EDWCs (19.25 ppb) for direct and indirect water sources. The resulting chronic exposure estimates are below ARIA's level of concern (<100% cPAD): U.S. general population at 13% cPAD and all other population subgroups with the most highly exposed population subgroup being children 1-2 years old with 63% cPAD.

Cancer Dietary Risk

Pyrimethanil is classified as a Group C carcinogen based on thyroid follicular cell tumors in both sexes of the 2-year rat study (NOAEL = 17 mg/kg/day). The HED Cancer Peer Review Committee (CPRC) recommended the MOE approach (i.e., threshold consideration; MOE is equal to NOAEL divided by chronic exposure). Since the cPAD (0.17 mg/kg/day) is protective of non-cancer and cancer end points, a separate cancer risk is not necessary.

Residential Exposure

Currently, there are no registered/proposed uses of pyrimethanil that result in residential exposures. Therefore, a residential exposure assessment was not performed.

Aggregate Risk

The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Since there are no registered/proposed uses of pyrimethanil that result in residential exposures, the acute and chronic aggregate risk assessments were equal to the acute dietary and chronic dietary estimates (food and water only), respectively. The acute and chronic aggregate exposure to the U.S. population and all other subpopulations from the uses of pyrimethanil does not exceed ARIA's level of concern.

Occupational Exposure/Risk

Based on the proposed new uses, the most highly exposed occupational pesticide handlers are expected to be mixer/loaders using open-pour loading of liquid formulations, applicators using open-cab, airblast sprayers and aerial applicators. It is anticipated that most ground applications will be applied by the grower. It is unlikely that pesticide

handlers would be exposed continuously for 30 days or more (short-term duration exposures). In this case, the short-term and intermediate-term (1 – 6 months) duration exposures (dermal and inhalation) have the same toxicological endpoints. Therefore, in the event that intermediate-term exposure were to occur, the risks estimated for short-term exposure are adequate to describe those for intermediate-term exposures as well. The combined MOE for dermal and inhalation exposure (1100, 960, and 5300 for mixer/loaders, airblast sprayers and aerial applicators, respectively) is not of concern, if workers wear gloves as directed on the label.

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. The highest likely exposure for the proposed new uses is from hand harvesting. A MOE of 490 has been determined for hand harvesting. A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The most conservative estimate (i.e., highest exposure/risk) of post-application exposure results in MOEs > 100. Therefore, the proposed risk does not exceed ARIA's level of concern.

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy (as it relates to an imported crop), ARIA and HED estimate risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food consumption. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all proposed/registered food uses/tolerances of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure from traditional dietary patterns among specific subgroups.

Review of Human Research

Past pyrimethanil risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and

inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED) and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies in these multi-pesticide generic exposure databases, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

Regulatory Recommendations and Data Deficiencies:

Recommendations

The tolerances proposed by the registrant in the current petitions are listed in Table 1.0, along with ARIA's recommended tolerance levels.

Pending submission of a revised Section B (see requirements under Directions for Use), and a revised Section F (see requirements under Proposed Tolerances), the residue chemistry, toxicology, and occupational exposure databases support conditional registration and establishment of permanent tolerances as summarized in Table 1.0. For an unconditional registration, the petitioner is instructed to resolve all deficiencies associated with the toxicological requirements (see Toxicology).

Table 1.0. Tolerance Summary for Pyrimethanil.

Commodity	Proposed / Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
40 CFR §180.518 (a)(1)			
Caneberries subgroup 13-07A	12	12	*Caneberry, crop subgroup 13-07A*
Bushberries subgroup 13-07B	6.0	6.0	*Bushberry, crop subgroup 13-07B*

Data Deficiencies/Requirements

Toxicology:

- Mouse carcinogenicity study was previously requested (TRX# 0050408, J. Kidwell, 24/APR/2003) and this requirement has not been fulfilled.
- Immunotoxicity study (required as a result of the revisions of 40 CFR §158).

Residue Chemistry:

- Adjuvants were not used in any of the submitted residue field trials. Since adjuvants were not used in the submitted residue field trials, the label should prohibit such uses on caneberries and bushberries.
- A summary of the recommended tolerances along with recommendations for

commodity definitions are presented in Table 1.0. The petitioner is required to submit a revised Section F to reflect the recommendations in Table 1.0.

Note to PM: The residue definition for the tolerance expression for CFR §180.518 (a) *General* should be as follows: "Tolerances are established for residues of pyrimethanil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only pyrimethanil (4,6-dimethyl-*N*-phenyl-2-pyrimidinamine)."

2.0 Ingredient Profile

Pyrimethanil is an anilinopyrimidine fungicide that inhibits the secretion of fungal enzymes which are required during the infection process. Pyrimethanil blocks the ability of the fungus to degrade and digest the plant tissues, thus stopping penetration and development of the disease. The precise mechanism of inhibition of enzyme secretion has not been fully established. Protein synthesis is not inhibited, and evidence suggests that extracellular enzymes accumulate inside the fungus, their release being blocked in the presence of the fungicide. Pyrimethanil penetrates rapidly into the plant tissues, where it stops the development of the disease, providing a significant curative action. *In vitro*, germ tube extension and mycelial growth are inhibited.

Pyrimethanil does not exhibit cross-resistance to sterol-inhibitors, dicarboximides, benzimidazoles, quinone outside inhibitors, or phenylamides, but may exhibit cross-resistance in certain plant pathogenic fungi including anilinopyridine (AP) compounds such as cyprodinil and mepanipyrim.

2.1 Summary of Proposed Uses

Table 2.1. Summary of Directions for Use of Pyrimethanil.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Small Berries (caneberries and bushberries)						
Ground, air, or chemigation	Fluopyram/Pyrimethanil 500 SC Fungicide (264-xxx)	0.33-0.66	2	1.33	0	Do not apply this product for more than 2 sequential applications before rotating to a fungicide from a different functional group.

The submitted label for is adequate to allow evaluation of the residue data relative to the proposed use. Since adjuvants were not used in the submitted residue field trials, the label should prohibit such uses on caneberries and bushberries.

2.2 Structure and Nomenclature

Table 2.2. Test Compound Nomenclature.

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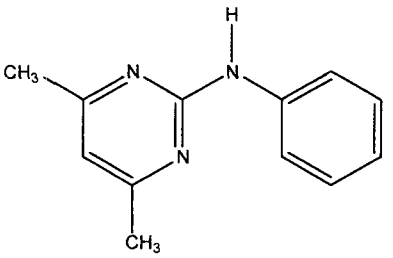
Chemical structure	
Common name	Pyrimethanil
Company experimental name	NR*
IUPAC name	N-(4,6-dimethylpyrimidin-2yl)aniline
CAS name	4,6-dimethyl-N-phenyl-2-pyrimidinamine
CAS #	53112-28-0
End-use product/(EP)	Fluopyram/Pyrimethanil 500 SC Fungicide (EPA File Symbol 264-xxx)

*NR = Not Reported

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of the Technical Grade Test Compound.		
Parameter	Value	References
Melting point	96°C	The Pest Manual. British Crop Protection Council. Twelfth Edition, Editor: C.D.S. Tomlin.
pH (water solution at 25°C)	6.1	
Specific gravity at 20°C	1.15	
Water solubility (g/l at 25°C)	0.121	
Solvent solubility (g/l at 20°C)	acetone – 389, ethyl acetate – 617, methanol – 176, methylene chloride – 1000, *n*-hexane – 23.7, toluene – 412	
Vapor pressure at 25°C	2.2 mPa	
Octanol/water partition coefficient log (K_{OW})	2.84	
UV/visible absorption spectrum	No UV absorption above 290 nm	Pest Management Regulatory Agency Health, Canada, 2006.

