Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2006-04

Pyrimethanil

The reduced-risk technical grade active ingredient pyrimethanil and associated end-use product Scala SC Fungicide (containing 400 grams pyrimethanil per litre) have been granted temporary registration under the Pest Control Products Regulations for the control of apple and pear scab, *Botrytis cinerea* and *Penicillium* spp. storage diseases on apples, Botrytis bunch rot on grapes, *Botrytis cinerea* on strawberries and early blight on potatoes.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Bayer CropScience's reduced-risk active ingredient pyrimethanil and the associated end-use product Scala SC Fungicide for the control of apple and pear scab, *Botrytis cinerea* and *Penicillium* spp. storage diseases on apples, Botrytis bunch rot on grapes, *Botrytis cinerea* on strawberries and early blight on potatoes.

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value. The Agency has concluded that the use of pyrimethanil and the associated end-use product Scala SC Fungicide for control of apple and pear scab, *Botrytis cinerea* and *Penicillium* spp. storage diseases on apples, Botrytis bunch rot on grapes, *Botrytis cinerea* on strawberries and early blight on potatoes in accordance with the label has merit and value consistent with the Pest Control Product Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of pyrimethanil and the associated end-use product Scala SC Fungicide for control of apple and pear scab, *Botrytis cinerea* and *Penicillium* spp. storage diseases on apples, Botrytis bunch rot on grapes, *Botrytis cinerea* on strawberries and early blight on potatoes have been granted temporary registration, under the Pest Control Products Regulations.

Methods for analyzing pyrimethanil environmental media are available to research and monitoring agencies upon request to the PMRA.

Bayer CropScience Inc. will be carrying out confirmatory studies as a condition of temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document (PRDD) and request comments from interested parties before proceeding with a final regulatory decision.

A summary of the Agency's findings in support of this decision is found in this Regulatory Note.

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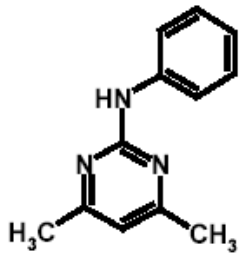
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substance and Impurities

1.1.1 Identification of the Technical Grade Active Ingredient

Active substance	Pyrimethanil
Function	Fungicide
Chemical name	
IUPAC	*N*-(4,6-dimethylpyrimidin-2-yl)aniline
CAS	4,6-dimethyl-*N*-phenyl-2-pyrimidinamine
CAS number	53112-28-0
Molecular formula	$C_{12}H_{13}N_3$
Molecular weight	199.28
Structural formula	
Nominal purity of active ingredient	98% (limits: 96–100%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade pyrimethanil does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.

1.2 Physical and Chemical Properties of Active Substances and End-Use Product(s)

Technical Product—Pyrimethanil

Property	Result	Comment
Colour and physical state	Off-white, crystalline powder	
Odour	Almost odourless	
Melting point or range	96.3°C	
Boiling point or range	Not applicable	
Density	1.15 g/mL at 20°C	
Vapour pressure at 20°C	1.1×10^{-3} Pa	
Henry's law constant at 20°C	$K = 3.58 \times 10^{-8}$ atm m^3/mol or $1/H = 6.84 \times 10^5$	The active ingredient is non-volatile from water or moist soil. Calculated by the reviewer.
Ultraviolet (UV)—visible spectrum	No UV absorption above 290 nm	
Solubility (g/L) in water at 20°C	**pH** **Solubility** 4.2 0.160 6.1 0.121 9.9 0.099	
Solubility (g/L) in organic solvents at 25°C	**Solvent** **Solubility** Dichloromethane 1000 Ethyl acetate 617 Toluene 412 Acetone 389 Methanol 176 n-Hexane 24	
n-octanol–water partition coefficient (K_{ow})	log K_{ow} = 2.84 at 25°C	
Dissociation constant (pK_a)	3.52 at 20°C	
Stability (temperature)	Stable at 54ºC for 14 days	

End-Use Product—Scala Brand SC Pyrimethanil Fungicide

Property	Result
Colour	Beige
Odour	Negligible
Physical state	Liquid
Formulation type	Aqueous suspension
Guarantee	400 g/L (limits: 388–412 g/L)
Formulants	The product does not contain any United States Environmental Protection Agency (USEPA) List 1 or 2 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	High density polyethylene bottles or drums
Density	1.065 g/mL at 20°C
pH of 1% dispersion in water	7.4 at 20°C
Oxidizing or reducing action	The product does not contain components with oxidizing or reducing properties.
Storage stability	Stable under ambient conditions (39 months at 25°C) when stored in high density polyethylene packaging.
Explodability	The product does not contain components with explosive properties.

1.3 Details of Uses

Scala SC Fungicide is an aqueous suspension concentrate (SC) that contains 400 grams of pyrimethanil per litre. Scala SC is proposed for the control of apple and pear scab, Botrytis bunch rot on grapes, Botrytis grey mould on strawberries and early blight on potatoes. The proposed application rates range from 0.75 to 2.0 litres of product per hectare (300–800 g a.i./ha), applied from one to six times per season per disease, and preharvest intervals (PHIs) of 1 to 72 days. Minimum proposed carrier volumes are 300 L/ha for vegetable crops and 1000 L/ha for fruit crops.

According to the Fungicide Resistance Management Action Committee (FRAC) this active ingredient falls within the anilinopyrimidine (Group 9) family of fungicides, which are rated as having a medium risk of resistant strains developing if restrictions are not placed on their use. Resistance to Group 9 Fungicide has been documented in strains of *Botrytis* (causative agent of bunch rot and grey mould) and *Venturia* (causative agent of scab).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Substance as Manufactured

An isocratic reverse phase high performance liquid chromatographic (HPLC) method of analysis is used to determine the active substance in the technical product. Three HPLC methods, i.e., gas chromatographic (GC), UV/VIS spectroscopic and ion chromatographic method, are used to determine the significant related impurities present at > 0.1% in the technical product. Validation data for method specificity, linearity, accuracy and precision were submitted. The HPLC method used for the determination of the active ingredient was assessed to be precise with a relative standard deviation of 0.23% as well as specific as demonstrated by the absence of interferences at the retention time of the analyte. The various methods used for the determination of impurities were shown to be specific, precise with a relative standard deviation ranging from 1.24 to 7.3% and sensitive, with limits of detection (LOD) ranging from 0.005% to 0.09%. Recoveries of impurities ranged from 71.7% to 99.5%.

2.2 Method for Formulation Analysis

An isocratic HPLC method of analysis is used to determine the active substance in the formulation. Quantitation of the active was by external standard. The analytical method for the determination of the active in Scala SC Fungicide is shown to be linear over a range of 1.6–12 mg/ 100 mL, precise with a relative standard deviation of 0.90% and accurate as demonstrated by a mean recovery of 99.3% (n = 5). The specificity was shown by the absence of analytical interferences at the retention time of the analyte. The method is assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

2.3.1 Multiresidue Methods for Residue Analysis

Pyrimethanil Residues in Plant Matrices

The behaviour of pyrimethanil through the multiresidue methods (MRMs) was evaluated using the Multiresidue Protocols A through G of the United States Food and Drug Administration *Pesticide Analytical Manual* (PAM), Volume 1. Pyrimethanil was not evaluated through Protocols A and B because it does not possess an N-methylcarbamate structure (Protocol A) or a carboxylic acid or phenolic moiety (Protocol B). The results from Protocol C (gas chromatographic screening) indicated that pyrimethanil

chromatographed with a reasonable relative retention time (rrt_c) of 0.67 (relative to chlorpyrifos). Furthermore, pyrimethanil displayed no response on the electron capture detector, but when using a nitrogen phosphorus detector, pyrimethanil produced a 50% full scale deflection (FSD) when 0.6 ng was injected in the instrument (compared to 1.9 ng for chlorpyrifos to produce the same size peak). Pyrimethanil was completely eluted from Florisil (only in 50% ethyl ether:petroleum ether or methylene chloride eluant #3). Pyrimethanil was completely recovered from grape samples using Protocol D with average recoveries of 133.4% at the 0.05 ppm spiking level and 112.8% at the 5.0 ppm spiking level. Protocol D was suitable for the analysis of pyrimethanil residues in non-fatty foods. Under Protocol E, very poor recoveries (0% for the 0.05 ppm spiking level and 12.8% for the 5.0 ppm spiking level) were observed from grape samples when using the ethyl ether:petroleum ether elution system and poor recoveries (60.0% for 0.05 ppm spiking level and 49.2% for 5.0 ppm spiking level) were also observed when using the methylene chloride elution system. Protocol E was not suitable for the analysis of pyrimethanil residues in non-fatty foods. Under Protocol F, no recovery was obtained from cottonseed oil spiked at 0.05 ppm using either of the two elution systems. At the 5.0 ppm spiking level, average recoveries were 28% when using the ether elution system and 78% when using the methylene chloride elution system. Accordingly, Protocol F was not suitable for the analysis of pyrimethanil residues in fatty foods. Pyrimethanil was not evaluated through Protocol G because it does not possess a substituted urea moiety. Protocol D of the United States Food and Drug Administration MRMs was shown to be suitable for the analysis of pyrimethanil in non-fatty foods.

Metabolite AN2 (AE C614276) and Metabolite AN3 (AE C614277) in Livestock Matrices

The behaviour of the two metabolites AN2 and AN3 through the MRMs was evaluated using the Multiresidue Protocols A through G of the United States Food and Drug Administration PAM Vol. 1. AN2 and AN3 were not evaluated through Protocol A because they do not possess an N-methylcarbamate structure. As both AN2 and AN3 have acid structures, they were evaluated through Protocol B. But first, AN2 and AN3 had to be tested under Protocol C to determine their chromatographic behaviours. AN2 demonstrated greater than 50% deflection in all the modules tested (DG1, DG5, DG13, DG17 and DG18) with reasonable relative retention times. AN3 demonstrated greater than 50% deflection in modules DG5 and DG17, in the other modules tested, 1000 ng of AN3 injected were not detected. AN3 showed reasonable relative retention times in all of the modules tested. As the test substances chromatographed with sufficient response and resolution under Protocol C, recovery data were obtained using Protocols B, D, E and F. Under Protocol B, the test substances were applied to a non-fatty matrix (skim milk) and a fatty matrix (cow muscle; ground beef). No recoveries were obtained for either matrix. Accordingly, Protocol B was not suitable for the analysis of residues of the metabolites AN2 and AN3 in non-fatty food (skim milk) and in fatty food (cow muscle). Under Protocol D, the average recoveries in skim milk samples were 70.4% for AN2 and 0% for AN3 at the 0.05 ppm spiking level and 60.5% for AN2 and 5.8% for AN3 at the 0.25 ppm spiking level. Protocol D was not suitable for the analysis of residues of the metabolites AN2 and AN3. The test substances were not evaluated through Protocols E and F because they were not recoverable from Florisil at a level above 30%. AN2 and

AN3 were not evaluated through Protocol G because they do not possess a substituted urea moiety. Multiresidue methods were shown to be unsuitable for the analysis of the two metabolites AN2 and AN3 in livestock matrices.

2.3.2 Methods for Residue Analysis of Plants and Plant Products

Based on the grape, apple, tomato, lettuce and carrot metabolism studies, the residue of concern (ROC) for enforcement and risk assessment purposes was defined as the parent, pyrimethanil. Method DGM C05/98-0, used for data gathering and proposed as the enforcement method, determined pyrimethanil residues in various fruit and vegetable crops.

Briefly, acetone was added to the sample, followed by homogenization. The sample was filtered under vacuum into a Büchner flask using filter paper. An aliquot of the filtrate was centrifuged for two minutes to separate layers. Aliquots of the extract were acidified then washed with hexane before basifying to enable solvent partitioning. The upper hexane layer was discarded, and the extract was washed with fresh hexane. Saturated sodium hydrogen carbonate was added by gentle agitation, followed by extraction with a solvent mixture (hexane/ethyl acetate, 3:1, v/v) by vigorous shaking or centrifugation. The partition was repeated with fresh solvent mixture and the organic layers were combined. The organic extract was dried at 50°C under dry nitrogen, then dissolved in hexane. Final clean-up was by elution through silica solid-phase extraction, followed by determination by gas chromatography with mass spectrometric detection (GC-MS). Pentachloro-benzene was used as an internal standard and a GC marker compound. The limit of quantitation (LOQ) for all plant matrices was reported to be 0.05 ppm.

Analytical method DGM C05/98-0 was validated adequately, with mean recoveries ranging from 74% to 100% (at 0.05 ppm spiking level) and from 79% to 94% (at 0.5 ppm spiking level) using a variety of fruit and vegetable matrices (potato, carrot, tomato, green bean, lettuce, sweet pepper, strawberry, raspberry, apple, grape and banana). An independent laboratory validation (ILV) was successfully completed using potatoes, grapes, lettuce as well as wheat grain and straw.

Residue analytical method DGM C05/98-0 was successfully radio-validated using lettuce leaves collected from the metabolism study as it was capable of extracting 95.8% of the total radioactive residues (TRRs). Furthermore, the method was able to extract the ROC component (pyrimethanil) at 81.3% of the TRRs (5.82 ppm). This result was comparable to the result observed in the nature of the residue study (77.2%; 5.53 ppm); thus, indicating that Method DGM C05/98-0 adequately extracted residues of bioincurred pyrimethanil from plant matrices.

Method DGM C05/98-0 is considered acceptable for the determination of pyrimethanil residues in plant matrices and can be used for enforcement.

2.3.3 Methods for Residue Analysis of Food of Animal Origin

In livestock tissues, the ROC for enforcement and risk assessment purposes was defined as pyrimethanil and metabolite AN2. In milk, the ROC was defined as pyrimethanil and metabolite AN3.

Background

Results from the dairy cow metabolism study showed that the predominant metabolite identified in milk and kidney was AN2 [2-(4-hydroxyanilino)-4,6-dimethylpyrimidine; also referred to as AE C614276], which was present as conjugates (glucuronide and/or sulfate conjugates). In muscle, renal fat and liver matrices, no ^{14}C-residues were characterized or identified. Accordingly, the original analytical methodology (RAM AN/01/01) targeted pyrimethanil and the major metabolite AN2. However, during the analytical phase of the dairy cow feeding study, an unknown compound was seen in milk samples at higher levels than metabolite AN2. This unknown compound was confirmed to be the metabolite, AN3 [2-anilino-4,6-dimethylpyrimidin-5-ol; also referred to as AE C614277]. Therefore, the original analytical method was modified such that the metabolite AN3 in milk samples may be analyzed.

Analytical Method RAM AN/01/01 Version 2 was developed for data gathering and enforcement purposes in order to determine residues of pyrimethanil, AN2 (AE C614276) in tissues and AN3 (AE C614277) in milk.

Briefly, homogenized livestock tissues (except fat) were extracted with acetonitrile/0.6M HCl (92:8, v/v). Fat samples were extracted with acetonitrile under reflux conditions. Milk samples were extracted with concentrated HCl/acetonitrile (1:50, v/v), centrifuged and filtered. The remaining milk solids were further extracted with pH 7 phosphate buffer/acetonitrile (1:1, v/v), centrifuged, filtered and extracted once more with acetonitrile. Following filtration, the extract (was acidified, fat tissue only) was adjusted to a known volume by addition of acetonitrile. An aliquot of the extract was partitioned three times into hexane to eliminate fat or oil that might still be present in the extract. The hexane fractions were discarded. The resulting extract was evaporated to dryness and reconstituted in methanol.

Enzyme Hydrolysis of Milk and Kidney Matrices

In milk and kidney matrices only, as the predominant metabolites were identified as conjugates (glucuronide and/or sulfate conjugates) of AN2 and AN3, the methanol extracts for these matrices were subjected to enzyme digestion with β-glucuronidase and sulfatase at 37°C overnight. The pH of the milk hydrolysate was adjusted to 7. Both milk and kidney hydrolysates were partitioned into ethyl acetate, evaporated to dryness and reconstituted in acetone.