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

Pyrimethanil is of low acute toxicity by the oral, inhalation, and dermal routes (Toxicity Category III). It is slightly irritating to the eyes and non-irritating to the skin in rabbit studies. Pyrimethanil is not a dermal sensitizer. Subchronic and chronic oral toxicity studies in rats, mice, and dogs primarily resulted in decreased body weight and body-weight gains, often accompanied by decreased food consumption. The major target organs in rats and mice were the liver and thyroid. In subchronic studies in rats and mice, liver toxicity was manifested as increased absolute and relative liver weights.

Histopathological changes in the liver were primarily associated with increased evidence of hypertrophy in centrilobular hepatocytes. In a subchronic toxicity study in mice, increases in absolute thyroid weight were observed, associated with exfoliative necrosis and pigmentation of follicular cells. In a subchronic toxicity study in rats, thyroid effects were manifested as an increased incidence and severity of follicular epithelial hypertrophy and follicular epithelial brown pigment. Thyroid toxicity was the result of liver enzyme induction that led to increased metabolism and excretion of thyroid hormones in rodents.

In the acute neurotoxicity study in rats, ataxia, decreased motor activity, decreased body temperature, decreased hind limb grip strength in males, and dilated pupils were observed in females at 1000 mg/kg (limit dose). However, no signs of neurotoxicity were evident following repeated dosing at doses up to 430 mg/kg/day in the subchronic neurotoxicity (SCN) study in rats. Although the study was not conducted at doses up to 1000 mg/kg/day (limit dose), a new study is not required because the results of a repeat study at a higher dose will not impact the current endpoints used for risk assessment. The risk assessment utilizes points of departure that are 19-25X lower than the NOAEL observed in the SCN. In addition, no evidence of neuropathology was seen in neurotoxicity studies or in the subchronic or chronic studies in mice, rats, and dogs.

There was no quantitative or qualitative evidence of increased susceptibility following prenatal exposure (in rats and rabbits), or postnatal exposure (in rats). There were no effects on fertility or reproduction in the two-generation reproduction study in rats.

In a carcinogenicity study in mice, there was no increase in the incidence of any tumor types in either sex. However, the mouse carcinogenicity study was considered as inadequate for assessing the carcinogenic potential of pyrimethanil by Developmental and Reproductive Toxicology (DART; TRX# 0050408, J. Kidwell, 24/APR/2003) because the high dose in the existing study was judged to be inadequate. In a carcinogenicity study in rats, benign thyroid follicular cell adenomas were seen at the high dose in both sexes. The CPRC (TRX# 0050189, Y. Yang and E. Rinde, 11/FEB/1997) classified pyrimethanil as a Group C- possible human carcinogen and recommended that a threshold or MOE approach be used to estimate cancer risk to humans. The threshold approach was recommended because the thyroid tumors associated with administration of pyrimethanil in Sprague-Dawley rats may be due to a disruption in the thyroid-pituitary status and since pyrimenthanil is considered to be nonmutagenic. .

3.1.1 Adequacy of the Toxicity Database

The toxicology database for pyrimethanil is complete with the exception of the following data gaps:

- A mouse carcinogenicity study was requested by the DART (TRX# 0050408, J. Kidwell, 24/APR/2003) because the high dose in the existing study was judged to be inadequate for assessing the carcinogenic potential of pyrimethanil.

- Immunotoxicity study (required as a result of the revisions of 40 CFR §158).

3.1.2 Evidence of Neurotoxicity

Clinical signs of neurotoxicity (ataxia, decreased motor activity, decreased body temperature, decreased hind limb grip strength in males, and dilated pupils) were observed in females in the acute neurotoxicity study in rats at the limit dose only (1000 mg/kg). However, there was no evidence of neurotoxicity in the subchronic neurotoxicity study in rats tested up to 430 mg/kg/day. In addition, no evidence of neuropathology was seen in the neurotoxicity studies or the subchronic or chronic toxicity studies in rats, dogs, and mice.

3.1.2.1 Determination of Susceptibility

Based on the results in developmental toxicity studies in rats and rabbits, there is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to pyrimethanil. There is no evidence of qualitative or quantitative increased susceptibility following pre-/post-natal exposure to pyrimethanil in two generation reproduction study. There were no effects on fertility or reproduction in the two-generation reproduction study in rats.

3.1.2.2 Degree-of-Concern Analysis

There are no concerns or residual uncertainties for pre- and/or postnatal toxicity following exposure to pyrimethanil.

3.1.3 Recommendation for a DNT Study

Based on the weight-of-evidence presented, the HIARC (2003) concluded that a developmental neurotoxicity (DNT) study is not required for pyrimethanil since there is no evidence of neuropathology and no neurotoxic signs up to 430 mg/kg/day in a subchronic neurotoxicity study in rats. The only evidence of neurotoxicity occurred after an acute dose level of 1000 mg/kg (the limit dose), which is 10-50Xhigher than the doses used to establish endpoints for risk assessment.

HIARC noted, as seen in the CPRC report, that the effects on the thyroid-pituitary status were associated with the large increase in uridine diphosphate glucuronosyl transferases (UDPGT) seen in the 14-day dietary rat study. The effects seen in the thyroid and the liver, while treatment-related, are not severe in nature, and in each of these studies there is a wide dose spread (~10-fold difference between NOAELs and LOAELs) which provides a measure of protection for any potential effects reflecting increased sensitivity

or susceptibility in offspring. Additionally, the endpoints selected for risk assessment will cover any concern for thyroid or liver effects seen at higher doses.

3.2 FQPA Considerations

Based on previous HIARC conclusions (2003) and the pyrimethanil risk assessment team's re-evaluation of the hazard and exposure data, the FQPA SF can be reduced to 1x. The recommendation is based on the following:

- There is no evidence of qualitative or quantitative increased susceptibility following pre-/post-natal exposure to pyrimethanil in the developmental toxicity studies in rats and rabbits or in the two generation reproduction study in rats.
- There are no residual uncertainties concerning pre- and postnatal toxicity.
- The toxicology database for pyrimethanil does not show any evidence of treatment-related effects on the immune system. In a 90-day oral toxicity study with rats, a slight decrease in thymus weight was observed at 529 mg/kg/day (HDT). However, several other non-immune organs were decreased in weight and there was also a decrease in overall body weight, which explains the findings. Therefore, the overall weight of evidence suggests that this chemical does not directly target the immune system. Although an immunotoxicity study is required as a part of new data requirements in the 40 CFR Part 158 for conventional pesticide registration, the Agency does not believe that conducting a functional immunotoxicity study will result in a lower POD than that currently used for overall risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for lack of this study.
- Evidence of neurotoxicity was observed at a very high dose (the limit dose) in the acute neurotoxicity study in rats. However, the study has a clear NOAEL, which is being utilized as the point of departure for the acute dietary exposure scenario, and there was no evidence of neurotoxicity observed in the subchronic neurotoxicity study in rats.
- A developmental neurotoxicity study is not required. In addition, although decreases in thyroid hormone levels were observed in adult rats in a special 14-day dietary study (due to increased metabolism by the liver), a comparative thyroid assay in young and adult rats is not required. The HIARC (2003) based this decision on the following: the effects seen on the thyroid and the liver in the database, while treatment-related, are not severe in nature; and in each of the studies that show an effect on thyroid hormone levels, as well as in all studies chosen for endpoint selection, there is a wide dose spread (~10-fold difference between NOAELs and LOAELs) which provides a measure of protection for any potential effects linked to decreased thyroid hormone levels in offspring. In addition, the decrease in thyroid hormone in the special 14-day study was relatively mild (≤24%), statistically significant at only one time point, observed at a high dose (379 mg/kg./day), and compensated for by an increase in TSH. Any possible decrease in thyroid hormone levels at the doses chosen for risk assessment would be undetectable. And, there was no indication of any

developmental toxicity in offspring, except for decreased body weight, in the 2-gen. reproduction toxicity study.