Derivatization Step of All Extracts

All sample extracts were derivatized by methylation with TMSD [(trimethylsilyl)diazomethane] for an hour at 50–55°C. The samples were diluted to a known volume with ethyl acetate and were then quantitated by capillary gas chromatography with ion trap mass spectrometer (GC-MS/MS Ion Trap). Methylation converts AE C614276 (AN2) to AE C599789 (methylated AN2) and AE C614277 (AN3) to AE 0815072 (methylated AN3). The two methylated entities were the chromatographic targets of the GC-MS/MS analysis. The analysis of pyrimethanil residues used the precursor ion 198 m/z and the quantitation ion 182 m/z. For the methylated metabolites AE C599789 and AE 0815072, the precursor ion was 229.1 m/z and the quantitation ion was 214 m/z and/or 213 m/z. The LOQ was reported as 0.01 ppm in milk and as 0.05 ppm in livestock tissues for each analyte.

Method RAM AN/01/02 is the same method as RAM AN/01/01 Version 2 except it includes all the modifications and/or clarifications recommended by the independent laboratory.

Limited method validation data for pyrimethanil and the metabolite AN2 were generated during the development of Method RAM AN/01/01. When spiked at the LOQ (0.01 ppm for milk and 0.05 ppm for livestock tissues), the individual recoveries were within the guideline requirements of 70–120%. Method validation conducted concurrently with the cow feeding study indicated that when spiked at the LOQ, the recoveries of pyrimethanil, metabolite AN2 and metabolite AN3 (in milk only) were generally within the guideline requirement of 70–120%. However, standard deviations reached 25% in whole milk for pyrimethanil residues and 22% in kidney for AN2 residues. For the analysis of AN2 residues in muscle samples spiked at 0.05 ppm (LOQ), variable recoveries were observed (68%–137%). It was determined that Method RAM AN/01/01 Version 2 was not very robust. Based on the method validation data, Method RAM AN/01/01 Version 2 (or RAM AN/01/02) was considered conditionally acceptable for livestock matrices. To use Method RAM AN/01/01 Version 2 as the enforcement method for the analysis of residues of pyrimethanil and the metabolite AN2 in livestock tissues and metabolite AN3 in milk, the registrant must provide information describing the various conditions that may be implemented to optimize the method recoveries and provide new recovery data validating the implemented changes to the method in livestock matrices.

An ILV was conducted to verify the reliability and reproducibility of Method RAM AN/01/01 Version 2, for the determination of pyrimethanil and the two metabolites AN2 and AN3 in livestock matrices. Method RAM AN/01/01 Version 2 was successfully validated at the third attempt using milk and marginally successfully validated at the third attempt using muscle.

The extraction efficiency of the GC-MS analytical method RAM AN/01/01 Version 2 was evaluated using ^{14}C-spiked samples of beef kidney and milk. Approximately 67% and 103% of the bioincurred residues in beef kidney and milk, respectively, were extracted. Beef kidney and milk were considered the two most difficult matrices to analyze. In contrast, in the dairy cattle metabolism study, ~90% of the TRRs in these

matrices was extracted. The difference may be explained by the low levels of radioactivity in the spiked samples (0.130 ppm in kidney and 0.029 ppm in milk) used for the radio-validation experiment, which were generated separately and not taken from the original metabolism study. The overall accountability was considered acceptable.

3.0 Impact on Human and Animal Health

3.1 Effects Having Relevance to Human and Animal Health

3.1.1 Absorption, Distribution, Metabolism and Excretion

3.1.1.1 Rats

Rats (strain not specified; 3 males/group) were administered (^{14}C)-pyrimethanil (radiochemical purity 98%) orally once a day over a period of 28 days (10 mg/kg), with periodic sacrifices at days 1, 3, 5, 8, 11, 17, 23, 28 and 32 for residue analysis of organs/tissues. Detectable levels of radiolabel were found in the adrenals, blood, kidney, liver, spleen and thyroid following repeated exposure for 28 days. Only the blood and liver displayed detectable levels of radiolabel after a single dose (24-hour sample). On repeated dosing, detectable residues appeared in the kidney, thyroid and adrenals on dosing days 3, 17 and 23 respectively, with all other tissues below the level of quantification throughout. Four days after the last dose, detectable levels of radiolabel were found only in the liver, kidney and thyroid. It appeared that the levels in blood, kidney and thyroid continued to increase with increased exposure time, while the level in the adrenal appeared to have reached a plateau, and that residues in the liver appeared to be declining.

The majority (~97% low dose; ~65% high dose) of the administered dose of radiolabelled SN 100309 following single oral exposures to rats (Sprague-Dawley Crl:CD(SD)BR; 5/sex) at dose levels of 11.8 mg/kg or 800 mg/kg was eliminated within 24 hours; the major route of elimination was via the urine (74–76% at low dose; 65–67% at high dose). Approximately 21–23% of the low dose was excreted via the feces, and ~15–18% of the high dose was eliminated via the feces. Radiolabelled material was detected only in the liver and carcass following low dose exposure but was detected at the high dose in nearly all tissues measured (except the pituitary [all], eyes [4/5], and renal fat [2/5]). The concentration of radiolabel remaining in the liver (only organ for comparison) at 96 hours was dose-related. The highest residues were in the liver, kidney, thyroid and blood at the high dose. The overall recovery of radiolabel following single-dose exposures was > 94% at the high dose and > 101% at the low dose. No sex differences were observed. Tissue levels were measured at only one time point; therefore, no statement regarding bioaccumulation can be made.

Pyrimethanil technical was shown to be metabolized extensively in the Crl:CD(SD)BR rat (both sexes) following single oral doses of radiolabelled ^{14}C-pyrimethanil at 11.8 mg/kg or 800 mg/kg or 14 consecutive daily oral doses of unlabelled pyrimethanil at 10 mg/kg/day followed by a single (10 mg/kg) oral dose of ^{14}C-pyrimethanil. None of the parent compound, pyrimethanil, was found in the urine following any exposure regimen. In the feces, small amounts of parent material (~6%, ~4% and ~11% of total radiolabel in the low-, repeat low- and high-dose rats, respectively) were found following all exposures. The main pathways of metabolism involved oxidation to phenols in either or both aromatic rings, and the minor pathways involved oxidation of the methyl group to the corresponding alcohol. Minor differences in metabolism were observed between the high- and low-dose exposures, the single low-dose and repeat low-dose exposures and between the sexes, but none appear to be of any toxicological significance.

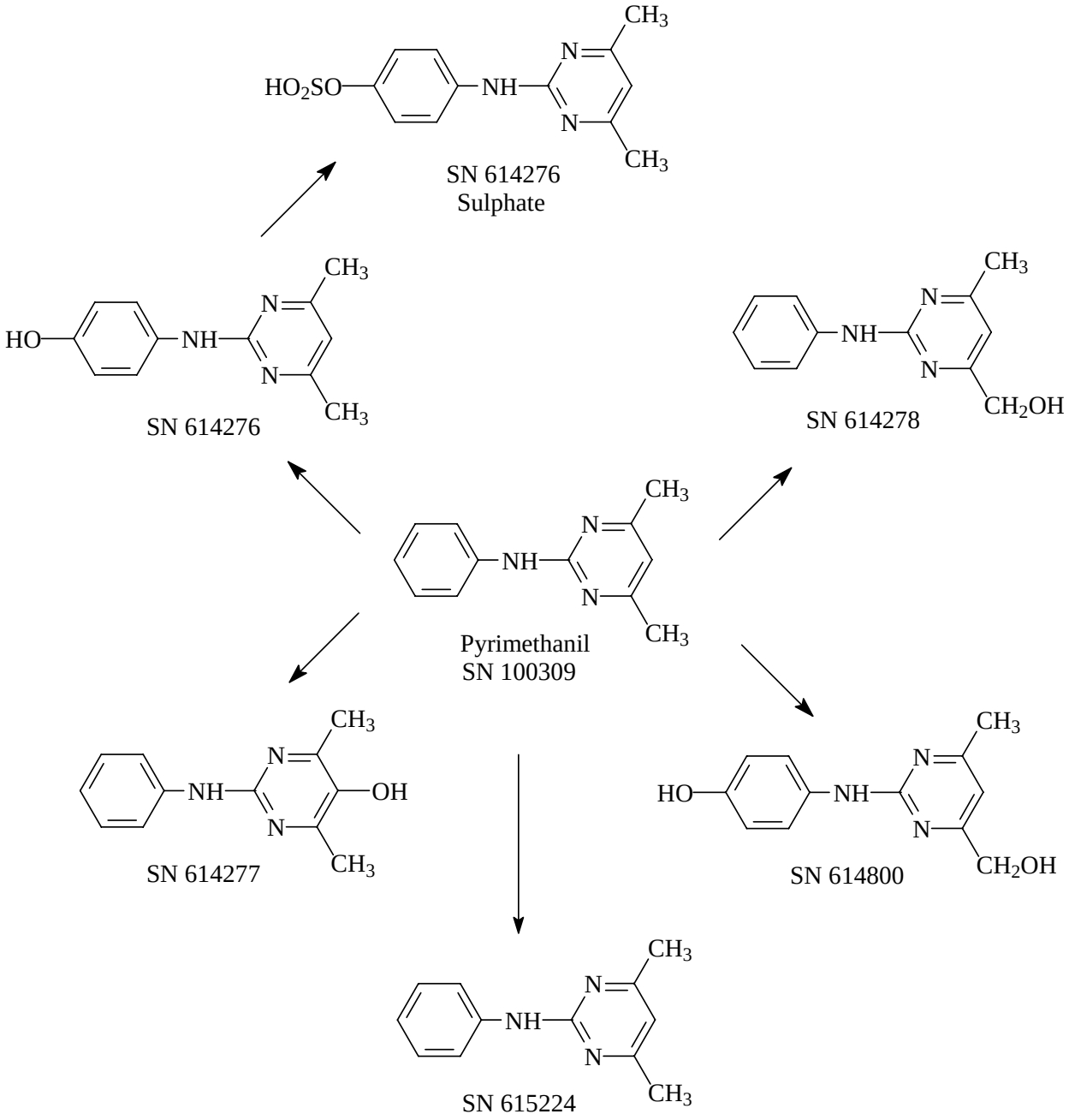
Following 14 days of repeated oral exposure to unlabelled pyrimethanil (purity: 99.4%) in Sprague-Dawley Crl:CD(SD)BR rats (5/sex), at a dose level of 10 mg/kg, the majority (~90%) of a single administered dose of ^{14}C-pyrimethanil was eliminated within 24 hours with the urine as the major route of elimination (~72%). Approximately 17–18% of the administered dose was eliminated in the feces. Radiolabel was detected only in the liver, kidney and blood at study termination (24 hours postdose). The highest residue level was in the liver in both sexes. The overall recovery of radiolabel was ~91%.

Male and female Sprague-Dawley (Crl:CD(SD)BR), 14/sex, were administered, by oral gavage, a single oral dose of either 10 or 800 mg ^{14}C-pyrimethanil/kg bw. One animal of each sex was sacrificed at 45 and 90 minutes, and at 3, 6, 12, 24 and 48 hours postdosing, frozen and prepared for quantitative whole-body autoradiography. In general, radioactivity was rapidly absorbed and distributed; absorption was more prolonged in the high dose group. Residue levels in blood and highly perfused tissues increased in a dose-dependent manner with the high dose group displaying biphasic absorption kinetics possibly attributable to the dosing vehicle (1% gum tragacanth). Low dose (10 mg/kg bw) administration resulted maximal concentrations of radioactivity within 45 minutes. Tissue levels > 10 µg equivalents/g tissue were observed in the lachrymal glands, Harderian gland (females only), kidney, liver and white fat while tissue levels > 1 µg equivalents/g tissue were observed in all other tissues except for bone and eye in males. Tissue levels declined rapidly thereafter, and by 6 hours postdose, levels of > 1 µg equivalents/g tissue were detected only in kidney, liver and white fat (female). Following high dose administration (800 mg/kg bw), peak tissue radioactivity was achieved between 3–6 hours in males and in 6–12 hours in females. Maximum concentrations of > 100 µg equivalents/g tissue were detected in the adrenal gland, brown and white fat, Harderian gland, lachrymal glands, kidney, liver and spleen of both sexes as well as in blood, lymph nodes, myocardium, ovary, pancreas and salivary glands of females. Tissue levels declined rapidly thereafter such that by 24-hours postdose levels of > 10 µg equivalents/g tissue were detected only in kidney, liver and thyroid of males. Levels in females were higher at the 24-hour postdosing with concentrations in the adrenal, kidney, liver, ovary and pancreas > 50 µg equivalents/g tissue. By 48-hour postdose, radioactivity was detected in only the liver (38 µg equivalents/g tissue) and thyroid (19 µg equivalents/g tissue) of high-dose females. Irrespective of the dose level, radiolabelled

SN 100309 was rapidly cleared in rats, leaving virtually no quantifiable residues remaining in all analyzed tissues 48 hours after dosing.

Single oral doses (10 or 800 mg/kg bw) of ^{14}C-radiolabelled pyrimethanil (purity ≥ 98%) were administered to Crl:CD(SD)BR rats to investigate the tissue distribution and clearance of radiolabelled test substance over 24–48 hours. Peak tissue concentrations were achieved in 1 hour (low dose) and between 2 and 10 hours (high dose). Clearance of radiolabel was rapid at the low dose but more protracted in the high dose animals due to prolonged absorption of the test material from the gut. The highest concentrations were found in kidneys, liver, thyroid, renal fat, ovaries, adrenals and gastrointestinal tract. These tissues also retained radioactivity up to study termination.

Figure 3.1.1.1.1 Proposed Pathway for Metabolism of Pyrimethanil in Rats



3.1.1.2 Mice

In a metabolism study, groups of 5 male and 5 female mice were administered by gavage a single oral dose of 10 mg ^{14}C-phenyl-labelled pyrimethanil/kg bw as a suspension in 1% gum tragacanth. Animals were maintained for 96 hours after dosing and radioactivity in blood, urine, feces, tissues and organs was determined by liquid scintillation counting. Following a single oral dose of 10 mg/kg bw, radiolabelled material was rapidly absorbed and excreted with > 95% eliminated within 24 hours. Urinary excretion was the major route of elimination, accounting for ~84–90% of the administered dose. The overall recovery was 108–109%. The excretion profile was similar for male and female mice. The radioactivity levels remaining in the tissues after 96 hours postdosing were confined to the residual carcass, liver, kidney and blood with all the other major organs and tissues having residues below the limit of detection.

3.1.1.3 Dogs

A single oral dose (10 mg/kg bw in a gelatin capsule) of phenyl-radiolabelled pyrimethanil (purity ≥ 98%) was administered to 3 male and 3 female beagle dogs. Animals were maintained for three days after dosing. At different time intervals, blood samples were taken and urine and feces were collected during cage washings. Tissues and organs were collected at terminal sacrifice for determination of radioactivity by scintillation counting. Following a single oral dose of 10 mg/kg bw, radiolabelled material was rapidly excreted. Over 70% of the administered dose was excreted after 24 hours, with fecal excretion accounting for ~56% of the overall recovered radiolabelled dose while urinary excretion accounted for around 33%. Total recovery of radiolabel was 95±1.6%. The excretion profiles for males and females were very similar. Plasma levels, as determined throughout the 72-h postadministration period, peaked during the first 2 hours after dosing and declined slowly thereafter with terminal half-lives around 12–13 hours for both sexes. The tissue distribution of radioactivity was determined after 72 hours with most tissues barely above the LOD. Detectable residues were observed in the adrenals, gastrointestinal tract, bile, liver, spleen and thyroid. Residue levels in bile at necropsy were significantly greater than those found in the liver or kidneys, providing strong evidence in support of predominant biliary excretion of pyrimethanil in dogs.

3.1.2 Acute Toxicity—Technical and Formulation

Technical—Pyrimethanil

Technical pyrimethanil (98%) was considered to be of low acute toxicity by the oral, dermal and inhalation routes; oral and dermal lethal doses 50% (LD_{50}s) > 4.1 g/kg bw, inhalation lethal concentration 50% (LC_{50}) > 1.98 mg/L) in Sprague Dawley rats. Pyrimethanil was also found to be of low acute toxicity by the oral route in mice (LD_{50} > 4.0 g/kg bw). It was non-irritating when applied to the skin and the eye of New Zealand white (NZW) rabbits. Results of skin sensitization testing using guinea pigs, employing the Buehler method and guinea pig maximization test, were negative.

Based on the acute toxicity testing results, no precautionary hazard statements are required.

Formulation—Scala SC Fungicide
Scala SC Fungicide (pyrimethanil, 38.33% a.i.) has a low acute toxicity by the oral (LD_{50} > 5000 mg/kg bw) and dermal (LD_{50} > 4000 mg/kg bw) routes and is slightly toxic via inhalation (LC_{50} >1.26 mg/L) in rats. This formulation was minimally irritating to the eye and mildly irritating to skin in rabbits. Scala SC Fungicide did not elicit a dermal sensitization response in guinea pigs via the Magnusson-Kligman maximization method.

Based on the results of acute toxicity testing, the signal words “Caution Poison” and “Caution Skin Irritant” are required to be displayed on the primary display panel of the formulation.

3.1.3 Genotoxicity

No evidence of mutagenic potential of pyrimethanil was observed in vitro with the Ames Bacterial Mutation Test or in an unscheduled DNA synthesis assay with rat hepatocytes. Under the conditions of an in vitro mammalian cell gene mutation assay (cultures of normal [$HGPRT^+$] Chinese hamster ovary [CHO] cells), pyrimethanil was considered non-mutagenic for point mutations, frame-shift mutations and deletions. Pyrimethanil was not clastogenic in the presence or absence of metabolic activator at any dose level tested. In an in vitro chromosomal assay using human lymphocytes, pyrimethanil did not cause an increase chromosomal aberrations, with and without metabolic activation. Pyrimethanil did not induce micronuclei in an in vivo mouse micronucleus assay. Based on the data presented, pyrimethanil was not considered to be genotoxic under the conditions of the tests performed.

3.1.4 Subchronic and Chronic Toxicity

The subchronic and chronic toxicity of pyrimethanil was investigated in mice, rats and dogs. A series of range-finding 28-day and 90-day studies were conducted initially. These studies were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Subchronic and Chronic Toxicity in the Mouse

In a subchronic toxicity study, technical grade SN 100309 (97.7–97.9% w/w) was administered to 20 Crl:CD-1(ICR)BR strain mice/sex/dose *ad libitum* in the diet at dose levels of 0, 80, 900 or 10 000 ppm (equal to 0, 12, 139 and 1864 mg/kg bw/day in males and 0, 18, 203 and 2545 mg/kg bw/day in females) for 13 weeks. The control group received untreated diet (*ad libitum*) throughout the study.

There were no treatment-related mortalities and no treatment-related clinical observations, water consumption changes or hematology findings. Lower body weights and body-weight gains were noted in both sexes at 10 000 ppm. These effects were

associated with increased food consumption indicating a decreased food efficiency in these animals. Treatment-related clinical chemistry findings included decreased serum glucose levels in males at 10 000 ppm and increased serum cholesterol and total bilirubin levels in females at 10 000 ppm. Increased liver weights were noted for both sexes at 10 000 ppm. Gross pathological findings included dark discolouration of the thyroid and thyroid enlargement in males at 10 000 ppm and kidney stones in one female at 10 000 ppm. Histopathological findings were noted in the urinary bladder, kidneys, liver and thyroid gland at 10 000 ppm. In the bladder, uroliths were detected in both sexes with females also exhibiting hyperplasia of the urinary bladder epithelium. Slight tubular dilatation was noted in the kidneys of males. Glycogen depletion was noted in the liver in both sexes as indicated by decreased margination of the cytoplasm and reduced periodic acid Schiff (PAS) method staining intensity in males (PAS staining not done in females). In the thyroid light to severe exfoliative necrosis of the follicular cells was noted in males. Minimal exfoliative necrosis of the follicular cells was also noted in one female. Slight to severe pigmentation of the follicular cells was noted in both sexes. The severity ranged from slight to severe in males and minimal to moderate in females. Staining indicated that the pigment was composed mainly of mature lipofuscin with a small amount of the early form. Thyroid weights were not determined.

The lowest observed adverse effect level (LOAEL) was 10 000 ppm (equal to 1864 and 2545 mg/kg bw/day for males and females, respectively) based on decreased body weight, body-weight gain and food efficiency, clinical chemistry findings, increased liver weights, gross pathological and/or histopathological findings in the urinary bladder, kidneys, liver and thyroid gland in one or both sexes at this dose level. The no observed adverse effect level (NOAEL) was 900 ppm (equal to 139 and 203 mg/kg bw/day for males and females, respectively).

In a carcinogenicity study (MRID 433016-15), technical grade SN 100309 (96.0–97.3% w/w) was administered to Crl:CD-1(ICR)BR mice (51/sex/dose) in diet at dose levels of 0, 16, 160 and 1600 ppm (0, 2.0, 20.0 or 210.9 mg/kg bw/day, males; 0, 2.5, 24.9 or 253.8 mg/kg bw/day, females) for 80 weeks.

There were no treatment-related mortalities or clinical observations. There was a dose-related increase in males in the percentage of deaths occurring prior to week 56, but there was no dose-related adverse effect on survival in either sex and adequate numbers of mice of both sexes were available at study termination. No toxicologically significant findings were observed on body weight or body-weight gain, water consumption, clinical pathology or organ weights at study termination. Necropsy of the decedent animals showed an increase in urogenital tract lesions in treated males by week 52, and the increase was significant in the high dose males. The lesions consisted of inflammation of the glans penis, preputial gland adenitis or abscesses, seminal vesiculitis or distension and urinary bladder distension, cystitis, with the greatest incidence at 1600 ppm. The trend did not continue to the terminal sacrifice. No adverse treatment-related effects were observed in clinical pathology or organ weights at study termination.

The LOAEL for non-neoplastic effects in male rats was 1600 ppm (210.9 mg/kg bw/day) based on increased urogenital tract lesions. The NOAEL for non-neoplastic effects was established at 160 ppm (20 mg/kg bw/day). A LOAEL was not determined for females. The NOAEL for non-neoplastic effects was established at 1600 ppm (253.8 mg/kg bw/day).

The high dose chosen by the study investigators was equivalent to the high dose administered to rats during the two-year chronic toxicity/carcinogenicity study, which was found to be tumorigenic. This high dose was able to elicit signs of toxicity in the male mice and is thus considered to be acceptable according to the United States Office of Prevention, Pesticides and Toxic Substances as well as to the Organisation for Economic Co-operation and Development (OECD) guideline requirements. There was no treatment-related increased incidence of tumours in the treatment groups when compared with controls, up and to and including 1600 ppm (equal to 210.9 mg/kg bw/day in males and 253.8 mg/kg bw/day in females) in males and females, the highest dose tested. Therefore, under the conditions of this study, SN 100309 (96.0–97.3% a.i.) was not considered to be carcinogenic in mice.

3.1.4.2 Subchronic and Chronic Toxicity in the Rat

In a subchronic toxicity study, technical grade SN 100309 (95.3–98.1% w/w) was administered to 10 Crl:CD(SD)BR strain rats/sex/dose *ad libitum* in the diet at dose levels of 0, 80, 800 or 8000 ppm (equal to 0, 5.4, 55 and 529 mg/kg bw/day in males and 0, 6.8, 67 and 626 mg/kg bw/day in females) for 13 weeks. Additional supplementary control and high dose groups each comprising 10 animals/sex were similarly treated for 13 weeks then maintained on untreated diet for 4 weeks to determine the reversibility of any finding. The control group animals received untreated diet *ad libitum* throughout the study.

There were no mortalities, no treatment-related clinical signs and no treatment-related water consumption, hematology, clinical chemistry, ophthalmoscopic or gross pathology findings. Lower body weights and body-weight gains were noted for both sexes at 8000 ppm. This was associated with a concomitant decreased food consumption. Over the reversibility period, there was partial recovery in body-weight gain in both sexes at 8000 ppm. Food efficiency was lower for both sexes at 8000 ppm during the first week, however, for the remainder of the study food efficiency was comparable to controls. Increased protein was noted in the urine of males at 8000 ppm, varying from trace to moderate amounts. Additionally, changes in the colour of the urine specimens were noted for both sexes at 8000 ppm, varying from light brown to dark in males and brown to dark in females. Following the four-week reversibility period, trace to slight amounts of protein were still noted in the urine in males; however, the colour appeared to return to normal for both sexes. Increased liver weights were noted for both sexes at 8000 ppm. Although the increased liver weights may be secondary to the lower body-weight gain noted in these animals, correlating histopathological findings, specifically minimal centrilobular hepatocellular hypertrophy, were also noted in these animals. Following the 4-week reversibility period, absolute liver weights were significantly lower for males at

8000 ppm. Histopathological findings noted in the liver included minimal hypertrophy of centrilobular hepatocytes in males at 800 ppm and in both sexes at 8000 ppm and decreased margination of hepatocyte cytoplasm in males at 800 and 8000 ppm. The decreased margination of the hepatocytes was considered to be secondary to hepatocyte hypertrophy. These findings were likely adaptive in nature and not toxicologically significant. Histopathological findings in the thyroid included an increased incidence and severity of follicular epithelial hypertrophy, accumulation of lipofuscin in the follicular epithelium and a slight increased incidence of colloid depletion in the follicular cells in both sexes at 8000 ppm. The follicular epithelial hypertrophy and depletion of colloid in the follicular cells are suggestive of an increased thyroid stimulating hormone (TSH) stimulation of the follicular cells in these animals. Following the 4-week recovery period, the histopathological findings noted in the liver and thyroid were no longer apparent.

The LOAEL was 8000 ppm (equal to 529 and 626 mg/kg bw/day for males and females, respectively) based on lower body weight, body-weight gain and food consumption, urinalysis findings and histopathological findings in the thyroid in one or both sexes at this dose level. The NOAEL was 800 ppm (equal to 55 and 67 mg/kg bw/day for males and females, respectively).

In a combined chronic/carcinogenicity study (MRID 433016-12 and 433016-13), (pyrimethanil, 95.5–97.6% a.i.) Sprague-Dawley Crl:CD(SD)BR rats (70/sex/group) were treated at dose levels of 0, 32, 400 or 5000 ppm (equal to 0, 1.3, 17 or 221 mg/kg bw/day for males and 0, 1.8, 22, 291 mg/kg bw/day for females, respectively) in diet for 52 weeks (interim sacrifice) or 104 weeks (main study). Treatment-related non-neoplastic effects were observed, at termination in the high-dose animals as significantly decreased body-weight gains and food consumption. Moreover, effects on the liver in both sexes presenting as increased serum cholesterol (females only) and gamma-glutamyl transferase (GGT) levels (males only), significantly increased absolute liver weight in males and increased relative liver weight in both sexes, increased incidence of centrilobular hepatocellular hypertrophy and eosinophilic foci were noted in the 5000 ppm dose group. The thyroid gland in both sexes was affected at 5000 ppm with increases in the incidence of intra-epithelial deposition of brown pigment (lipofuscin), hypertrophy of follicular epithelium, depletion of colloid from and focal hyperplasia of follicular cells. Similarly, the non-neoplastic effects in the liver and thyroid were noted to a lesser extent at the interim sacrifice at 52 weeks. The LOAEL for chronic toxicity was 5000 ppm (equal to 221 mg/kg bw/day for males and 291 mg/kg bw/day for females) based on decreased body-weight gains, increased serum cholesterol and GGT levels, increased relative liver/body weight ratios, necropsy and histopathological findings. The NOAEL was established to be 400 ppm (equal to 17 mg/kg bw/day for males and 22 mg/kg bw/day for females).

Neoplastic lesions, identified as follicular cell adenomas, were noted in the 5000 ppm male and female animals; the incidence of this tumour was greater than the historical control range. The increased incidence of thyroid adenomas was considered treatment-related. No treatment-related effects were noted in either the 32 or 400 ppm animals. The doses used in this study were adequate for a combined toxicity and

carcinogenicity study based on a overall reduction in body-weight gains in rats given 5000 ppm for 2 years. As the mode of action of pyrimethanil on the thyroid appears to be through an indirect, extrathyroidal stimulatory mechanism, this tumorigenic finding may be of limited significance to humans. The type of tumour appearing in response to thyroidal stimulation is common in rats and is not believed to be relevant to humans. At the doses tested, there was a treatment-related increase in tumour incidence in the thyroid of treated animals when compared with control animals at the high-dose level of 5000 ppm (equal to 221 mg/kg bw/day for males and 291 mg/kg bw/day for females). Thyroid follicular cell adenomas were observed at an increased incidence in both male and female animals of the high-dose group. Under the conditions of the current study, SN 100309 was considered to be carcinogenic in rats.

3.1.4.3 Subchronic Toxicity in the Dog

In a subchronic toxicity study, technical grade SN 100309 (97.7–98.0% w/w) in 0.5% w/v methylcellulose in distilled water was administered via oral gavage to 4 beagle dogs/sex/dose at dose levels of 0, 6, 80 or 1000/800 mg/kg bw/day for 13 weeks. The high dose animals received 1000 mg/kg bw/day for the first 6 days and then a reduced dose of 800 mg/kg bw/day for the remainder of treatment. Males were sacrificed and necropsied on days 96 and 97. Females were sacrificed and necropsied on days 98 and 99.

There were no treatment-related mortalities. At 1000 mg/kg bw/day, there was an increased incidence of vomiting in all animals during the first 6 days of treatment resulting in a slight body-weight loss (approximately 4%). Food consumption was reduced during the first week in both sexes at 1000 mg/kg bw/day (approximately 23 and 16% for males and females, respectively). Consequently the dose level was reduced to 800 mg/kg bw/day. Clinical observations noted at 800 mg/kg bw/day included occasional to frequent vomiting, salivation, diarrhea and discolouration of the feces. Reduced activity was also noted in both sexes at the high dose. Clinical findings noted at 80 mg/kg bw/day included infrequent vomiting, salivation, diarrhea and discolouration of the feces. Reduced activity was noted in one male at 80 mg/kg bw/day. There were no treatment-related effects on body weight, body-weight gain, food consumption or food efficiency. Water consumption was markedly lower for both sexes at 800 mg/kg bw/day, approximately 30% and 19% lower for males and females, respectively. Slightly lower water consumption was also noted for both sexes at 80 mg/kg bw/day, approximately 9% and 17% lower for males and females, respectively. There were no treatment-related ophthalmoscopic, electrocardiography, hematology, clinical chemistry, organ weight, gross pathology or histopathological findings.

The LOAEL was 80 mg/kg bw/day based on increased incidence of vomiting, salivation, diarrhea, discolouration of the feces, reduced activity and decreased water consumption in one or both sexes at this dose level. The NOAEL was 6 mg/kg bw/day.

In a 1-year toxicity study, technical grade SN 100309 (96.3–96.9% w/w) in 0.5% w/v methylcellulose in distilled water was administered via oral gavage to 4 beagle

dogs/sex/dose at dose levels of 0, 2, 30 or 400/250 mg/kg bw/day for 52 weeks. The high dose animals received 400 mg/kg bw/day for the first 8 days and then a reduced dose of 250 mg/kg bw/day for the remainder of treatment. Males were sacrificed on days 369 and 370, and females were sacrificed on days 371 and 372.

There were no mortalities and no treatment-related ophthalmoscopic, electrocardiography, hematology, clinical chemistry, urinalysis, organ weight, gross pathology or histopathology findings. At 400 mg/kg bw/day, increased incidences of vomiting/emesis were evident within 30 minutes to 6 hours postdosing in 4/4 males and 3/4 females during the first week of treatment. After reducing the dose to 250 mg/kg bw/day, vomiting/emesis were still present; however, the number of incidences was reduced in both sexes. Other clinical findings noted at the high dose included incidents of diarrhea and coloured feces in the majority of the animals throughout the study. Males and females at the high dose exhibited lower body weight and body-weight gain throughout the study. By week 52, body weight was approximately 7% lower for the high dose males and approximately 13% lower for the high dose females. Overall body-weight gain (weeks 0–52) was approximately 50% and 73% lower for males and females, respectively. The lower body-weight gain noted in the high dose females was associated with a concomitant decrease in food consumption (approximately 16%). Overall water consumption was reduced by approximately 35% and 26% for the high dose males and females, respectively. Overall food efficiency was lower in both sexes at the high dose, approximately 50% and 98% lower in males and females, respectively.

The LOAEL was 250 mg/kg bw/day based on increased incidence of vomiting, salivation, diarrhea, discolouration of the feces, decreased body weight, body-weight gain, food consumption, food efficiency and water consumption in one or both sexes at this dose level. The NOAEL was 30 mg/kg bw/day.