- Although a repeat mouse carcinogenicity study at adequate doses was requested, an uncertainty factor to account for the lack of the study is not required. A repeat study is not likely to yield a POD lower than the current POD (17 mg/kg/day) selected for the cRfD, since there was no evidence of tumors in the mouse carcinogenicity study up to 254 mg/kg/day.
- There are no residual uncertainties with respect to exposure data. The dietary food exposure assessment utilizes tolerance-level residues (established or recommended) and 100% CT for all proposed/established commodities. By using these assumptions, the acute and chronic exposures/risks will not be underestimated. The dietary drinking water assessment utilizes water concentration values generated by models and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations which will not likely be exceeded.
- There are no residential uses.

The FQPA SF recommended by the pyrimethanil review team assumes that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

3.3 Dose-Response Assessment

3.3.1 Acute-Population Adjusted Dose (aPAD) - Females age 13-49

The developmental toxicity study in rabbits was used to select the endpoint for establishing the aPAD for females 13-49 years of age. An UF of 100x (10x for inter-species extrapolations, 10x for intra-species variations, and a FQPA SF of 1x) and the NOAEL (45 mg/kg/day) were used to calculate the aPAD. The aPAD of 0.45 mg/kg is (developmental LOAEL of 300 mg/kg/day) based upon increase in fetuses with 13 thoracic vertebrae and 13 pairs of ribs at 300 mg/kg. These developmental anomalies may be the result of a single dose and are therefore relevant to pregnant females.

3.3.2 Acute Population Adjusted Dose (aPAD) - General Population

An aPAD of 1 mg/kg is established for the general population including infants and children based on decreased motor activity, ataxia, decreased body temperature, hind limb grip strength, and dilated pupils following a single high dose (1000 mg/kg) in the acute neurotoxicity study in rats. An UF of 100x (10x for inter-species extrapolations, 10x for intra-species variations, and a FQPA SF of 1x) and the NOAEL (100 mg/kg/day) were used to calculate the aPAD.

3.3.3 Chronic-Population Adjusted Dose (cPAD)

A cPAD is established based upon the chronic toxicity study with rats. In this study, the LOAEL of 221 mg /kg/day is based on decreased body-weight gains, increased serum cholesterol and GGT, increased relative liver/body-weight ratios, necropsy, and histopathological findings in the liver and thyroid. An UF of 100x (10x for inter-species extrapolations, 10x for intra-species variations, and a FQPA SF of 1x) and the NOAEL (17 mg/kg/day) were used to calculate the cPAD. The cPAD for pyrimethanil is equal to 0.17 mg/kg/day.

3.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

There are no residential uses for pyrimethanil. Therefore, an incidental oral endpoint was not chosen.

3.3.5 Dermal Absorption

A dermal absorption study was submitted (MRID No. 46630101) and reviewed (DP# 322065, P.V. Shah, 23/FEB/2009). A dermal absorption factor of 51% was chosen based on results from the *in vivo* dermal absorption study in rats. Previously, HED used a dermal absorption factor of 37.2% (DP# 322065, K. Lowe, 04/JAN/2007). This dermal absorption factor was based on preliminary review of the MRID 46630101; however, subsequent to a detailed review HED concluded that the dermal factor of 51% is more appropriate for this dermal exposure assessment.

3.3.6 Dermal Exposure (Short- and Intermediate-Term)

The short- and intermediate term dermal and inhalation endpoints for use in risk assessment are established for pyrimethanil. The effects seen were decreased mean body weights and body-weight gains observed in the reproduction study with rats. The NOAEL is 23.1 mg/kg/day. The level of concern (LOC) for occupational dermal exposure is a MOE < 100.

3.3.7 Long-Term Dermal Exposure (Long-Term)

The long term dermal exposure endpoints for use in risk assessment have been chosen for pyrimethanil based on the combined chronic/carcinogenicity study in rats. The effects seen were decreased body weight gains, increased serum cholesterol, increased relative liver/body weight ratios, necropsy and histopathological findings in the liver and thyroid at a LOAEL of 221 mg/kg/day (NOAEL of 17 mg/kg/day).

3.3.8 Inhalation Exposure (Short- and Intermediate-Term)

An inhalation toxicity study was not submitted. The short- and intermediate-term inhalation exposures for use in risk assessment have been chosen for pyrimethanil based on the reproduction study in rats. The effects seen were decreased mean body weights and body weight gains at 5000 ppm (294 mg/kg/day, male; 343 mg/kg/day, female). The Agency has assumed that absorption via the inhalation route is complete (100%).

3.3.9 Long-Term Inhalation Exposure

The long-term inhalation exposure for use in risk assessment has been chosen for pyrimethanil based on the combined chronic/carcinogenicity study in rats. The effects seen were decreased body weight gains, increased serum cholesterol, increased relative liver/body weight ratios, necropsy and histopathological findings in the liver and thyroid at a LOAEL of 221 mg/kg/day and a NOAEL of 17 mg/kg/day.

Based on the available toxicity database and the Agency's current practices, the inhalation risk for pyrimethanil was assessed using an oral toxicity study. The Agency sought expert advice and input on issues related to this route to route extrapolation approach (i.e. the use of oral toxicity studies for inhalation risk assessment) from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route to route extrapolation of toxicity data. If any new policies or procedures are developed, the Agency may revisit the need for an inhalation toxicity study for pyrimethanil and/or a re-examination of the inhalation toxicity risk assessment.

3.3.10 Level of Concern for Margin of Exposure

The target MOEs for occupational and non-dietary residential exposure risk assessments are as follows:

Table 3.3.10. Summary of Levels of Concern for Risk Assessment.

Route	Duration		
	Short-Term (1-30 days)	Intermediate-Term (1-6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	NA	NA	NA
Dermal	NA	NA	NA
Inhalation	NA	NA	NA

3.3.11 Classification of Carcinogenic Potential

Pyrimethanil was classified as a Group C - possible human carcinogen based on thyroid follicular cell tumors in both sexes in the 2-year toxicity/carcinogenicity study in rats (NOAEL = 17 mg/kg/day). Since the tumors are considered to be threshold phenomena, the CPRC recommended the MOE approach. Since the cPAD is considered protective of non-cancer and cancer end points, a separate cancer risk assessment is not required.

3.3.12 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. An aggregated exposure risk assessment is not required since there are no residential uses for pyrimethanil at this time.

3.3.13 Summary of Toxicological Doses and Endpoints for Pyrimethanil for Use in Human Health Risk Assessments

The selected toxicity endpoints are summarized in Tables 3.3.13.a and 3.3.13.b.

Table 3.3.13.a. Summary of Toxicological Doses and Endpoints for Pyrimethanil for Use in Dietary and Non-Occupational Human-Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL= 45 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.45 mg/kg/day aPAD =0.45 mg/kg/day	Developmental Toxicity - Rabbit: LOAEL = 300 mg/kg/day based on increases in fetuses with 13 thoracic vertebrae and 13 pairs of ribs.
Acute Dietary (General Population, including Infants and Children)	NOAEL = 100 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 1 mg/kg/day	Acute Neurotoxicity- Rat: LOAEL = 1000 mg/kg/day based on decreased motor activity, ataxia, decreased body temperature, hind limb grip strength, and dilated pupils.
Chronic Dietary (All Populations)	NOAEL= 17 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.17 mg/kg/day cPAD = 0.17 mg/kg/day	Chronic Toxicity - Rat: LOAEL = 221 mg/kg/day based on decreased body weight gains; increased serum cholesterol and GGT, increased relative liver/body weight ratios, necropsy and histopathological findings in the liver and thyroid.
Cancer (oral, dermal, inhalation)	Pyrimethanil was classified as a Group C carcinogen based on thyroid follicular cell tumors in both sexes of the 2-year rat study (NOAEL = 17 mg/kg/day); the CPRC recommended the MOE approach (i.e., threshold consideration). Since the cPAD is protective of non-cancer and cancer end points, a separate cancer risk assessment is not necessary.			