3.1.5 Reproductive and Developmental Toxicity

In a 2-generation reproduction study (1 litter/generation) (MRID 433016-23, 433450-08), technical grade SN 100309 (Purity: 96.2–97.2%) was administered *ad libitum* in the diet to Sprague-Dawley Crl:CD(SD)BR rats (P_1, 30/dose/sex; P_2, 25/dose/sex) at dose levels of 0, 32, 400 or 5000 ppm (equal to 0, 1.9, 23.1 and 294 mg/kg bw/day for P_1/P_2 males, [premating]; 0, 2.2, 27.4 and 343 for P_1/P_2 females, [premating] during premating, gestation and lactation periods). On postnatal day 4, all litters were culled to 8 pups/litter (4/sex/litter, as nearly as possible). These selected animals from the F_1 generation were used as the P_2 animals.

There were no treatment-related mortalities observed in the P_1/P_2 males or females. In the high-dose group, reduced mean body-weight gain was observed in both sexes; this reduction was increased in females during gestation and lactation despite the high-dose females consuming more food than controls. Fur staining in high-dose females during gestation and lactation was also observed. Gross necropsy findings of the P_1 animals were unremarkable. There were no treatment-related mortalities or clinical observations in the P_2 pups. High-dose P_2 pups weighed less than controls from lactation day (LD) 1 (birth)

through LD 21 (weaning). During the P_2 premating period, mean food consumption in both sexes was decreased in the high-dose group during the premating phase. As with the P_1 generation, food consumption and fur staining by P_2 females in the high-dose group was increased during gestation and lactation. Weight gain in these females was also increased during lactation. Female fertility and fecundity indices were not significantly different in the high-dose females. Gross necropsy and Histopathological findings of the P_1 animals were unremarkable. There were no treatment-related mortalities or clinical observations in the F_2 pups. High-dose F_2 pups weighed less than controls from LD 4 through LD 21 and mean weight gain was decreased from LD 1 to LD 21. Gross necropsy findings were unremarkable.

The LOAEL for parental toxicity was 5000 ppm (294 mg/kg bw/day, males; 343 mg/kg bw/day, females) based on decreased mean body weights and body-weight gains; the NOAEL was established at 400 ppm (23.1 mg/kg bw/day, males; 27.4 mg/kg bw/day, females). The LOAEL for offspring toxicity was established at 5000 ppm (294 mg/kg bw/day, males; 343 mg/kg bw/day, females) based on decreased pup body weights on LD 21; the NOAEL was established at 400 ppm (23.1 mg/kg bw/day, males; 27.4 mg/kg bw/day, females). The NOAEL for reproductive toxicity in males and females was 5000 ppm (294 mg/kg bw/day, males; 343 mg/kg bw/day, females).

In a rat developmental toxicity study, SN 100309 (96.3–97.0% w/w), prepared as a suspension in aqueous 1% methylcellulose, was administered to 30 mated adult female Sprague-Dawley rats/dose at dose levels of 0, 7, 85 or 1000 mg/kg bw/day by oral gavage from days 6 through 15 of gestation. Dosing volume was adjusted daily, based on dam weight during the dosing period.

There were no treatment-related mortalities. Clinical signs were limited to females at 1000 mg/kg bw/day and included hair loss, slight to moderate emaciation and/or hunched posture. Body weight was significantly lower at 1000 mg/kg bw/day from gestation day 9 onwards (approximately 4–10%). This was attributed to the significantly lower body-weight gain during gestation days 6–15 (approximately 39–44%). Overall body-weight gain was approximately 42% lower at 1000 mg/kg bw/day. The lower body-weight gain was associated with a concomitant lower food consumption during gestation days 6–15 (approximately 17–21%). Body-weight gain and food consumption appeared to recover slightly during the post-treatment period, however, they remained lower when compared to controls. There were no treatment-related gross pathological findings. Caesarian section parameters were unaffected by treatment at dose levels up to and including 1000 mg/kg bw/day. Gravid uterine weight was not provided. The LOAEL for maternal toxicity was 1000 mg/kg bw/day based on lower body weight, body-weight gain and food consumption at this dose level. The NOAEL for maternal toxicity was 85 mg/kg bw/day. Mean litter and mean foetal weight were significantly lower at 1000 mg/kg bw/day (approximately 7 and 14%, respectively). There were no treatment-related external, visceral or skeletal findings observed at any dose level. There were no treatment-related effects on the total number of fetuses or litters with external, visceral or skeletal findings. There was no evidence of any treatment-related irreversible structural change at any dose level up to and including 1000 mg/kg bw/day, the highest

dose tested; therefore, under the conditions of this study, SN 100309 was not considered to be teratogenic. The LOAEL for developmental toxicity was 1000 mg/kg bw/day based on lower mean litter and foetal weight at this dose level. The NOAEL for developmental toxicity was 85 mg/kg bw/day. On the basis of the maternal and developmental NOAELs, there does not appear to be an increased susceptibility of the fetus to in utero exposure to SN 100309.

In a rabbit developmental toxicity study, technical grade SN 100309 (97.1% w/w), prepared as a suspension in aqueous 0.1% methylcellulose, was administered to 18–19 adult female NZW rabbits/dose at dose levels of 0, 7, 45 or 300 mg/kg bw/day by oral gavage from days 7 through 19 of gestation. Dosing volume was adjusted daily, based on dam body weight during the dosing period. There were no treatment-related mortalities. Three animals at 300 mg/kg bw/day became emaciated and were subsequently sacrificed. Treatment-related clinical signs were noted at 300 mg/kg bw/day and included increased severity and duration of reduced and/or no feces and small fecal pellets. These generally appeared at onset of treatment (gestation day 7) and persisted throughout the remainder of the study. During the treatment period (gestation days 7–19), overall body-weight gain was approximately 29% lower for females at 300 mg/kg bw/day. This was due to a treatment-related body-weight loss noted during gestation days 7–9. These animals also exhibited reduced food consumption throughout the treatment period. There were no treatment-related gross pathological findings. Cesarian section parameters were unaffected by treatment at dose levels up to and including 300 mg/kg bw/day. Gravid uterine weight was unaffected by treatment. There were no abortions at any dose level.

The LOAEL for maternal toxicity was 300 mg/kg bw/day based on reduced and/or no feces and small fecal pellets, body-weight loss during gestation days 7–9, overall lower body-weight gain and food consumption at this dose level. The NOAEL for maternal toxicity was 45 mg/kg bw/day. Mean fetal weight was lower at 300 mg/kg bw/day (approximately 9–12%). In addition, there was an increase in the number of runted fetuses (fetal incidence 3.7% vs 0.6% for controls; defined as < 20 g body weight) at 300 mg/kg bw/day. The incidence was above the upper range of the historical control values (0–1.4%). These findings were considered to be mainly due to embryonic growth retardation which may be related to the reduced maternal food consumption noted throughout the treatment period and the body-weight loss noted in the dams during gestation days 7–9. There was no evidence of treatment-related irreversible structural changes; therefore, under the conditions of this study, SN 100309 was not teratogenic. The LOAEL for developmental toxicity was 300 mg/kg bw/day based on lower mean fetal weights and increased incidence of runted fetuses at this dose level. The NOAEL for developmental toxicity was 45 mg/kg bw/day. On the basis of the maternal and developmental NOAELs, there does not appear to be an increased susceptibility of the fetus to in utero exposure to SN 100309.

3.1.6 Neurotoxicity (acute, delayed and subchronic)

In an acute neurotoxicity study, groups of 12 Sprague-Dawley (CD) rats/sex received a single oral (gavage) dose of Pyrimethanil Technical (99.8% w/w) in 0.5% methylcellulose at dose levels of 0, 30, 100 or 1000 mg/kg bw. The functional observational battery (FOB) and motor activity evaluation were performed before treatment and on days 1 (commencing approximately 1½ to 2½ hours postdosing), 8 and 15. At study completion (day 16), five animals/sex/group were subjected to a whole-body perfusion (and subsequent brain measurements). Those rats in the control and high dose groups underwent a neuropathological evaluation. All other animals were euthanised at study completion and subjected to a gross pathological examination.

There was no mortality, no treatment-related overt clinical signs of toxicity and no treatment-related effects on body weight, body-weight gain or food consumption. FOB examinations showed an increased number of males and females at 1000 mg/kg bw exhibited a slight to moderate overall gait incapacity characterized by slight to moderate ataxic gait in the majority of the animals and hypotonic gait in one male. Several females at 1000 mg/kg bw also exhibited dilated pupils and one male at 1000 mg/kg bw showed an abnormal response to the air righting reflex test (i.e., landed on his side). Other findings noted at 1000 mg/kg bw included significantly reduced hindlimb grip strength for males and significantly lower body temperatures for both sexes. Motor activity was also significantly reduced in both sexes at 1000 mg/kg bw. Habituation was not affected by treatment. These findings were apparent on the day of treatment (day 1) and were resolved by the next test occasion on day 8. There were no treatment-related gross pathological findings, no treatment-related effects on brain weight, brain length or brain width measurements and no treatment-related neuropathological findings. The findings noted in the FOB and motor activity examinations on day 1 in both sexes at 1000 mg/kg bw were considered be treatment-related; however, due to their transient nature and in the absence of any corroborating treatment-related gross pathological findings or neuropathological findings in the central or peripheral nervous system, they were not considered to be due to neurotoxicity per se.

The LOAEL for systemic toxicity was 1000 mg/kg bw based on the transient gait incapacity characterized by ataxic gait, dilated pupils, decreased hindlimb grip strength, decreased body temperature and reduced motor activity in one or both sexes at this dose level. The NOAEL for systemic toxicity was 100 mg/kg bw. The LOAEL for neurotoxicity was not determined. The NOAEL for neurotoxicity was 1000 mg/kg bw, the highest dose tested.

In a subchronic neurotoxicity screening study, Pyrimethanil Technical Fungicide (99.8% a.i.) was administered to 12 young adult Sprague-Dawley rats/sex/dose *ad libitum* in the diet at dose levels of 0, 60, 600 or 6000 ppm (equal to 0, 4.0, 38.7 and 392 mg/kg bw/day, respectively, in males and 0, 4.6, 44.3 and 430 mg/kg bw/day, respectively, in females) for 13 weeks. Neurobehavioral assessment (FOB and motor activity testing) was performed in 12 animals/sex/group during weeks 4, 8 and 13. At study termination, 5 animals/sex/group were euthanised and perfused for neuropathological examination. A

neuropathological examination of perfusion-fixed central and peripheral nervous tissues was conducted on the control and high-dose animals. All animals were subjected to a gross pathological examination following 13 weeks of treatment.

There was no mortality and no treatment-related overt clinical signs of toxicity. For males at 6000 ppm, body weight was approximately 3–4% lower throughout the study. During the first week, body-weight gain was approximately 21% lower, this correlated with lower food consumption (approximately 12%). Body-weight gain remained slightly lower (approximately 3–13%) throughout the remainder of the study; however, food consumption was generally comparable to controls. For females at 6000 ppm, body weight was approximately 2–8% lower throughout the study. Body-weight gain was lower throughout the study, ranging from 15–22% lower, this correlated with lower food consumption (approximately 9–15%). No treatment-related findings were noted during the FOB or motor activity examinations in either sex. Habituation was not affected by treatment. There were no treatment-related gross pathological findings, no treatment-related effects on brain weight, brain length or brain width measurements and no treatment-related neuropathological findings.

The LOAEL for systemic toxicity was 6000 ppm (equal to 392 and 430 mg/kg bw/day for males and females, respectively) based on decreased body weight, body-weight gain and food consumption. The NOAEL was 600 ppm (equal to 38.7 and 44.3 mg/kg bw/day for males and females, respectively). The LOAEL for neurotoxicity was not determined. The NOAEL for neurotoxicity was 6000 ppm (equal to 392 and 430 mg/kg bw/day for males and females, respectively).

3.1.7 Special Studies

Hepatic enzyme induction was investigated in male Sprague-Dawley rats. Technical SN 100309 (99.4% w/w) was administered orally as a suspension in 0.5% gum tragacanth to groups of 6 animals/sex/dose at concentrations of 0, 100 or 200 mg/kg bw twice daily for 4 days.

There was no mortality. Increased liver weight was noted at 100 and 200 mg/kg bw; however, the increase was not dose-related. Total CYP450 content was increased slightly at both 100 and 200 mg/kg bw; however, the increase was not significant. The CYP b5 content was significantly increased at 200 mg/kg bw. This membrane-bound heme protein enhances the catalytic activity of some cytochrome P450 isoforms, particularly members of the P450 3A family. There was no treatment-related increase in lauryl acid hydroxylase activity at 100 or 200 mg/kg bw, indicating that no peroxisome proliferation occurred and that there was no induction of the CYP450 4A subfamily of enzymes that are responsible for fatty acid β-oxidation and ω-hydroxylation. There was a significant increase in the ethoxyresorufin-O-deethylase (EROD) activity, which suggests induction of the CYP450 1A subfamily. Pentoxyresorufin-O-dealkylase (PROD) was significantly increased at both 100 and 200 mg/kg bw, which may suggest induction of the CYP2B6 subfamily; however, the increase was not dose-related. The positive control substances phenobarbitone, clofibrate and β-naphthaflavone, produced the appropriate responses.

These data suggest that technical grade SN 100309 may be a weak inducer mainly of the phenobarbitone type, however; the magnitude of the induction is extremely low.

3.1.7.1 Weight of Evidence Regarding Carcinogenic Potential of Pyrimethanil

Thyroid homeostasis and hepatic microsomal uridine diphosphoglucuronyl transferase (UDPGT) activity was investigated in male Sprague-Dawley rats. Technical grade SN 100309 (96.2% w/w) was administered *ad libitum* in the diet to 10 animals/dose at concentrations of 0 or 5000 ppm (equivalent to 0 and 379 mg/kg bw/day, respectively) for 14 days. Five animals from treated and control groups were then sacrificed and necropsied following treatment. The remaining animals were given untreated diet for the 14 days regression (off-dose) period then sacrificed and necropsied. The control animals received untreated diet throughout the study.

There were no mortalities and no treatment-related clinical signs of toxicity or gross pathology findings. Lower body weight, body-weight gain and food consumption were noted in the first week of the study. The lower food consumption may be due to the food not being palatable. Decreased tri-iodothyronine (T3) and thyroxine (T4) levels and increased TSH levels were noted in the treated animals by 6 hours. In addition, reverse T3 (rT3) levels (biologically inactive) were also increased in the treated animals. The increase in the rT3 levels was most likely due to increased peripheral de-iodination of T4, which is seen as a rapid response mechanism for control of thyroid hormone balance. Acute or chronic stress can cause a shift in the direction of peripheral de-iodination of T4 from T3 to rT3. By day 8, T3, T4 and rT3 levels were generally comparable to control levels for the remainder of the study, and this was most likely due to the increased TSH levels adequately compensating for the increased metabolism of T3 and T4. TSH levels remained elevated compared to controls throughout the treatment period. At day 15, UDPGT activity was increased. Following the 14-day recovery period, T3, T4 and rT3 levels were generally comparable to controls; however, TSH levels and UDPGT activity remained significantly elevated following the reversibility period. Increased liver weights were noted in the treated animals at the interim (day 15) necropsy. Increased thyroid weights were noted in the treated animals at both the interim (day 15) and final necropsies (day 29). In the liver an increased incidence of minimal to slight centrilobular hepatocellular hypertrophy was noted in the treated animals. This was associated with increased liver weights and is consistent with induction of UDPGT. In the thyroid, an increase in the severity of colloid depletion (moderate to severe vs minimal to slight in the controls) and follicular cell hypertrophy (slight to moderate vs minimal to moderate in controls) was noted in the treated animals.

Additionally, the treated animals also exhibited an increased incidence of follicular epithelial hyperplasia. The severity was also increased in the treated animals (minimal to moderate vs minimal for the controls). The histopathological findings noted in the thyroid in the treated animals were considered to be indicative of increased TSH stimulation of the thyroid gland. These histopathological findings appeared to be reversible following the 14-day reversibility period. The increased metabolism of T4 via hepatic enzyme conjugation appears to be responsible for the increase in serum TSH

concentration. Hepatic microsomal enzymes play an important role in thyroid homeostasis because glucuronidation is the rate limiting step in biliary excretion of T4 and sulfation by phenol sulfotransferase for the excretion of T3. Therefore, induction of the hepatic microsomal phase II biotransformation system can increase the metabolism of thyroid hormones via glucuronidation or sulfation resulting in increased clearance and decrease serum thyroid hormone levels that can trigger a compensatory increase in TSH levels. During sustained exposure to the enzyme inducing agent, prolonged stimulation of the thyroid gland by TSH can lead to the development of thyroid follicular cell hypertrophy, hyperplasia and eventually neoplasia.