Table 3.3.13.b. Summary of Toxicological Doses and Endpoints for Pyrimethanil for Use in Occupational Human-Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and LOC for Risk Assessment	Study and Toxicological Effects
Short (1-30 days) and Intermediate	Oral NOAEL= 23.1 mg/kg/day	Occupational LOC for MOE =	Reproductive Toxicity - Rat LOAEL = 294 mg/kg/day based on

Table 3.3.13.b. Summary of Toxicological Doses and Endpoints for Pyrimethanil for Use in Occupational Human-Health Risk Assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and LOC for Risk Assessment	Study and Toxicological Effects
(1- 6 months) Term Dermal	(dermal absorption = 51%)	100	decreased mean body weights and body-weight gains.
Long-Term Dermal (>6 months)	Oral study NOAEL= 17 mg/kg/day (dermal absorption = 51%)	Occupational LOC for MOE = 100	Chronic Toxicity -Rat LOAEL = 221 mg/kg/day based on decreased body-weight gains; increased serum cholesterol and GGT, increased relative liver/body-weight ratios, necropsy and histopathological findings in the liver and thyroid.
Short (1-30 days) and Intermediate (1- 6 months) Term Inhalation	Oral NOAEL= 23.1 mg/kg/day (inhalation absorption = 100%)	Occupational LOC for MOE = 100	Reproductive Toxicity - Rat LOAEL = 294 mg/kg/day based on decreased mean body weights and body-weight gains.
Long-Term Inhalation (>6 months)	Oral study NOAEL= 17 mg/kg/day (inhalation absorption = 100%)	Occupational LOC for MOE = 100	Chronic Toxicity - Rat LOAEL = 221 mg/kg/day based on decreased body-weight gains, increased serum cholesterol and GGT, increased relative liver/body-weight ratios, necropsy and histopathological findings in the liver and thyroid.
Cancer (oral, dermal, inhalation)	Group C with a MOE approach for quantification of human cancer risk. Since the cPAD is protective of non-cancer and cancer end points, a separate cancer risk is not necessary (see above).		

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). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.4 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any

adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Pyrimethanil is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

4.0 Public Health and Pesticide Epidemiology Data

Based on the usage patterns and the lack of residential use sites, no incident reports are expected at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The qualitative nature of the pyrimethanil residue in plant commodities is adequately understood based on acceptable metabolism studies in lettuce, grapes, and tomatoes. The HED MARC has determined that for risk assessment and tolerance expression, parent only is the residue of concern. Future new uses on root crops whose tops are significant food/feed items will require the analysis of samples for metabolite AEC614278.

5.1.2 Metabolism in Rotational Crops

Caneberries and bushberries are typically not rotated. Therefore, residue data pertaining to confined and field accumulation in rotational crops are not germane to this tolerance petition.

5.1.3 Metabolism in Livestock

Caneberries and bushberries have no livestock food/feed items of regulatory interest; therefore, issues pertaining to livestock metabolism, analytical methods and storage

stability data for and residues in livestock commodities are not addressed in the current petition.

5.1.4 Analytical Methodology

A residue analytical method entitled "Analytical Method for the Determination of Residues of ZK 100309 in Vines, Strawberries, and Apples by HPLC" was submitted in conjunction with an earlier pyrimethanil petition, PP#4E4384, for the establishment of a tolerance on imported wine grapes. The method has been subjected to a successful validation by ACB/BEAD (DP# 288256, E. Kolbe, 07/JUL/2004). This method is adequate for enforcement of the proposed tolerances.

5.1.5 Environmental Degradation

EFED studies indicated that pyrimethanil is expected to be moderately persistent in the environment. Aerobic metabolism is expected to be the major route of degradation for pyrimethanil in the environment. The only major degradate is 2-amino-4,6-dimethylpyrimidine (degradate 1). Although it may be less toxic than the parent, degradate 1 is expected to be more mobile and more persistent in the environment than the parent. MARC recommended that parent and degradate 1 are the residues of concern for drinking water.

5.1.6 Comparative Metabolic Profile

The major route of dissipation for pyrimethanil is expected to be aerobic metabolism for both aqueous and terrestrial environments. Pyrimethanil partitions into the sediment, but is stable to anaerobic (total system) degradation in both soil and sediment systems. Pyrimethanil is stable to both hydrolysis and aqueous photolysis at environmental pHs, but is susceptible to photolysis in soil.

In plants, pyrimethanil is the only significant residue ranging from essentially all of the total radioactive residues (TRR) in carrots and tomatoes to 44% in lettuce. Limited metabolism of pyrimethanil occurs with minor amounts (less than 10%) of the phenyl and pyrimidyl hydroxylated metabolites (AE C614276, AE C614277, AE C614278, and AE C621312) being released after acid hydrolysis. Analysis of the foliage from apples and carrots confirmed that the metabolism of pyrimethanil in plants proceeded primarily via hydroxylation of the aromatic ring structures as well as the methyl groups.

In livestock, pyrimethanil is rapidly metabolized and excreted from lactating dairy cows. The observed total radioactive residues in edible tissues and milk were as follows: milk maximum residue of 0.069 ppm; liver - 0.363 ppm; kidney 0.249 ppm, and muscle 0.017 ppm. The metabolic pathway is similar to that of plants involving hydroxylation of the phenyl and pyrimidine rings as well as hydroxylation of the methyl substituents. Further metabolic reactions occur including cleavage of the phenyl ring to produce substituted pyrimidines. The major metabolite was AE C614276 (46% of the kidney residues, 63% of the milk residues resulting from hydroxylation of the phenyl ring. Hydroxylation of

the pyrimidinyl ring of pyrimethanil resulted in formation of minor amounts of AE C614277. Hydroxylation of the methyl groups of pyrimethanil resulted in formation of minor amounts of AE C614278. Hydroxylation of the methyl groups of AE C614276 resulted in formation of minor amounts of AE C614800.

In rats, when pyrimethanil was administered orally, it was absorbed rapidly and eliminated within 24 hours. The major routes of elimination were the urine (approximately 72% of the administered dose), and the feces (17-18% of the administered dose). The main pathways of metabolism involved oxidation to phenols in either or both aromatic rings. The minor pathways of metabolism involved oxidation of the methyl group to the corresponding alcohol.

5.1.7 Toxicity Profile of Major Metabolites and Degradates

The primary residue of concern in both crop and animal commodities is pyrimethanil. In the animal metabolism, since major metabolites are produced following the oral administration of pyrimethanil, toxicology data for metabolites are completely supported by data obtained for pyrimethanil.

5.1.8 Pesticide Metabolites and Degradates of Concern

The residues which are regulated in plant commodities are pyrimethanil, *per se* (40 CFR §180.518). For risk assessment purposes, the residues of concern are; 1) pyrimethanil for plant commodities; 2) in livestock, pyrimethanil + metabolite AEC614276 for ruminant muscle, fat and byproducts; 3) pyrimethanil + metabolite AEC614277 for milk. In drinking water, residues of concern are pyrimethanil + Degradate 1 (2-amino-4,6-dimethylpyrimidine).

Table 5.1.8. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Pyrimethanil, *per se*	Pyrimethanil, *per se*
	Rotational Crop	Pyrimethanil, *per se*	Pyrimethanil, *per se*
Livestock	Ruminant	Pyrimethanil + AEC614276 for muscle, fat and byproducts. For milk, pyrimethanil + AEC614277.	Pyrimethanil + AEC614276 for muscle, fat and byproducts. Pyrimethanil + AEC614277 for milk.
	Poultry	Not Applicable	Not Applicable
Drinking Water		Parent (Pyrimethanil) + Degradate 1 (2-amino-4,6-dimethylpyrimidine)	Not Applicable

5.1.9 Drinking Water Residue Profile

EFED reassessed pyrimethanil for the proposed new uses presented in this memo (DP# 373344, D. Spatz, no date specified).