These data suggest that subchronic and chronic dietary exposure to SN 100309 can result in disruption of thyroid homeostasis due to induction of hepatic microsomal glucuronyltransferases leading to increase clearance of thyroid hormones, reduction in serum T3 and T4 levels and a compensatory increase in serum TSH levels. These data also suggest that these findings are reversible following cessation of treatment. In addition, these data could account for the thyroid related findings, including an increased incidence of thyroid follicular cell adenomas, noted in both sexes following 2-year dietary exposure to SN 100309 at 5000 ppm.

In a 7-day feeding study, groups of Sprague-Dawley Crl:CD(SD)BR male rats (6/group) were fed either a control diet or diets containing 5000 ppm technical pyrimethanil (509 mg/kg bw/day), 2000 ppm propylthiouracil (177 mg/kg bw/day) or 1000 ppm phenobarbital (109 mg/kg bw/day) for 7 days. On day 8, animals were injected intraperitoneally with radiolabelled iodine (^{125}I). Six hours later, all animals were killed exactly 2.5 minutes after intraperitoneal injection of either saline or potassium perchlorate. Perchlorate inhibits the uptake of iodine, which the thyroid uses to make TSH, and can discharge accumulated iodide in the thyroid even if the ion channels were blocked by propylthiouracil. As perchlorate does not interfere with the metabolism of iodine, it is useful for the study of iodine transport in the thyroid. Propylthiouracil is a direct-acting goitrogen that affects the thyroid by blocking ion channels, thus preventing iodine uptake and release. Propylthiouracil prevents organification of iodine within the thyroid and subsequent thyroid hormone synthesis. Phenobarbital is an indirect-acting goitrogen that increases extrathyroidal thyroxine conjugation and biliary excretion. By comparing the thyroid-stimulating effects of pyrimethanil with propylthiouracil and phenobarbital, it can be determined whether pyrimethanil stimulates the thyroid through a direct or indirect mechanism.

There were no mortalities during the study. Animals treated with technical pyrimethanil had no adverse clinical effects. Propylthiouracil-treated rats showed reduced activity and piloerection, while phenobarbital treatment resulted in reduced activity, unsteady gait, reduced muscle tone, piloerection and wasted body condition. Group mean weights of animals treated with either technical pyrimethanil or propylthiouracil were lower than controls at days 4, 7 and 8, and total body-weight gains (19.6% and 12.2%, respectively) were reduced compared to the control (35.4%). The food consumption was decreased by 6% at day 3 in animals treated with technical pyrimethanil compared with controls. Reduced food consumption in rats treated with propylthiouracil was seen at days 3 and 7

(~46% and ~26%, respectively). Treatment with 5000 ppm of technical grade SN 100309 resulted in an increase in ^{125}I uptake but no significant increase in perchlorate-induced discharge of ^{125}I. Iodine (^{125}I) was significantly increased in the thyroid of animals treated with either technical pyrimethanil or phenobarbital (150 and 221% of the corresponding saline controls, respectively). There was no significant discharge of ^{125}I after perchlorate administration in either the phenobarbital- or technical pyrimethanil-treated group. There was no significant discharge of ^{125}I (61%) after perchlorate administration. The propylthiouracil-treated group showed a significant reduction in ^{125}I uptake (65% of the control) and a significant discharge of ^{125}I (61%) after perchlorate administration. At necropsy, increased thyroid weights (+76%) and relative thyroid/body weight ratio (+113%) were seen in animals treated with propylthiouracil when compared with the control. The results indicated that findings in animals treated with technical pyrimethanil were similar to those obtained with treatment of phenobarbital and different from propylthiouracil. Treatment with 5000 ppm technical grade SN 100309 resulted in an increase in ^{125}I uptake but no significant increase in perchlorate-induced discharge of ^{125}I. These data were consistent with the proposed mode of action of an indirect, extrathyroidal mechanism that may be responsible for histopathological changes in the thyroid, consistent with stimulation.

International Agency for Research on Cancer (IARC 1999) has provided the following three criteria for assessing the significance of thyroid tumours in rodents as potential human carcinogens:

- genotoxicity based on in vitro and in vivo assays;
- hormonal imbalance under the conditions of the carcinogenicity assay; and
- a defined mechanism for hormonal imbalance.

Pyrimethanil was not genotoxic in any of the in vitro or in vivo studies submitted. Pyrimethanil increases the activity of UDPGT that metabolizes T4, causing an increase in TSH that stimulates hormone production in the thyroid gland. Thus, pyrimethanil appears to meet the criteria for compounds not expected to cause thyroid tumours in humans at doses below those altering thyroid homeostasis.

Based on weight of evidence, the thyroid tumours in rats are of limited significance to humans. The thyroid tumours in rats occur at doses at which there is significant non-neoplastic pathology, and the mechanistic data provide support for the pathological changes in the thyroid. Non-genotoxic compounds causing thyroid adenomas in rats at doses at which there is significant non-neoplastic pathology are generally not considered to be human carcinogens.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for pyrimethanil is 0.17 mg/kg bw/day. The most appropriate studies for selection of toxicity endpoints for chronic dietary exposure was the chronic oncogenicity study in rats with a NOAEL of 17 mg/kg bw/day. This was supported by the long-term mouse study, the one-year dog study and a multigenerational reproduction (parental and offspring toxicity) study. The ADI was

based on the treatment-related decreases in body weights and histopathological liver alterations (hypertrophy, slight necrosis and increased size of hepatocytes). A total uncertainty factor of 100 is required to account for standard uncertainty factors of 10× for interspecies extrapolation and 10× for intraspecies variability.

$$\text{ADI} = \frac{17 \text{ mg/kg bw/day}}{100} = 0.17 \text{ mg/kg bw/day}$$

3.3 Acute Reference Dose

The acute neurotoxicity study in rats was selected based on ataxic gait, dilated pupils, decreased hind limb strength, motor activity and body temperature seen after a single dose of 1000 mg/kg bw pyrimethanil. The acute NOAEL was 100 mg/kg bw.

Uncertainty factor: 100 is applied to the NOAEL of 100 mg/kg bw/day.

Acute reference dose (ARfD) = 1 mg/kg bw/day

3.4 Toxicological Endpoint for Assessment of Occupational, Residential and Bystander Risks

Pyrimethanil is of low toxicity by the oral, dermal and inhalation routes and is non-irritating to the eyes and skin. Pyrimethanil is not a potential dermal sensitizer (see Table 3.1.1). The Scala SC Fungicide formulation is of low toxicity by the oral and dermal routes and is slightly toxic via inhalation. It is mildly irritating to skin, minimally irritating to eyes and is not considered to be a dermal sensitizer.

The toxicological endpoints selected are based on adverse effects seen in short-term, intermediate and long-term studies. Pyrimethanil is not acutely neurotoxic, mutagenic or carcinogenic in a manner relevant to humans and is extensively and rapidly metabolized and almost completely excreted within 48 hours. No significant tissue accumulation was evident. Pyrimethanil is not a developmental or reproductive toxicant. No increased susceptibility of fetuses to in utero exposure of pyrimethanil was demonstrated in the developmental toxicity studies in rats and rabbits. For short- and intermediate-term exposure, the NOAEL of 30 mg/kg bw/day from the one-year dog study with a target margin of exposure (MOE) of 100 was selected.

For the acute aggregate risk assessment, the NOAEL of 100 mg/kg bw from rat acute neurotoxicity study was selected, based on the acute reference dose.

A dermal absorption study was not submitted; therefore, a default dermal absorption value of 100% was used.

3.5 Impact on Human or Animal Health

3.5.1 Occupational Exposure and Risk

3.5.1.1 Handler Exposure and Risk

Farmers and custom applicators have potential for exposure to pyrimethanil during application to apples, pears, grapes (table, juice and wine), strawberries and potatoes. Only ground application is proposed (groundboom, airblast). Typical areas treated per day are 16 ha with airblast equipment for both farmers and custom applicators in orchards and vineyards; 5 ha per day for farmers and 32 ha per day for custom applicators in strawberries; and 80 ha per day for farmers and 300 ha per day for custom applicators in potatoes. Farmers and custom applicators would typically be exposed once every 7–10 days, 2–6 times during the growing season. There is potential for intermittent exposure over a short to intermediate term (1–8 weeks) starting as early as spring and continuing throughout the summer.

Exposure estimates for mixers, loaders and applicators are based on data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. The PHED subsets for liquid open mixing/loading and both groundboom and airblast application were used to estimate exposure during mixing/loading/application outdoors and were considered acceptable and applicable to the use scenario. With a few exceptions, the PHED estimates meet the criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement (NAFTA) Technical Working Group on Pesticides. The personal protective equipment considered in the PHED assessment was a single layer of clothing and gloves for mixer/loaders and a single layer for applicators. All exposure estimates were based on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part (best-fit). Systemic exposure estimates were determined based on a 100% dermal absorption value. The primary route of exposure was dermal, less than 15% was by inhalation.

Table 3.5.1.1.1 Summary of Mixer/Loader/Applicator Daily Exposure Estimates and Margins of Exposure for Pyrimethanil

Scenario	Daily Exposure (µg a.i./kg bw/day)		Margin of Exposure[1]
	Use	Exposure[2]	
Mixer/Loader/Applicator	Open cab groundboom (farmer/custom) Potatoes, strawberries	4.95–111.45	270–6050
Mixer/Loader/Applicator	Closed cab groundboom (custom) Potatoes, strawberries	82.09	365
Mixer/Loader/Applicator	Open cab airblast (farmer/custom) Apples, pears and grapes	81.08–162.15	185–370

1 MOE = NOAEL/exposure, target MOE of 100, NOAEL of 30 mg/kg bw/day (1-year dog study)
2 Exposure = PHED unit exposure (dermal value × dermal absorption rate + inhalation value) × total a.i. handled per day (application rate × area treated per day) / body weight (70 kg)

3.5.1.2 Postapplication Exposure and Risk

There is potential for postapplication exposure to workers re-entering field crops and orchards treated with Scala SC Fungicide to perform activities such as irrigating, weeding, thinning, scouting and hand harvesting. The number of applications ranges from two to six depending on the crop. Half lives range from one to five days. Thus, re-entry workers could be exposed to Scala SC residues intermittently throughout the growing season for an intermediate-term duration.

The primary route of exposure for re-entry workers is dermal through contact with foliar residues. Inhalation exposure is expected to be negligible as the vapour pressure of Scala SC is 2.2×10^{-3} Pa at 20°C and 1.1×10^{-3} Pa for pyrimethanil. Dermal exposure to workers re-entering treated areas is calculated by combining crop dislodgeable foliar residue (DFR) data together with activity-specific transfer coefficients (TCs). Activity TCs are based on data generated by the Agricultural Re-entry Task Force, of which Bayer CropScience Inc. is a member.

The applicant submitted three studies designed to establish a dissipation curve for pyrimethanil after application to apples, grapes and strawberries at four sites in the United States: one site in Pennsylvania, two sites in California and one site in New York. At each site, pyrimethanil was applied 2 to 4 times at rates of 0.488 to 0.796 kg a.i./ha using groundboom or airblast application equipment with a 7-day interval between applications. Dislodgeable residues were sampled from the leaves using a Birkestrand leaf puncher. Each sample consisted of 40 leaf punches and was taken in triplicate. Samples were taken before and after each application, and at least 9 times up to 35 days

after the last application. Analyses were performed for the samples taken before and after the first application. A control plot at each site was used to sample untreated leaves for field recovery.

In the apple study, after 4 applications of 0.488 kg a.i./ha, the peak residue value of 0.976 µg/cm^2 was observed after the second application. The residues degraded rapidly and reached the LOQ by seven days postapplication. In the strawberry study, after 3 applications of 0.796 kg a.i./ha, the peak residue value of 1.814 µg/cm^2 was observed immediately after the first application in New York while the peak residue value of 2.283 µg/cm^2 was observed after the first application in California. The residues reached the LOQ by 14 and 21days postapplication in New York and California respectively. For grapes, after 2 applications of 0.796 kg a.i./ha, the peak residue of 1.553 µg/cm^2 was observed after the first application. Pyrimethanil residues did not accumulate with successive applications. Regression lines were plotted using the natural log (ln) of the residue values vs the days after the final application. R^2 values were 0.69, 0.85, 0.89 and 0.97, and the half lives were 3, 2, 4 and 1 days for strawberries (California site), strawberries (New York site), grapes and apples, respectively.

These studies were well conducted and are considered acceptable.

The Pennsylvania apple study was used to estimate residues on apples and pears in Canada because the application rate and application equipment used are the same as those proposed for Canada. The New York strawberry study was used to estimate residues on strawberries and potatoes in Canada because the application rate and application equipment used are the same as those proposed for Canada and the New York site (versus California) is climatically more relevant to Canadian growing regions. The California grape study will be used to estimate residues in grapes in Canada because the application rate and application equipment are the same as those proposed for Canada.

Standard defaults were used for all crops including an assumption that workers spend 8 hours a day working and have a 70-kg body weight. Since the applicant is a member of the Agricultural Re-entry Task Force, the transfer coefficients based on Agricultural Re-entry Task Force data were used for risk assessment purposes. In addition, a dermal absorption value of 100% was used in the postapplication exposure assessment.

Table 3.5.1.2.1 Occupational Postapplication Exposure Estimates and Margins of Exposure for Pyrimethanil

Scenario	TCs (cm^2/hour)	Exposure (day 0) mg/kg bw/day[1]	Margin of Exposure[2]	Re-entry Interval
Apples, pears (0.4 kg a.i./ha)				
Thinning	3000	0.335	90	24 hours
Hand harvesting	1500	0.167	179	None required
Pruning/scouting	500	0.056	538	None required
Hand weeding	100	0.011	2690	None required
Apples (0.8 kg a.i./ha)				
Thinning	3000	0.669	45	24 hours
Hand harvesting	1500	0.355	90	24 hours*
Pruning/scouting	500	0.112	269	None required
Hand weeding	100	0.02	1345	None required
Grapes (all)				
Cane turning/girdling	10 000	1.771	17	24 hours
Training, tying, hand harvesting, pruning, thinning and leaf pulling	5000	0.886	34	24 hours
Scouting	1000	0.177	169	None required
Hand line irrigation, hand weeding and hedging	500	0.089	339	None required
Potatoes				
Scouting/hand line irrigation	1500	0.311	96	None required
Hand weeding	300	0.062	483	

Scenario	TCs (cm^2/hour)	Exposure (day 0) mg/kg bw/day[1]	Margin of Exposure[2]	Re-entry Interval
Strawberries				
Hand harvesting, pinching, pruning and training	1500	0.311	96	None required
Scouting, hand line irrigation, hand weeding and mulching	400	0.083	363	

[1] Exposure = DFR × transfer coefficient × hours spent working per day (8) × dermal absorption (100%) / body weight (70 kg)

[2] MOE = NOAEL/exposure, NOAEL of 30 mg/kg bw/day (1-year dog study) with a target MOE of 100

* The preharvest interval for apples sprayed at 0.8 kg a.i./ha is 14 days, so no hand harvest re-entry interval is required on the label.

3.5.2 Residential Exposure and Risk

There are no residential uses; therefore, a residential exposure assessment was not required.

3.5.3 Bystander Exposure and Risk

For the proposed agricultural use scenario, bystander exposure during application was considered minimal compared to mixer/loader/applicator and re-entry worker scenarios and, therefore, not quantified.

Adults and youth hand harvesting at pick-your-own operations have the potential for acute exposure to Scala SC residues as this activity is only expected to occur once per year in strawberries and apples. Exposure estimates were generated following the guidance in the USEPA *Draft Standard Operating Procedures for Residential Assessments*. Dermal exposure to bystanders re-entering treated strawberry fields or apple orchards is calculated by combining crop-specific DFR with activity-specific TCs. For the bystander risk assessment, the acute reference dose based on the NOAEL of 100 mg/kg bw from rat acute neurotoxicity study was selected.