For surface water, Tier II PRZM-EXAMS screening drinking water concentrations for combined residues of pyrimethanil (parent + 2-amino-4,6-dimethylpyrimidine) in raw surface source water for uses on small berries (caneberries and bushberries) are not expected to exceed 23.69 µg/L for the peak 1- in-10 year concentration; 19.25 µg/L for the 1-in-10 year annual mean concentration; and, 7.98 µg/L for the 30 year annual average concentration. There is a previously recommended EDWC of 37.8 µg/L for peak (1 in 10 years; acute) based on the registered seasonal application rate of 2.1 lb ai/A on strawberry in Florida (DP Barcodes D283999 and D290313, 10/22/03; D353180, 01/08/09). Therefore, since it is the higher estimate, the previously estimated concentration of **37.8 µg/L** is also recommended for the peak 1- in-10 year concentration in surface water for this action. Since no other previous assessments for exceed the small berry surface water estimates for the annual mean concentration (1 in 10 years, chronic) of **19.25 µg/L** and **7.98 µg/L** (long term mean 30 years average; cancer) it is recommended that these EDWCs be used for chronic and cancer assessments, respectively.

For ground water, Tier I SCI-GROW screening concentration of combined total residues (pyrimethanil + 2-amino-4,6-dimethylpyrimidine) for uses on small berries (caneberries and bushberries) are not expected to exceed 2.41 µg/L, which is lower than 4.8 µg/L for previously estimated exposure based on the registered seasonal application rate of 2.1 lb ai/A on strawberry in Florida (DP Barcodes D283999 and D290313, 10/22/03; D353180, 01/08/09). Therefore, the previously estimated concentration of **4.8 µg/L** is recommended for the ground water EDWC

Table 5.19. Estimated Drinking Water Concentrations for Combined Total Residues, Parent (Pyrimethanil) Plus Major Degradate (2-amino-4,6-dimethylpyrimidine).

Chemical	Acute (peak) Surface Water Concentration (ppb)	Annual Average Surface Water Concentration 1-in-10 yr (ppb)	Annual Average Surface Water Concentration 1-in-30 yr (ppb)	Ground Water Concentration (ppb)
Pyrimethanil plus 2-amino-4,6-dimethylpyrimidine.	37.8 [1]	19.25 [2]	7.98 [2]	4.8 [1]

[1] Strawberry in Florida at application rate of 2.1 lb ai/A on (DP# 283999 and 290313, 10/22/03; DP# 353180, 01/08/09)
[2] Small Berries (DP# 373344, D. Spatz, no date specified).

In this assessment, the annual average surface water concentration (19.25 ppb) and the acute peak surface water concentrations (37.8 ppb) were used for chronic and acute dietary exposure assessments, respectively.

5.1.10 Food Residue Profile

Crop Field Trials

The proposed use on caneberries and bushberries is as a foliar application two times at 0.33 – 0.66 lb ai/A with a maximum of 1.33 lb ai/A/season with a PHI of 0 days. Since adjuvants were not used in the submitted residue field trials, the label should prohibit such uses on caneberries and bushberries.

The data-collection method used to generate residue data in conjunction with magnitude of the residue studies associated with this petition is HPLC-MS/MS Method DGM C05/98-0. Berries were extracted with acetone and the extraction solution filtered, diluted and placed into HPLC vials. The adequacy of the method for data collection was verified by fortifying control samples of caneberries and bushberries with pyrimethanil that bracketed the measured residue levels. Method recoveries were within the acceptable range of 70-120% for all fortified samples. The limit of quantitation (LOQ) and limit of detection (LOD) were reported as 0.05 ppm and 0.0084 ppm in blueberry, and 0.05 ppm and 0.012 ppm in caneberry, respectively.

The caneberry and blueberry samples analyzed in this study were held in frozen storage for a maximum of 353 and 348 days (~12 months), respectively, prior to analysis of pyrimethanil residues. Previously submitted freezer storage stability data indicated that residues of pyrimethanil were stable for 12 months in lettuce, grape, carrot, tomato and for 22 months in apple. The existing storage stability data are adequate to support the submitted residue field trials.

The submitted field trial residue data for blackberry, raspberry, and blueberry are adequate. The field trial data reflect the proposed use pattern, an adequate number of trials were conducted in the appropriate geographic regions, and samples were analyzed for the residue of concern using validated data-collection methods. Blackberries and raspberries are the representative commodities for caneberries and blueberries are the representative commodity for bushberries. Using the maximum residue limit (MRL) spreadsheet for the residue data sets indicate that the requested tolerances of 12 ppm for caneberries and 6.0 ppm for bushberries are appropriate. ARIA recommends for the requested tolerances. However, a revised Section F is required to correct the commodity definitions to caneberry, crop subgroup 13-07A and bushberry, crop subgroup 13-07B.

There are no processed food items of regulatory interest for caneberries or bushberries. However, the petitioner has submitted a washing and cooking study on blueberries. Washing berries did not significantly change the pyrimethanil residues (washing processing factor of 1.0X). Washing and cooking berries reduced the pyrimethanil residues by a factor of 0.7X. There are no theoretical concentration factors for blueberry commodities.

There are no livestock food/feed items of regulatory concern for caneberries and bushberries; therefore, a discussion of livestock residues is not germane to this petition.

Analytical standards for pyrimethanil, with an expiration date 9/1/08, are currently available in the EPA National Pesticide Standards Repository. Standards for the regulated metabolites (AEC614276 and AEC614277) are not available and should be submitted; however, this is not a deficiency for this petition.

Caneberries and bushberries are typically not rotated. Therefore, residue data pertaining to confined and field accumulation in rotational crops are not germane to this tolerance petition.

Table 5.1.10. Summary of Residue Data from Crop Field Trials with Pyrimethanil.

Commodity	Total Applic. Rate (lb ai/A) (kg ai/ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT*	Median	Mean	Std. Dev.
Caneberry	1.413-1.450 (1.583-1.626)	0	10	1.50	8.46	8.38	2.30	3.34	2.69
Blueberry	1.419-1.441 (1.590-1.615)	0	16	1.05	5.76	5.13	2.00	2.25	1.22

*HAFT = highest-average field trial; NA = not applicable to this submission.

Food Processing Study

There are no processed food items of regulatory interest for caneberries or bushberries. However, the petitioner has submitted a washing and cooking study on blueberries. Washing berries did not significantly change the pyrimethanil residues (washing processing factor of 1.0X). Washing and cooking berries reduced the pyrimethanil residues by a factor of 0.7X. There are no theoretical concentration factors for blueberry commodities.

5.1.11 International Residue Limits

There are no Codex, Canadian, or Mexican MRLs established for pyrimethanil *per se* in/on caneberries or bushberries; therefore, there are no international harmonization issues for this action.

5.2 Dietary Exposure and Risk

Unrefined acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using DEEM-FCID™, Version 2.03 which use food consumption data from the U.S. Department of Agriculture's CSFII from 1994-1996 and 1998. The analyses were performed to support Section 3 requests for the proposed new uses/tolerances of pyrimethanil in/on caneberry and bushberry.

5.2.1 Acute Dietary Exposure/Risk

The unrefined acute assessment assumed that pyrimethanil residues are present in all commodities at tolerance levels and that 100% of all crops are treated. DEEM-FCID™

Version 7.81 default processing factors were used as necessary when empirical processing factors were not available. Drinking water was incorporated directly into the dietary assessment using the EDWCs generated by the PRZM/EXAMS and SCI-GROW water models.

The resulting acute dietary exposure estimates for food and water combined are below ARIA's level of concern (i.e., <100% of the aPAD) for the general U.S. population and all population subgroups at the 95th percentile of the exposure distribution. Using the DEEM-FCID™ software, dietary exposure is estimated at 10% of the aPAD for the general U.S. population, 35% of the aPAD for all infants <1 years old, the population subgroup with the highest estimated acute dietary exposure to pyrimethanil and 13% of the aPAD for the females 13-49 years of age population. Therefore, the acute dietary risk assessment shows that for all included commodities plus drinking water, the acute dietary risk estimates are below ARIA's level of concern for the general population subgroups and females 13-49 years of age (i.e., <100% aPAD).

5.2.2 Chronic Dietary Exposure/Risk

The unrefined acute and chronic assessments assumed that pyrimethanil residues are present in all commodities at tolerance levels and that 100% of all crops are treated. DEEM™ Version 7.81 default processing factors were used to estimate residues in all commodities as appropriate when empirical processing factors are not available. As in the acute scenario, drinking water was incorporated directly into the chronic dietary assessment using the EDWC values generated by the PRZM/EXAMS and SCI-GROW ground water models.

The resulting chronic dietary exposure estimates for food and water combined are well below ARIA's level of concern (i.e., <100% of the cPAD) for the overall U.S. population and all population subgroups. Using the DEEM-FCID™ software, dietary exposure is estimated at 13% of the cPAD for the general U.S. population and 63% of the cPAD for children 1 to 2 years old, the population subgroup with the highest estimated chronic dietary exposure to pyrimethanil. The chronic dietary risk assessment shows that for all included commodities plus drinking water, the chronic dietary risk estimates are below ARIA's level of concern (i.e., <100% cPAD).

Table 5.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Pyrimethanil.

Population Subgroup	Acute Dietary[1] 95th Percentile			Chronic Dietary[1]		
	aPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% aPAD	cPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	1.0 mg/kg bw/day	0.097137	10	0.17 mg/kg bw/day	0.022760	13
All Infants (< 1 year old)		**0.349212**	**35**		0.091462	54
Children 1-2 years old		0.336156	34		**0.107312**	**63**

Table 5.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Pyrimethanil.

Population Subgroup	Acute Dietary[1] 95th Percentile			Chronic Dietary[1]		
	aPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% aPAD	cPAD (mg/kg/day)	Dietary Exposure (mg/kg/day)	% cPAD
Children 3-5 years old		0.244965	25		0.074166	44
Children 6-12 years old		0.128114	13		0.033824	20
Youth 13-19 years old		0.060222	6		0.013439	8
Adults 20-49 years old		0.052651	5		0.012208	7
Adults 50+ years old		0.063148	6		0.016648	10
Females 13-49 years old	0.45 mg/kg bw/day	0.057385	13		0.013376	8

[1] Population subgroups with the highest exposure and risk are in **bold type**. %aPAD and %cPAD are shown to nearest whole number.

5.2.3 Cancer Dietary Risk

Relating to the carcinogenic potential of pyrimethanil, it is classified as "a Group C carcinogen" based on thyroid follicular cell tumors in both sexes of the 2-year rat study. The Agency has determined that cancer dietary risk concerns due to long-term consumption of pyrimethanil residues are adequately addressed by the chronic dietary exposure analysis using the reference dose. A separate cancer dietary assessment was not conducted for pyrimethanil as the chronic assessment is considered protective for carcinogenic effects.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Currently, there are no registered/proposed uses of pyrimethanil that result in residential exposures. Therefore, a residential exposure assessment was not performed.

6.1 Other (Spray Drift, etc.)

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 the ground application method employed for pyrimethanil. 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. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that should 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 with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessment and Risk Characterization

The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Since there are no registered/proposed uses of pyrimethanil that result in residential exposures, the acute and chronic aggregate risk assessments are equal to the acute dietary and chronic dietary estimates (food and water only), respectively.

7.1 Acute Aggregate Risk

No acute residential/recreational exposures are expected. In the case of pyrimethanil, the acute aggregate risk is composed of exposures to pyrimethanil residues in food and drinking water and is equivalent to the acute dietary risk discussed in Section 5.2. As shown in Table 5.2, the acute risk estimates do not exceed the Agency's level of concern for the general U.S. population and all population subgroups.

7.2 Short- and Intermediate-Term Aggregate Risk

Pyrimethanil is not registered for residential uses. Therefore, short- and intermediate term residential exposures are not expected.

7.3 Long-Term Aggregate Risk

A long-term aggregate risk assessment was not performed, because long-term residential exposure to pyrimethanil (i.e., >6 months) is unlikely to occur based upon the use patterns. Specifically, in the case of pyrimethanil, the chronic aggregate risk is composed of exposures to pyrimethanil residues in food and drinking water and is equivalent to the chronic dietary risk discussed in Section 5.2. As shown in Table 5.2, the chronic risk estimates do not exceed the Agency's level of concern for the general U.S. population and all population subgroups.

7.4 Cancer Risk

Pyrimethanil is classified as a Group C carcinogen based on thyroid follicular cell tumors in both sexes of the 2-year rat study (NOAEL = 17 mg/kg/day); the CPRC recommended the MOE approach (i.e., threshold consideration; MOE = NOAEL ÷ chronic exposure) when assessing risk because there appeared to be sufficient evidence for relating thyroid tumors in the rat to a disruption of the thyroid-pituitary status (see TXR No. 0052257 for full discussion). A separate cancer dietary assessment was not conducted for pyrimethanil as the chronic assessment is considered protective for carcinogenic effects.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for pyrimethanil and any other substances, and pyrimethanil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has assumed that pyrimethanil does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

The proposed new uses were evaluated in the cited memorandum and the resulting occupational exposure/risks were reviewed by the HED Science Advisory Council for Exposure (ExpoSAC; DP# 362618, M. Dow, 07/APR/2009).

9.1 Handler Risk

Based upon the proposed use pattern, ARIA/RD believes the most highly exposed occupational pesticide handlers will be 1) mixer/loaders using open-pour loading of liquid formulation, 2) applicators using open-cab ground-boom sprayers, 3) applicators using open cab airblast sprayers, 4) aerial applicator and 5) "chemigators" i.e., those person involved in "setting up" an irrigation system to include injection of the pesticide.

Persons involved in preparing irrigation systems to simultaneously apply a pesticide (chemigation) are not formally assessed. Typically, such systems are essentially closed systems where concentrate is metered into the irrigation stream. Chemigators are not expected to be more highly exposed than are mixer/loaders using open-pour loading of liquids. Therefore, estimates of exposure and risk to mixer/loaders are adequate to describe exposure and risk to chemigators.

Occupational handlers are expected to be exposed to short-term duration exposures (1 - 30 days). Private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. The ExpoSAC procedure directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as

hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available PHED and other exposure data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, ground-boom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED/RD determine the most appropriate levels of personal-protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical-resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical-specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" **and the use of protective gloves** or other PPE as might be necessary.

The product label directs applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and water-proof gloves in Category A (such as butyl rubber, natural rubber, neoprene rubber or nitrile rubber), all $\geq$ 14 mils.

The toxicological parameters used in this risk assessment are taken from the HED Toxicological Endpoint Selection (TES) Module (dedicated database) 14/JUN/2008 and from DP# 362617 dated 10/MAR/2009. The occupational short-term and intermediate-term dermal toxicological POD is identified from a rat reproduction study where the toxic effects identified were decreases in body weight and body weight gain in adult animals. The NOAEL is 23.1 mg ai/kg bw/day. The level of concern is for MOEs < 100.

A dermal absorption factor of 51% was identified from an *in vivo* dermal absorption study in the rat (MRID 46630101; Pers. Comm., DP# 362617, P.V. Shah, 10/MAR/2009). Previously, the HED had used a dermal absorption factor of 37.2 % (DP# 322065, K. Lowe, 04/JAN/2007) based on a preliminary review of MRID 46630101. However, upon subsequent review, HED concluded that 51% is the appropriate dermal absorption factor for use in risk assessment.