Table 3.5.3.1 Adult and Youth Postapplication Exposure and MOEs for Pick-Your-Own Strawberries and Apples

Population	Dermal Exposure[1] (mg/kg/day)	Dermal MOE[2]
Strawberries		
Adults	0.078	1282
Youth (10–12 year old)	0.140	714
Apples		
Adults	0.084	1195
Youth (10–12 year old)	0.150	666

[1] Dermal exposure = DFR (µg/cm^2) × TC (1500 cm^2/hr for both adults and youths) × 2 hours × 100% dermal absorption × conversion factor (mg/µg)/ body weight (70 kg for adults, 39 kg for youths). The DFR value is based on the mean peak values from the study.

[2] MOE = NOAEL/exposure, based on a NOAEL of 100 mg/kg/day with a target of 100.

An aggregate risk assessment is required as adults and youth have potential for exposure to pyrimethanil residues from both dietary (food and drinking water) and pick-your-own sources via the dermal routes. The aggregate risk assessment is presented in Section 4.2.

4.0 Residues

4.1 Residue Summary

4.1.1 Nature of the Residue in Plants

Grape

Pyrimethanil radiolabelled in the phenyl ring was painted twice onto grapes and leaves of plants, maintained in a greenhouse, 45 days and 21 days before harvest, at a rate of 0.8 kg a.i./ha/application. When harvested 21 days following the second application, the average TRRs in grapes was 30 ppm. The treated grapes were washed with dichloromethane (removing 32.9–57.7% of the TRRs), homogenized and extracted with various organic solvents (releasing approximately 52% of the TRRs). The parent, pyrimethanil, accounted for the majority of the extractable radioactivity (93% of the TRRs). Non-extractable residues accounted for ≤ 3% of the TRRs (~0.83 ppm).

Apple

Pyrimethanil, radiolabelled either in the phenyl or the pyrimidyl rings, was streaked onto apple trees (both fruits and leaves), maintained outdoors, at a seasonal rate of ~1.8 kg a.i./ha. The application was made at growth stage 76 (fruit 20–30 mm in diameter). Apples and leaves were harvested 42 days after application. Treated apple fruit

and leaf samples were washed with dichloromethane (removing 10–25% of the TRRs on fruit and 38–39% of the TRRs on leaves), homogenized and extracted with various organic solvents. Approximately 2–6% of the radioactivity remained unextractable. Pyrimethanil was identified as the predominant residue in apples (75.6% of the TRRs [9.08 ppm] in the phenyl label study and 67.8% of the TRRs [6.23 ppm] in the pyrimidyl label study). Pyrimethanil was not extensively metabolized in apples. The metabolic profile for the two radiolabels was similar suggesting that cleavage of the diaryl amine linkage of the parent molecule was not a significant pathway in apples.

Tomato

Pyrimethanil radiolabelled either in the phenyl or the pyrimidyl ring was applied using a micropipette to either foliage or fruit of tomato plants grown hydroponically in climate controlled growth chambers. A total of 4 applications were made 4, 3, 2 and 1 weeks before harvest, each at a rate of 0.8 kg a.i./ha. Samples of fruit and leaves were washed with dichloromethane (removing 88–91% of TRRs on fruit and 84% of TRRs on leaves), homogenized and extracted using a variety of organic solvents. In tomato fruits, the majority of the TRRs (96.9%–97.6%) appeared to be associated with the peel. Approximately 0.5% of the TRRs in fruits and 1% of the TRRs in leaves were unextractable. Pyrimethanil was identified as the predominant residue in tomatoes (96%–97% of the TRRs).

Lettuce

Pyrimethanil, radiolabelled in the pyrimidyl ring, was applied twice to lettuce maintained under outdoor conditions as a foliar spray, 32 and 21 days before harvest, at a rate of 0.8 kg a.i./ha/application. Lettuce samples were collected at 0, 18 and 32 days after the first application. Samples were washed with dichloromethane (removing 81.0–99.0% of TRRs at PHIs of 1–18 days and 32% of TRRs at the PHI of 32 days) followed by extraction with chloroform:methanol:water. The remaining radioactivity was recovered in the aqueous extract. Unextractable ^{14}C-residues accounted for approximately 0.5–8.0% of the TRRs (0.3–1.5 ppm). Additional extractions with acid/base or enzymes were performed. The results demonstrated that as the amount of radioactivity in the surface wash decreased, a corresponding increase in radioactivity in the extract was observed, suggesting penetration and translocation of pyrimethanil in lettuce. In all cases, the predominant residue was the parent.

Carrot

Pyrimidyl-2-^{14}C-pyrimethanil was applied twice, either to soil or as a foliar treatment to carrot plants at growth stages BBCH 43 (when leaves have fully developed and roots are expanding) and BBCH 47 (21 days before crop was mature). Both application types were conducted following two different treatment regimes; either at a rate of 0.80 kg a.i./ha/application or 2.40 kg a.i./ha/application for a total seasonal rate of either 1.60 kg a.i./ha or 4.80 kg a.i./ha. Whole carrot plants were harvested 1 day and 21 days after each application with the final sample collected at maturity (growth stage BBCH 49).

Approximately 84–92% of the TRRs in carrot roots were extracted with organic solvents. Pyrimethanil was identified as the predominant residue in mature carrot roots harvested

21 days after the last application (70–89% of the TRRs). The metabolites AN2, 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine; AN4, 6-methyl-2-(phenylamino)-4-pyrimidinemethanol; and AN7, 2-amino-4,6-dimethylpyrimidine were identified (~1% of TRRs) in mature carrot roots following soil application of pyrimethanil. In carrot foliage approximately 77–85% of TRRs was in the dichloromethane surface wash, one day after foliar treatment while only 18% of TRRs was found in the dichloromethane wash, 21 days after foliar treatment. In mature foliage, approximately 48–53% of the TRRs was identified as pyrimethanil. Also identified in mature foliage were the minor metabolites AN2, AN4 and AN7 (0.2–1% of TRRs).

The metabolism of pyrimethanil occurred primarily via hydroxylation with minimal cleavage of the diaryl amine bond. The resulting hydroxylated metabolites (AN2, AN3, AN4 and AN5) underwent conjugation with glucose (or other C-6 sugars). A minor degradation route, only observed in carrot foliage following a foliar treatment, was cleavage of the amine linkage between the phenyl and the pyrimidyl rings of the parent molecule yielding metabolite AN7 (see Figure 4.1.1.1).

The ROC may be defined as pyrimethanil. The metabolism of pyrimethanil in plants is adequately understood.

Confined Accumulation in Rotational Crops

Pyrimidyl-2-^{14}C-pyrimethanil was applied to bare soil (sandy loam) at an application rate of 2.4 kg a.i./ha. Lettuce, radish and wheat were planted 30, 130 and 300 days after treatment (DAT). The TRRs at the 30 DAT interval ranged from 0.231 ppm (radish roots) to 8.201 ppm (wheat straw), while at the 130-DAT interval, TRRs ranged from 0.012 ppm (radish root) to 0.082 ppm (wheat straw). Residues in plant samples from the 300 days after treatment interval ranged from 0.009 ppm (lettuce) to 0.152 ppm (wheat straw). The predominant metabolites identified in rotational crops were AN7 and AN5 (up to 15% of the TRRs in 30-DAT lettuce). The magnitude of the residues in the rotational crops from the confined crop rotation study triggered a need for field accumulation studies.

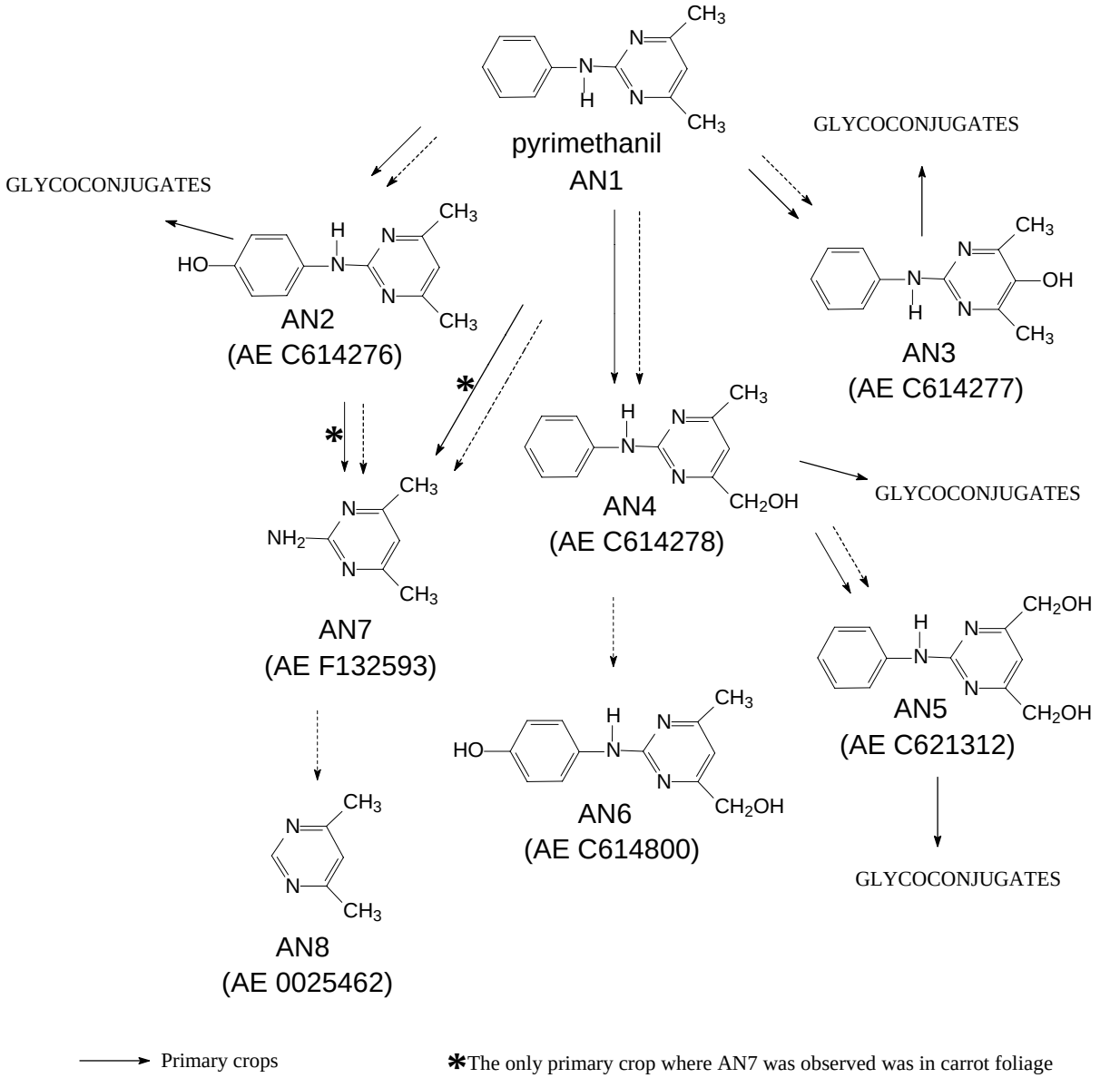
The metabolic pathway of pyrimethanil in wheat, as the secondary crop, proceeded via similar processes as that in the primary crops. Moreover, the metabolism of pyrimethanil occurred primarily via hydroxylation to AN2, AN3, AN4 and AN5. Another degradation route, involving the cleavage of the diaryl amine linkage of pyrimethanil and the AN2 metabolite, yielded the metabolites AN7 and AN8. Overall, pyrimethanil and the soil metabolites AN7 and AN8 appear to have been readily taken up, translocated throughout the plant and subsequently metabolized (see Figure 4.1.1.1).

Field Accumulation in Rotational Crops

Pyrimethanil (Scala 40SC) was applied to potatoes that were planted as the primary crop, at a rate of 2.4 kg a.i./ha/season (3 foliar applications at 800 g a.i./ha). Following the last application, the primary crop (potato) was harvested. Winter wheat was planted 30 days after the last treatment. All wheat raw agricultural commodities (RACs) were collected at normal harvest. No pyrimethanil residues at or above the LOQ of the enforcement

method (0.05 ppm) were detected in/on forage, hay, straw and grain collected from the 30 days after treatment plot. Residues of AN5 (predominant metabolite identified in the confined rotational study) in all the wheat matrices were below the method LOD of 0.015 ppm. Based on these results, a minimum plantback interval of 30 days will be required on the Scala 40SC label for wheat and of 130 days for all other crops not listed on the label.

Figure 4.1.1.1 Proposed Metabolic Profile of Pyrimethanil in Plants
(primary and secondary crops)



4.1.2 Nature of the Residue in Livestock

Dairy Cow

^{14}C-pyrimethanil (radiolabelled position not reported) was fed to a lactating British Friesian cow at a dose level of 10 mg/kg feed/day for 7 consecutive days. The animal was sacrificed 24 hours after the final dose. Approximately 97% of the administered dose (136 ppm) was excreted in the urine and 0.003% of the administered dose (0.036 ppm) was recovered in edible tissues, demonstrating low tissue burden. TRRs in tissues were 0.017 ppm in muscle, 0.036 ppm in renal fat, 0.249 ppm in kidney and 0.363 ppm in liver. TRRs in bile were 1.771 ppm. Residues in milk appeared to increase biphasically, reaching 0.0645 ppm by the second day (47 hours), and then peaking again (0.0688 ppm) by the fifth day (119 hours). Minimal bioconcentration was observed in milk and tissues.

The parent, pyrimethanil was not detected in any of the tissues. The metabolite AN2 accounted for the majority of the radioactivity in urine (69% of the TRRs), while the metabolite AN2 and its associated sulfate and glucuronide conjugates accounted for the majority of the radioactivity in milk (64% of the TRRs) and kidney (46.3% of TRRs). In muscle, 52.9% (0.009 ppm) of the TRRs were organosoluble (hexane and methanol); however, as each of the extracts were less than 0.01 ppm, these were not analyzed further. Similarly, unextractable TRRs comprised 47.1% (0.008 ppm) and were not characterized further. In liver, most of the radioactivity appeared to be incorporated into peptides and amino acids.

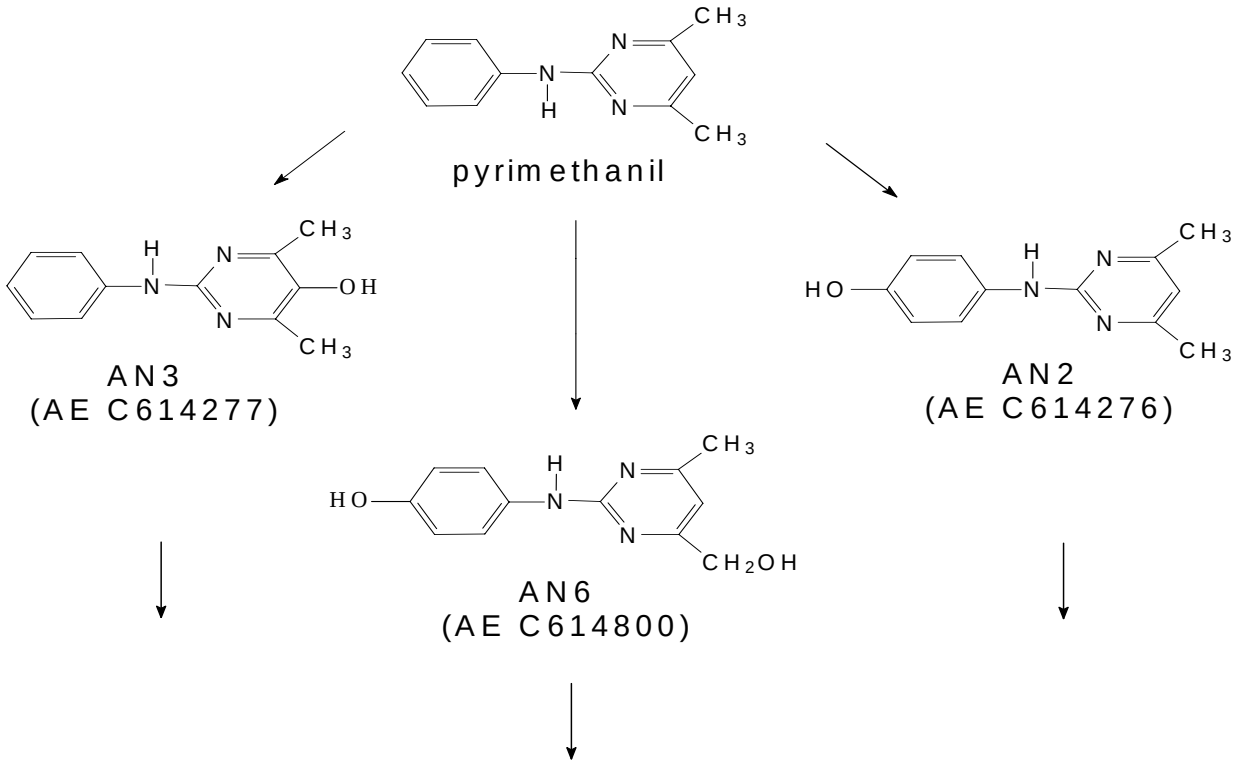
Based on the findings of the dairy cow metabolism study, the ROC in ruminant tissues may be defined as pyrimethanil and the metabolite AN2 (AE C614276) and in milk, may be defined as pyrimethanil and the metabolite AN3 (AE C614277) for enforcement and risk assessment purposes. The metabolism of pyrimethanil in ruminants is adequately understood.