The short- and intermediate-term inhalation toxicological POD is identified from the same study as the dermal POD. The NOAEL is 23.1 mg ai/kg bw/day and the toxic effects are the same as those identified for the dermal POD. HED and RD assume 100% absorption via the inhalation route of exposure. The level of concern for inhalation exposure is a MOE < 100.

Pyrimethanil is classified as a Group "C" – possible human carcinogen. A MOE method is recommended for use in risk assessment. See Table 9.1 for a summary of estimated

exposures and risks to occupational pesticide handlers. Since chronic or long-term exposures are not expected for the proposed uses, a cancer risk assessment is not necessary.

Table 9.1. Summary of Exposure & Risk to Occupational Handlers From Applying Pyrimethanil

Unit Exposure[1] mg ai/lb handled	Applic. Rate[2] lb ai/unit	Units Treated[3]	Avg. Daily Exposure[4] mg ai/kg bw/day	NOAEL[5] mg ai/kg bw/day	MOE[6]
Mixer/Loader - Liquid - Open Pour					
Dermal: SLNoGlove 2.9 SLWithGlove 0.023 Inhal. 0.0012	0.33 lb ai/A	350 A/day	Dermal: SLNoGlove 2.44 SLWithGlove 0.019 Inhal. 0.00198	23.1	No Glove 10 With Glove 1,100
Applicator - Ground-boom - Open-cab					
Dermal: SLNoGlove 0.014 SLWithGlove 0.014 Inhal. 0.00074	0.33 lb ai/A	80 A/day	Dermal: SLNoGlove 0.0027 SLWithGlove 0.0027 Inhal. 0.000279	23.1	No Glove 7,750 With Glove 7,750
Applicator - Air-blast - Open Cab					
Dermal: SLNoGlove 0.36 SLWithGlove 0.24 Inhal. 0.0045	0.33 lb ai/A	40 A/day	Dermal: SLNoGlove 0.0346 SLWithGlove 0.0231 Inhal. 0.00085	23.1	No Glove 650 With Glove 960
Aerial Applicator (Pilots not required to wear gloves)[7]					
Dermal: SLNoGlove 0.005 Inhal. 0.000068	0.33 lb ai/A	350 A/day	Dermal: SLNoGlove 0.00421 Inhal. 0.000112	23.1	No Glove 5300

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE," Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from draft product labeling provided by Bayer.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; ExpoSAC SOP No. 9.1. Revised 5 July 2000.
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated * absorption (51% dermal absorption; 100 % inhalation absorption) ÷ 70 kg Body Weight.
5. NOAEL = No-Observable Adverse-Effect Level.
6. MOE = Margin of Exposure = NOAEL ÷ ADD.
7. Only e.c. data are available for aircraft operators (enclosed cockpit = engineering control).

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to pyrimethanil. Provided mixer/loaders wear protective gloves as directed by the label, the estimated MOEs are all > 100. Therefore, the proposed new uses do not exceed RD's level of concern.

9.2 Postapplication Risk

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified transfer coefficients (TC) (cm^2/hr) relative to the various activities which express the amount of foliar contact over time, during each

of the activities identified. The highest (i.e., most conservative) TC for the proposed new uses is 1,100 cm^2/hr for hand harvesting. As a "screening" level assessment, RD herein uses the TC of 1,100 cm^2/hr which is for hand harvesting. The TC is appropriate to use since the product may be applied up until harvest.

NOTE: The TC, in this case, is based upon proprietary study data (MRID 46405901) from the ARTF. The data may NOT be used to support registrations requested by registrants who are not members, in good standing, of the task force. Bayer CropScience LP is a member of the ARTF thus not subject to issues of data compensation.

The TCs used in this assessment are from an interim TC SOP developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20% of the application rate is available as dislodgeable foliar residue on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/μg * 1/70 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54×10^8 $\mu g/lb$ * 2.47×10^{-8} A/cm^2.

0.33 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54×10^8 $\mu g/lb$ * 2.47×10^{-8} A/cm^2 = 0.74 $\mu g/cm^2$, therefore,

0.74 $\mu g/cm^2$ * 1,100 cm^2/hr * 8 hr/day * 0.001 mg/μg * 0.51 (51 % dermal absorption) ÷ 70 kg bw = 0.0474 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 23.1 mg/kg bw/day ÷ 0.0474 mg/kg bw/day = **490.**

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The most conservative estimate (i.e., highest exposure/risk) of post-application exposure results in MOEs > 100. Therefore, the proposed risk does not exceed ARIA/RD's level of concern.

As noted earlier, HED expects that typically, the proposed use patterns will result in short- and intermediate-term exposures. Since the expected exposures are not likely to be long-term, a cancer risk assessment is not needed.

9.3 Restricted Entry Interval (REI)

The Interim Worker Protection Standard (WPS) Restricted Entry Interval of 12 hours is adequate to protect agricultural workers re-entering the proposed crop use sites. For the uses covered by the WPS, the label REI is 12 hours.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

- Mouse carcinogenicity study was requested by the DART (TRX# 0050408, J. Kidwell, 24/APR/2003) because the high dose in the existing study was judged to be inadequate for assessing the carcinogenic potential of pyrimethanil. This requirement has not been fulfilled.
- Immunotoxicity study (required as a result of the revisions to 40 CFR §158)

10.2 Residue Chemistry

- Adjuvants were not used in any of the submitted residue field trials. Since adjuvants were not used in the submitted residue field trials, the label should prohibit such uses on caneberries and bushberries.
- A summary of the recommended tolerances along with recommendations for commodity definitions are presented in Table 1.0. The petitioner is required to submit a revised Section F to reflect the recommendations in Table 1.0.

10.3 Occupational and Residential Exposure

None

11.0 References:

DP# 361301, D. Rate, 05/MAR/2009
DP# 284866, D. Vogel, 15/NOV/2004
TXR#: 0052257, P.V. Shah, 02/DEC/2003
TXR#: 0050408, J. Kidwell, 24/APR/2003
TXR: 0050189, Y. Yang and E. Rinde, 11/FEB/1997
DP# 322065, P.V. Shah, 23/FEB/2009
DP# 284001, J. Morales and G. Kramer, 12/JAN/2004
DP# 288256, E. Kolbe, 07/JUL/2004
DP# 353180, M. Corbin, 08/JAN/2009
DP# 373344, D. Spatz, no date
DP# 372647, W. Cutchin, 02/FEB/2010

DP# 402624, W. Cutchin, 02/FEB/2010
DP# 362618, M. Dow, 07/APR/2009

Appendix A: Toxicity Profile Tables

Table A.1. Acute Toxicity Profile – Pyrimethanil.

Guideline No./Study Type	MRID No.	Results	Toxicity Category
870.1100/Acute oral toxicity	43345002	LD_{50} = 4149 mg/kg, M 5971 mg/kg, F	III
870.1200/Acute dermal toxicity	43345003	LD_{50} >5000 mg/kg	IV
870.1300/Acute inhalation toxicity	43301604	LC_{50} >1.98 mg/L	III
870.2400/Primary eye irritation	43345004	slight eye irritant	IV
870.2500/Primary dermal irritation	43345005	non irritant	IV
870.2600/Dermal sensitization	43301605	not a sensitizer	

Table A.2. Toxicity Profile for Pyrimethanil.