Laying Hen

A poultry metabolism study is not required for the petitioned uses.

The metabolic profile of pyrimethanil in the dairy cow was very similar to that in the rat. In the rat, pyrimethanil was absorbed and extensively metabolized. The metabolism of the parent proceeded primarily via oxidation of the anilino ring (I), with minor routes comprising of oxidation of the pyrimidyl ring or oxidation of the methyl groups of the pyrimidyl ring (II, III, IV or V). Similarly, the main route of metabolism of pyrimethanil in cattle was by oxidation to the phenol (I), including the glucuronic and sulfate conjugates, and elimination via the urine (see Figure 4.1.2.1). Minimal bioconcentration in muscle, milk or fat was observed.

Figure 4.1.2.1 Proposed Metabolic Profile of Pyrimethanil in Dairy Cow



CONJUGATES

Methods for Residue Analysis of Plants and Plant Products

A GC-MS method (DGM C05/98-0) was proposed for data-gathering and enforcement purposes. Briefly, samples were homogenized, extracted with acetone, filtered and centrifuged. Aliquots of the extract were acidified and washed with hexane before basifying to enable solvent partitioning. The upper hexane layer was discarded, and the extract was washed with fresh hexane. Saturated sodium hydrogen carbonate was added prior to partitioning with a solvent mixture (hexane/ethyl acetate, 3:1, v/v). The partitioning was repeated, and the organic layers were combined, dried under dry nitrogen and dissolved in hexane for clean-up by silica solid-phase extraction. Residues were determined by GC-MS.

The method LOQ for pyrimethanil residues was reported as 0.05 ppm. This method was found to give acceptable recoveries (mean recoveries ranging from 74–100% at the 0.05 ppm spiking level and from 79–94% at the 0.5 ppm spiking level) for the analysis of pyrimethanil in/on potato, carrot, tomato, green bean, lettuce, sweet pepper, strawberry, raspberry, apple, grape and banana.

The ILV demonstrated the reliability and reproducibility of Method DGM C05/98-0 for the determination of pyrimethanil in plant matrices.

A radiovalidation study conducted using lettuce samples collected from the metabolism demonstrated that the method can adequately extract and recover residues of pyrimethanil (81.3% of the TRRs comparable to 77.2% of the TRRs from the metabolism study) in/on plant matrices.

Therefore, method DGM C05/98-0 is valid as a data-gathering method and enforcement method for the determination of pyrimethanil residues in plant matrices.

Methods for Residue Analysis of Food of Animal Origin

A GC-MS/MS method (Method RAM AN/01/01 Version 2 superseded by RAM AN/01/02) was proposed for data-gathering and enforcement purposes. Briefly, homogenized livestock tissues (except fat) were extracted with acetonitrile/0.6M HCl (92:8, v/v). Fat samples were extracted with acetonitrile under reflux conditions. Milk samples were extracted with concentrated HCl/acetonitrile (1:50, v/v), centrifuged and filtered. The remaining milk solids were further extracted with pH 7 phosphate buffer/acetonitrile (1:1, v/v), centrifuged, filtered and extracted once more with acetonitrile. Following filtration, the extract (was acidified, fat tissue only) was adjusted to a known volume by addition of acetonitrile. An aliquot of the extract was partitioned three times into hexane. The hexane fractions were discarded. The resulting extract was evaporated to dryness, re-constituted in methanol and derivatized with trimethylsilyl diazomethane (TSMD) for analysis by GC-MS/MS.

In milk and kidney matrices only, the methanol extracts were subjected to enzyme digestion with β-glucuronidase and sulfatase at 37°C overnight to release the conjugates of the metabolites AN2 and AN3. Both milk and kidney hydrolysates were partitioned into ethyl acetate, evaporated to dryness, reconstituted in acetone and derivatized with TSMD for analysis by GC-MS/MS.

The method LOQ was reported as 0.01 ppm in milk and as 0.05 ppm in livestock tissues for each analyte (pyrimethanil, metabolites AN2 and AN3 [in milk]). This method was found to give unacceptable recoveries (68–137%) for the analysis of beef muscle. Standard deviations reached 25% in whole milk and 22% in beef kidney.

The ILV demonstrated the reliability and reproducibility of Method RAM AN/01/01 Version 2 for the determination of the ROC in milk and marginally support the reliability and reproducibility of Method RAM AN/01/01 Version 2 for the determination of the ROC in beef muscle.

A radiovalidation study conducted using kidney and milk samples spiked with ^{14}C-pyrimethanil indicated that the method can adequately extract and recover residues of pyrimethanil, AN2 and AN3 from kidney and milk samples.

Based on the submitted recovery data, Method RAM AN/01/01 Version 2 (or RAM AN/01/02) is considered conditionally acceptable for the analysis of residues of pyrimethanil and the metabolite AN2 in livestock tissues as well as metabolite AN3 in milk. To use Method RAM AN/01/01 Version 2 as the enforcement method, the registrant must provide information describing the various conditions that may be implemented to optimize the method recoveries and provide new recovery data validating the implemented changes to the method in livestock matrices.

Storage Stability Data—Plant/Livestock

The data presented in the freezer storage stability study indicated that residues of pyrimethanil were stable at -20°C for 12 months in grape, carrot, tomato and lettuce, 844 days (~28 months) in apple and 912 days (~30 months) in peach.

No freezer storage stability data were submitted for residues of pyrimethanil and the metabolites AN2 and AN3 in livestock matrices as well as for residues of pyrimethanil in apple processed fractions. Such data are required in order to validate the livestock feeding study and the apple processing study.

4.1.3 Crop Field Trials

Apple

Supervised crop field trials were conducted in the United States and in Canada [Zone 1 (3 trials), Zone 1A (1 trial), Zone 2 (1 trial), Zone 5 (5 trials), Zone 5B (3 trials), Zone 9 (1 trial), Zone 10 (1 trial), and Zone 11 (5 trials)] with Scala SC. Trials were conducted with either of the following application regimes: early season, late season and combination of early and late season. The trials in the United States were carried out with the early season treatment regime at a seasonal rate of 1800 g a.i./ha. Mature apples were harvested 72 days after the last application. Each of the Canadian trials consisted of 3 plots. Plot A received an early season application, Plot B received a combination of early and late season applications and Plot C received a late season application. Apple trees in Plot A were treated with 4 broadcast foliar spray applications at a rate of 400 g a.i./ha/application with retreatment intervals of 4–7 days for a maximum seasonal rate of 1600 g a.i./ha. Mature apples were harvested 65–72 days after the last application. Apple trees in Plot B were treated with 5 broadcast foliar spray applications. The first 4 applications were made at a rate of 400 g a.i./ha/application with retreatment intervals of 4–7 days. The fifth application was made 14 days prior to harvest at a rate of 800 g a.i./ha. The maximum seasonal rate for this plot was 2400 g a.i./ha. Mature apples were harvested 14 days after the last application. Apple trees in Plot C were treated with a single broadcast foliar spray application at a rate of 800 g a.i./ha. Mature apples were harvested 14 days thereafter.

The supervised residue trials conducted with the early season application satisfied the Canadian zonal requirements (as per Section 9 of Regulatory Directive DIR98-02, *Residue Chemistry Guidelines*). The maximum residues in apples, collected 72 days after the last application, were 0.16 ppm. Results from the decline study showed that pyrimethanil residues remained stable within the PHIs of 65 to 93 days.

The supervised residue trials conducted with the single late season application and the combination of early and late season applications did not satisfy the Canadian zonal requirements (as per DIR98-02) and accordingly, a national registration of pyrimethanil on apples (for late season and a combination of early and late season applications) could not be supported. However, for the combination of early and late season applications, a regional registration in Quebec and Ontario can be granted on a temporary basis pending the submission of an additional trial in Zone 5 conducted according to the label directions. The maximum residues of pyrimethanil in/on apples collected 14 days after the early and late season applications were 0.57 ppm (Zone 5 and Zone 5B only).

Pear

Supervised crop field trials were conducted in the United States [Zone 1 (1 trial), Zone 10 (2 trials), and Zone 11 (3 trials)]. Scala SC was applied at a seasonal rate of 1800 g a.i./ha. The results from these trials showed that pyrimethanil residues were all below 0.05 ppm (LOQ) in pears harvested 72 days following the last application. Results from the residue decline trial also showed that pyrimethanil residues were all below 0.05 ppm (LOQ) in pears harvested at PHIs of 65 to 93 days. Even though the residue data submitted appear consistent (all < 0.05 ppm; LOQ) the trials did not satisfy the Canadian zonal requirements (as per DIR98-02). However, based on a weight of evidence approach, the apple residue data (early season application) can be used as bridging data to support the registration of pyrimethanil on pear because apple is a representative crop of the pome fruits crop group (Crop Group 11). Furthermore, there were quantifiable residues in/on apples (up to 0.16 ppm) treated at 1.6 kg a.i./ha/season and harvested 72 days following the last application, thus representing a worse case scenario. Accordingly, the registration of pyrimethanil on pears can be supported.

Grape

Supervised crop field trials were conducted in France, Germany, Italy, Spain, Australia, New Zealand, South Africa and Chile where grape vines were treated at 0.8 to 1.0 kg a.i./ha. The maximum residues in grapes, collected 7 to 42 days after the last application, were 3.20 ppm. Consequently, a maximum residue limit (MRL) of 5 ppm was established to cover residues of pyrimethanil in/on imported grapes.

To support the domestic registration of Scala SC, additional supervised crop field trials conducted in the United States [Zone 1 (2 trials), Zone 10 (8 trials) and Zone 11 (2 trials)] and in Canada [Zone 5 (3 trials)] were submitted. Scala SC was applied at seasonal rates of 1.60–2.40 kg a.i./ha. The maximum residues in grapes, collected 7 days after the last treatment, were 2.56 ppm when treated at 1.60 kg a.i./ha and were 2.67 ppm when treated at 2.40 kg a.i./ha. Residue decline studies in grapes demonstrated that the established MRL of 5 ppm will not be exceeded when grapes are collected at a PHI of 7 days.

The supervised residue trials submitted did not satisfy the Canadian zonal requirements (as per DIR98-02). However, when the whole database for pyrimethanil residues in/on grapes is considered, no additional residue trials for pyrimethanil in/on grapes will be required.

Accordingly, the registration of pyrimethanil on grapes can be supported. Consequently, the established MRL to cover residues of pyrimethanil in/on imported grapes of 5 ppm is acceptable to cover residues of pyrimethanil in/on domestic grapes.

Strawberry

Supervised crop field trials were conducted in the United States and in Canada [Zone 1 (1 trial), Zone 2 (1 trial), Zone 3 (1 trial), Zone 5 (1 trial), Zone 5A (1 trial), Zone 5B (1 trial), Zone 10 (3 trials) and Zone 12 (1 trial)]. The number and location of the residue trials were in accordance with DIR98-02. Scala was applied at a seasonal rate of 2.40 kg a.i./ha. The maximum residues in strawberries, collected 1 day after the last treatment, were 2.44 ppm. Residue decline studies demonstrated that residues of pyrimethanil decreased with longer PHIs (0–21 days). Accordingly, the registration of pyrimethanil on strawberries can be supported.

Potato

Supervised crop field trials were conducted in the United States [Zone 1 (2 trials), Zone 2 (1 trial), Zone 3 (1 trial), Zone 5 (2 trials), Zone 5A (2 trials), Zone 9 (1 trial, Colorado), Zone 10 (1 trial), and Zone 11 (6 trials)]. The number and locations of the field trials were not in accordance with Section 9 of DIR98-02. However, these 16 trials represented a wide diversity of agronomic conditions and a large spectrum of geographical locations (from north to south and from west to east of the United States) for a total of 8 different zones. As residues of pyrimethanil in/on potatoes, treated with Scala 400 SC at a maximum seasonal rate of 1.50 kg a.i./ha and harvested 7 days following the last of 6 applications, were consistently below the method LOQ of 0.05 ppm, no additional trials were required. Accordingly, the registration of pyrimethanil on potato can be supported.

Field Tomato

Supervised crop field trials were conducted in the United States [Zone 1 (1 trial), Zone 2 (1 trial), Zone 3 (2 trials), Zone 5 (1 trial) and Zone 10 (11 trials)]. The number and locations of the field trials were in accordance with the United States Office of Prevention, Pesticides and Toxic Substances Guideline 860.1500. Scala was applied at a seasonal rate of 1.50 kg a.i./ha. The maximum residue in tomatoes collected 1 day after the last treatment was 0.38 ppm. The residue decline study showed a decline in residues with longer PHIs (0 to 21 days). Therefore, an MRL covering residues of pyrimethanil in/on imported tomatoes can be promulgated.

4.1.4 Processed Food/Feed

Grape

Pyrimethanil was applied to grape vines at 4 kg a.i./ha and the grapes were processed into juice, wet pomace, dry pomace, raisin and raisin waste. A comparison of the residues in the RAC with those in each processed fraction resulted in a reduction of the residues in juice (0.7×) and in a concentration of the residues in all the other processed fractions; 2.3× for wet pomace, 6.5× for dry pomace, 1.6× for raisins and 18.1× for raisin waste. An MRL of 8 ppm was established to cover residues of pyrimethanil in/on imported raisins.

Potato
Pyrimethanil was applied to potato plants at 7.5 kg a.i./ha equivalent to the highest theoretical concentration factor (5×) for potatoes. Potato tubers were harvested at a PHI of 7 days and processed into chips, flakes and wet peels. Residues of pyrimethanil in whole potato tubers (RAC) were all below the LOQ of 0.05 ppm. Therefore, the processed potato fractions were not analyzed. There is no expectation that the pyrimethanil residues will concentrate in the potato processed fractions (1×).

Apple
Pyrimethanil was applied to apple trees at 8.8 kg a.i./ha. The apple fruits were harvested at a PHI of 73 days and processed into wet pomace and juice. A comparison of the residues in the RAC with those in each processed fraction resulted in a reduction of the residues in juice (0.4×) and in concentration of the residues in wet pomace (4.1×).

Tomato
Pyrimethanil was applied to tomato plants at 7.6 kg a.i./ha. The tomatoes were harvested at a PHI of 1 day and processed into puree and paste. A comparison of the residues in the RAC with those in each processed fraction resulted in a reduction of the residues in puree (0.3×) and in concentration of the residues in paste (1.2×).

In the absence of freezer storage stability data demonstrating the stability of pyrimethanil residues in processed commodities, the validity of the data could not be determined.

4.1.5 Meat/Milk/Poultry/Eggs

Dairy Cow
Lactating Holstein cows were administered either 1, 3, 10 or 50 mg pyrimethanil/kg feed/day orally by gelatin capsule for 28 consecutive days. Cows were milked twice daily and tissue samples (muscle, liver, kidney and fat) were collected five hours after the last dose. No quantifiable residues of pyrimethanil were observed in tissue samples across all dose groups. Residues of the metabolite AN2 were below LOQ in beef liver, muscle and fat from the highest (50 ppm) dose group. In the kidney, average residue of the metabolite AN2 were 0.07 ± 0.01 ppm, 0.12 ± 0.02 ppm and 0.63 ± 0.35 ppm in the 3 ppm, 10 ppm and 50 ppm dose groups, respectively.