Guideline No./Study Type	MRID, (year)/ Classification/Doses	Results
870.3100(a) 90-Day Oral Toxicity (rat)	43345006 43301608 (1990, 1992)/ acceptable/guideline 0, 80, 800, 8000 ppm 0/0, 5.4/6.8, 54.5/66.7, 529.1/625.9 mg/kg/day [M/F]	NOAEL = 54.5 mg/kg/day [M], 66.7 mg/kg/day [F] LOAEL = 529.1 mg/kg/day [M], 625.9 mg/kg/day [F] based on ↓ body weights (20%), body-weight gain(30%), food consumption, brown urine, ↑ urinary protein; ↓ abs. heart, adrenal, spleen, thymus wts; ↑ rel. liver kidney, gonad wts, liver, thyroid hypertrophy.
870.3100(b) 90-Day Oral Toxicity (mouse)	43301606 (1991) acceptable/guideline 0, 80, 900, 10,000 ppm 0/0, 12/18, 139/203, 1864/2545 mg/kg/day [M/F]	NOAEL = 139 [M] mg/kg/day, 203 [F] mg/kg/day LOAEL = 1864 [M] and 2545 [F] mg/kg/day based on ↓ body-weight gain (7-12%),↑cholesterol, bilirubin [F/M], dark thyroids, ↑rel. liver weights, kidney, thyroid, bladder histopathology.
870.3150 90-Day Oral Toxicity (dog)	43301610 (1991) acceptable/guideline 0, 6, 80, 1000/800 mg/kg/day [M/F]	NOAEL = 80 mg/kg/day LOAEL = 1000/800 mg/kg/day based on ↓ water consumption, vomiting, diarrhea, salivation, hypoactivity.
870.3700(a) Developmental Toxicity (rat)	43301617 43345018 43301619 (1991) acceptable/guideline 0, 7, 85,1000 mg/kg/day	NOAEL = Maternal: 85 mg/kg/day Developmental: 85 mg/kg/day LOAEL = Maternal: 1000 mg/kg/day based on ↓ body weight, and body-weight gain. Developmental: LOAEL = 1000 mg/kg/day based on ↓ in mean litter weight and mean fetal weight.
870.3700(b) Developmental Toxicity (rabbit)	43301620 43301621 43301622 (1991) acceptable/guideline 0, 7, 45, 300 mg/kg/day	NOAEL = Maternal: 45 mg/kg/day Developmental NOAEL: 45 mg/kg/day LOAEL = Maternal: 300 mg/kg/day based on deaths, ↓ body wt, body wt gain, food consumption, production and size of fecal pellets. Developmental: 300 mg/kg/day based on deaths, ↓ body wt, body wt gain, food consumption, production and size of fecal pellets↓ fetal weight, ↑ fetal runts,

Table A.2. Toxicity Profile for Pyrimethanil.

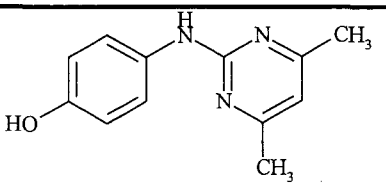
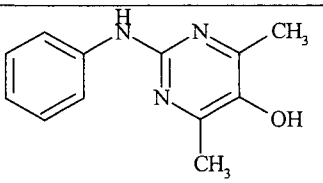
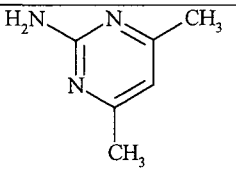
Guideline No./Study Type	MRID, (year)/ Classification/Doses	Results
		retarded ossification, 13 thoracic vertebrae and pairs of ribs.
870.3800 Two-Generation Reproduction and Fertility Effects (rat)	43301623 (1993) acceptable/guideline 0, 32, 400,or 5000 ppm 0/0,1.9/2.2,23.1/27.4, 294/343 mg/kg/day [M/F]	NOAEL = Systemic: 23.1 [M] mg/kg/day, 27.4 mg/kg/day [F] Repro: 294/343 mg/kg/day Offspring: 23.1 mg/kg/day [M], 27.4 mg/kg/day [F] LOAEL = Systemic: 294 mg/kg/day [M], 343 mg/kg/day [F] based on ↓ body weight (11-13%), and body-weight gain (11-17%) Repro: > 294/343 mg/kg/day Offspring: 294 mg/kg/day based on ↓ pup body weights on PND 21.
870.4100b Chronic Toxicity (dog)	43345007 43301614 (1992) acceptable/guideline 0, 2, 30, 400/250 mg/kg/day	NOAEL = 30mg/kg/day LOAEL = 250 mg/kg/day based on ↓ body weight, food & water consumption, food efficiency, ↑neutrophils, ↓ clotting time.
870.4200b Carcinogenicity (mouse)	43301615 (1992) unacceptable/guideline 0, 16, 160, 1600 ppm 0/0, 2/2.5, 20/24.9, 210.9/253 mg/kg/day [M/F]	NOAEL = 210.9 mg/kg/day [M], 253.8 mg/kg/day [F] No toxicologically significant effects were found.
870.4300 Combined Chronic/Carcinogenicity (rat)	43301612-3 (1993)/ acceptable/guideline 0, 32, 400, 5000 ppm 0/0, 1.3/1.8, 17/22, 221/291 mg/kg/day [M/F]	NOAEL = 17 mg/kg/day [M], 22 mg/kg/day [F] LOAEL = 221 mg/kg/day [M], 291 mg/kg/day [F] based on ↓ body-weight gain (5-15% [M]; 15-45% [F]) [10-15%@ 6 mos],↑ serum cholesterol, GGT, rel. liver weights; liver, thyroid histopathology [↑ thyroid adenomas].
870.6200a Acute-Neurotoxicity Screening Battery (rat)	45657221 45657220 (2001) acceptable/guideline 0, 30, 100, 1000 mg/kg/day	NOAEL = 100 mg/kg/day [M], 100 mg/kg/day [F] LOAEL = 1000 mg/kg/day [M], 1000 mg/kg/day [F] based on ↓ motor activity, ataxia, and ↓body temperature in both sexes, ↓ hindlimb grip strength in males, and ↑ dilated pupils in females on Day 1.
870.6200b Subchronic-Neurotoxicity Screening Battery (rat)	45657222 (1998) unacceptable/ guideline 0, 60, 600, 6000 ppm 0/0, 4/4.6, 38.7/44.3, 391.9/429.9 mg/kg/day [M/F]	NOAEL = 44.3 mg/kg/day [F] LOAEL = 429.9 mg/kg/day [F],> 391.9 mg/kg/day [M] based on ↓ body wt (8%), body wt gain (21%), food consumption (9-15%) [F]. No effects in males.
870.5100 Gene Mutation	43301624 (1990); 0, 15, 50, 150, 500 or 1500 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix) Acceptable/Guideline	There was no evidence of induced mutant colonies over background.
870.5300	43301625 (1991);	

Gene Mutation	0, 15, 50, 150, 500 or 1500 µg/plate in the presence and absence of mammalian metabolic activation (S9-mix) Acceptable/Guideline	There was no clear evidence of biologically significant induction of mutant colonies over background.

870.5375 Chromosome aberration	43301627 (1990); 0, 7.8, 31.3, or 62.5 µg/mL without metabolic activation (S9-mix) and to concentrations of 0, 31.3, 125 or 250, µg/mL with S9-mix. Acceptable/Guideline	There was no evidence of chromosome aberrations induced over background.
870.5395 Mammalian erythrocyte micronucleus test in mice	43301626 (1991); 0, 225, 450 or 900 mg/kg body weight Acceptable/Guideline	There was no statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in mouse bone marrow at any dose or harvest time.
870.5550 Unscheduled DNA synthesis in mammalian culture	43301628 (1991) 0, 100, 300 or 1000 mg/kg body weight Acceptable/Guideline	Negative in inducing unscheduled DNA synthesis in rat hepatocytes as a result of *in vivo* gastric intubation.

Appendix B: Metabolism Assessment

Table B.1. Pyrimethanil Metabolites of Concern.

Common name/ ID No.	Chemical name	Chemical structure
AE C614276	4-[4,6-dimethyl-2-pyrimidinyl)amino]phenol	
AE C614277	4,6-dimethyl-2-(phenylamino)-5-pyrimidinol	
Degradate 1	2-amino-4,6-dimethylpyrimidine.	

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Chemical Name: Pyrimethanil

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