In whole milk, no quantifiable residues of pyrimethanil were measured in any of the dose groups. In the 50-ppm dose group, although no quantifiable residues of AN2 were found in whole milk, residues of AN2 in skim milk were 0.015 ppm. Maximum residues of the metabolite AN3 were observed in milk samples collected on day 22 (0.025 ppm) for the 10-ppm dose group and on day 27 (0.088 ppm) for the 50-ppm dose group. Residues of AN3 in milk from the 1- and 3-ppm dose groups were non quantifiable, while residues of AN3 in milk fat and skim milk from the 50-ppm dose group were 0.031 ppm and 0.064 ppm, respectively.

Therefore, it is expected that crop feed commodities treated according to the use directions will not result in combined residues of pyrimethanil and AN2 exceeding

0.10 ppm and 0.13 ppm in meat and meat by-products, respectively. Combined residues of pyrimethanil and AN3 in milk are not expected to exceed 0.02 ppm.

Laying Hen
The requirement for a poultry feeding study was not triggered because pyrimethanil is not proposed for use on any crop that are fed to poultry.

Dietary Risk Assessment
The proposed domestic use of pyrimethanil on grapes, potatoes, strawberries, apples and pears and import of pyrimethanil-treated tomatoes do not pose an unacceptable acute or chronic non-cancer dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

The acute and chronic non-cancer dietary risk assessments included acute and chronic expected environmental concentrations (EECs) for groundwater that consisted of residues of pyrimethanil and the transformation product ZK 512723. The dietary risk assessment assumed that the toxicity of ZK 512723 is accounted for by the toxicity of pyrimethanil. Exposure to pyrimethanil from food and water for all of the population subgroups using conservative assumptions is only 12.90–57.10% of the ADI; therefore, it is not expected that the estimated dietary risk will change significantly on the basis of additional toxicological information for ZK 512723. However, as a condition of the temporary registration of pyrimethanil, the petitioner will be required to provide more information on the toxicological properties of ZK 512723.

4.2 Residues Relevant to Consumer Safety

Aggregate Exposure and Risk Assessment
Dermal exposure resulting from pick-your-own operations in strawberries and apples will be aggregated with acute and chronic dietary exposure. The dermal exposure values calculated for harvesting strawberries and apples will be added to the one day acute dietary exposure from eating fresh strawberries or apples plus the chronic daily dietary exposure for all commodities to give a one day estimate of exposure to bystanders who pick and eat treated fruit on the same day.

For the strawberry pick-your-own scenario, the refined chronic dietary exposure from food and water for adults (20–49) and youths (6–12) are 0.021979 and 0.045249, respectively. The acute dietary exposure from strawberry for the total population of 0.000412 mg/kg bw/day (95^{th} percentile; deterministic) was used. For the apple pick-your-own scenario, the refined chronic dietary exposure from food and water for adults (20–49) and youths (6–12) are 0.021979 and 0.045249, respectively. The acute dietary exposure from apples for the total population of 0.001291 mg/kg bw/day (95^{th} percentile; deterministic) was used.

Table 4.2.1 Aggregate Exposure for Both Adult and Youth Bystanders Performing Pick-Your-Own Activities in Strawberries and Apples

Population	Pick-Your-Own Dermal	Acute Dietary	Chronic Dietary	Aggregate[1]	MOE (target 100)[2]
	Strawberries (mg a.i./kg bw/day)				
Adults (20–49)	0.078	0.00041	0.021979	0.100	996
Youths (6–12)	0.14	0.00041	0.045249	0.186	539
	Apples (mg a.i./kg bw/day)				
Adults (20–49)	0.084	0.001291	0.021979	0.107	932
Youths (6–12)	0.15	0.001291	0.045249	0.197	509

[1] Aggregate exposure is the sum of dermal (from pick-your-own), acute dietary (commodity specific) and chronic dietary (from food and water) exposures.

[2] MOE = NOAEL/exposure, based on a NOAEL of 100 mg/kg bw from rat acute neurotoxicity study with a target of 100.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

The submitted data on the physicochemical properties of pyrimethanil were reviewed by the PMRA, Compliance, Lab Services and Regional Operations Division, Laboratory Services Subdivision. Pyrimethanil is very soluble in water and is expected to remain a neutral molecule at environmentally relevant pHs. The vapour pressure and Henry's law constant indicate that pyrimethanil is non-volatile. Furthermore, pyrimethanil has a low potential for light-induced phototransformation under environmental conditions.

The *n*-octanol–water partition coefficient indicates that pyrimethanil has a low potential to bioaccumulate. Data were not available on the physicochemical properties of the major transformation products.

5.2 Abiotic Transformation

Laboratory studies on the hydrolysis, phototransformation on soil and phototransformation in water were submitted to determine the effect of abiotic processes on pyrimethanil. In a hydrolysis study, the hydrolytic half-lives of pyrimethanil were estimated to be 722 days at pH 9 and 962 days at pH 7. The half-life of pyrimethanil at pH 5 could not be estimated because no transformation occurred. No major transformation products were detected at any pH. At environmentally relevant pHs (pH 5 and pH 7), hydrolysis is not expected to be an important route of transformation. Phototransformation of pyrimethanil is not expected to be an important route of

transformation on soil surfaces. A study of phototransformation on soil was waived because pyrimethanil shows minimal absorption of light above the 300 nm wavelength. Pyrimethanil does not phototransform in water, and the field dissipation times 50% (DT_{50}s) were of sufficient length to indicate that phototransformation on soil is not likely to be an important transformation pathway. The aqueous phototransformation of radiolabelled pyrimethanil was studied, and results indicate that pyrimethanil remains stable when irradiated at environmentally relevant pHs (pH 5, pH 7, pH 9).

5.3 Biotransformation

Laboratory studies on the biotransformation of pyrimethanil in aerobic soil, anaerobic soil, aerobic water/sediment and anaerobic water/sediment systems were reviewed to determine the effect of biotic (microbial) processes on pyrimethanil.

Biotransformation processes were examined in aerobic loamy sand, sandy loam and loam soils. Pyrimethanil transformed most rapidly in the sandy loam with a first-order DT_{50} of approximately 25 days. Transformation in the other soils was slower with first-order DT_{50}s of 70 and 72 days in the loam and loamy sand soil, respectively. These values would classify pyrimethanil as a slightly to moderately persistent pesticide in aerobic soils, according to the scheme of Goring et al. (1975). Two transformation products were detected at concentrations approaching 10% of the applied radiocativity (AR) in aerobic soil. One unidentified transformation product (U2) increased to a maximum 6.6% of the AR by the end of the study in the loamy sand without showing signs of decreasing. U2 was not identified in significant concentrations in either of the other soils tested. The second transformation product was identified as 2-amino-4,6-dimethylpyrimidine (ZK 512723) and increased to a maximum of 8.3% of the AR on day 62 and then decreased to 1.1% of the AR by the end of the study in the sandy loam. There were several minor transformation products identified in all soils tested, but none exceeded 5% of the AR at any time and most were below 1%.

The aerobic transformation of ZK 512723 was also studied in a loamy sand. Concentrations of ZK 512723 decreased from 98.0% of the AR to 7.4% over the course of the study. Four transformation products were detected, none of which exceeded 1.0% of the AR. The first-order DT_{50} was estimated to be 127 days, which classifies this transformation product as moderately persistent.

One study examining the biotransformation of pyrimethanil in an anaerobic sandy loam soil was reviewed. The concentration of pyrimethanil decreased from 99.4% of the AR at day 0 to 25.8% by the end of the study period. The only major transformation product was ZK 512723, which reached a maximum concentration of 13.6% of the AR on the 30th day of incubation and then decreased to 10.0% by the end of the incubation. The DT_{50} for pyrimethanil under anaerobic condition was estimated to be greater than 300 days, which classifies pyrimethanil as persistent in anaerobic soils.

Two studies on the aquatic biotransformation of pyrimethanil in water/sediment systems were reviewed. In the first study, the biotransformation of pyrimethanil was studied in

two aerobic water/sediment systems from Germany. The first system used a sandy loam sediment and the second system consisted of a sand. In the sandy-loam system, the concentration of parent compound decreased from 97.8% of the AR at day 0 to 51.4% at the end of the study period. In the sand test system, the concentration of the parent compound decreased from 98.9% of the AR at day 0 to 15.9% at the end of the study period. The DT_{50} (first-order) for the transformation of the parent compound was calculated to be 8.9 and 24 days in the water, 101 and 44 days in the sediment, and 121 and 40 days in the entire system for the sandy-loam and sand systems, respectively. No major transformation products were detected in the sandy-loam system. However, ZK 512723 had reached 6.1% of the AR by the last day of the incubation and was still increasing. The major transformation product detected in the sand system was also ZK 512723, with a maximum concentration of 10.4% of the AR, observed on the last day of incubation.

In the second study, the anaerobic biotransformation of pyrimethanil was studied in a pond water/sandy loam sediment system for 364 days. AR partitioned from the water to the sediments such that 92.8% was in the sediments by the end of the study and 40.8% of the AR could be attributed to the parent. In the sediment/water system as a whole, pyrimethanil decreased from 93.9% of the AR at day zero to a minimum of 69.4% at day 272. The first-order DT_{50} of pyrimethanil in the entire system was 566 days. There is little transformation of pyrimethanil in anaerobic sediment/water systems and pyrimethanil tends to associate with sediment. No major transformation products were formed over the course of the study.

Overall, biotransformation is an important route for the transformation of pyrimethanil under aerobic conditions in soil. However, pyrimethanil is expected to be persistent under anaerobic conditions. In aquatic environments, pyrimethanil rapidly partitions from water to sediment, which may act as a sink for this compound. Based on studies of biotransformation, pyrimethanil is expected to be slightly to moderately persistent in aerobic aquatic systems but persistent in anaerobic water/sediment systems.

5.4 Mobility

Adsorption-desorption studies in the United States were conducted on a soil (sandy loam, pH 8.0, 0.58% organic carbon) and a sediment (loamy sand, pH 6.3, 1.97% organic carbon). The results of these studies indicate that pyrimethanil has K_{oc} values of 438 and 686 in the loamy sand and sandy loam, respectively, which classify this pesticide as having low to moderate mobility in soil. Aged and unaged soil column leaching studies on a variety of soils in Europe found less than 5% of the AR was leached out of the 30-cm soil columns. However, these studies demonstrated that in four of five soils tested there was significant penetration of the AR into the soil (> 20 cm). The aged study also showed that the transformation product ZK 512723 penetrated the column to a depth exceeding 20 cm. The ratio of parent to transformation product decreased from 10:1 above 20 cm to about 3:1 below 20 cm, indicating that the transformation product may be more mobile than the parent. The results of the column leaching studies support the findings of the adsorption-desorption study.

5.5 Dissipation and Accumulation under Field Conditions

Results of terrestrial field dissipation and accumulation studies conducted in Canada (Branchton and Winchester, Ontario) in bare plots indicated that pyrimethanil was moderately persistent in soil, with decline time values of 75 and 153 days, respectively. The transformation product 2-amino-4,6-dimethylpyrimidine was detected at both sites. No residues were found below the 15-cm depth. Based on the estimated DT_{50}s, the carryover of pyrimethanil was calculated to be 17% and 24% for Branchton and Winchester, respectively. These field study results are in agreement with the findings from laboratory studies that indicate that in terrestrial environment pyrimethanil will be slightly to moderately persistent in soils and of low to moderate mobility.

5.6 Bioaccumulation

The log K_{ow} of pyrimethanil is 2.8, indicating no need for a fish bioconcentration study.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

Laboratory studies on the transformation of pyrimethanil in soil indicate that the biotransformation of pyrimethanil is an important transformation route in aerobic soil in comparison with phototransformation or hydrolysis. Hydrolysis is not an important transformation route with half-lives of 722 days at pH 9 and 962 days at pH 7. There are no major transformation products formed during hydrolysis. Phototransformation of pyrimethanil is also not expected to be an important route of transformation on soil surfaces. A phototransformation study was waived because pyrimethanil shows minimal absorption of light above the 300-nm wavelength, does not phototransform in water and because the field dissipation DT_{50}s were of sufficient length to indicate that phototransformation on soil is not likely to be an important transformation pathway.

The aerobic soil transformation of pyrimethanil was studied in three different soils. DT_{50} values ranged from 25–72 days depending on the type of soil, classifying pyrimethanil as a slightly to moderately persistent pesticide in aerobic soils according to the scheme of Goring et al. (1975). One major transformation product, ZK 512723, was detected in aerobic soil and a second unidentified transformation product reached a maximum of 6.6% of the AR by the end of the study. The aerobic transformation of ZK 512723 was also studied in a loamy sand. The DT_{50} was estimated to be 127 days, which classifies this transformation product as moderately persistent. One study examining the biotransformation of pyrimethanil in an anaerobic sandy loam soil was reviewed. The only major transformation product was 2-amino-4,6-dimethylpyrimidine. The DT_{50} for pyrimethanil under anaerobic condition was estimated to be in excess of 300 days, which classifies pyrimethanil as persistent in anaerobic soils. Adsorption-desorption studies in the United States were conducted on a soil and a sediment. The results of these studies indicate that pyrimethanil has K_{oc} values of 438 to 686, which classifies this pesticide as having low to moderate mobility in soil, based on the classification of McCall et al. 1981. Aged and unaged soil column leaching studies on a variety of soils in Europe found less than 5% of the AR was leached out of the 30-cm soil columns, but did find that there was

significant penetration of the AR into the soil (> 20 cm) in four of 5 soils tested. The aged column leaching study found that the major transformation product 2-amino-4,6-dimethylpyramidine also penetrated the column to a depth exceeding 20 cm, and the ratio of parent to transformation product decreased from 10:1 above 20 cm to about 3:1 below 20 cm, indicating that the transformation product may be more mobile than the parent. The results of the column leaching studies support the findings of the adsorption-desorption study.

A field dissipation study was conducted at sites in Branchton and Winchester, Ontario. The estimated DT_{50}s were 75 and 153 days, and DT_{90}s were 250 and 508 days at the Branchton and Winchester sites, respectively. These DT_{50}s would classify pyrimethanil as moderately persistent in soil. The transformation product ZK 512723 was detected at both sites. No residues were found below the 15-cm depth. Based on the estimated DT_{50}s the carryover of pyrimethanil was calculated to be 17% and 24% for Branchton and Winchester, respectively.

Overall the data on environmental fate in the terrestrial environment indicate that the major route of transformation will be aerobic biotransformation. Field studies with pyrimethanil support the findings in the laboratory, which indicate that in terrestrial environments pyrimethanil will be slightly to moderately persistent in soils and of low to moderate mobility. Field studies have shown that carryover of this pesticide from one growing season to the next is not expected to be a concern.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Laboratory studies indicate that biotransformation of pyrimethanil will be an important transformation pathway in aerobic aquatic systems as compared to biotransformation in anaerobic systems and abiotic processes. Hydrolysis is not an important transformation route with half-lives of 722 days at pH 9 and 962 days at pH 7. There are no major transformation products formed during hydrolysis. The aqueous phototransformation of radiolabelled pyrimethanil was studied, and results indicate that pyrimethanil remains stable when irradiated at environmentally relevant pHs (pH 5, pH 7, pH 9). A laboratory study on aerobic aquatic transformation indicated that pyrimethanil rapidly partitions to the sediment and that pyrimethanil will be slightly to moderately persistent in aerobic aquatic systems with aquatic aerobic DT_{50}s (first-order) of 40 and 121 days. The major transformation product in aerobic water was ZK 512723, which attained levels of 6.1 and 10.4% of the AR depending on the system tested and was continuing to increase when the studies were terminated. One laboratory study on the biotransformation of pyrimethanil in anaerobic aquatic systems was conducted with estimated DT_{50}s for pyrimethanil of 566 days in the entire system. These results indicate that, in anaerobic aquatic systems, pyrimethanil is rapidly partitioned from the water column to the sediment where it remains persistent. No major transformation products were formed over the course of the study.

Overall, the data on environmental fate in the aquatic environment indicate that the major route of transformation will be aerobic biotransformation. The data also indicate that the

parent and transformation product will partition to sediments where they will remain moderately persistent to persistent.

5.9 Expected Environmental Concentrations

5.9.1 Soil

The soil EEC was estimated to be 1.0 mg pyrimethanil/kg soil, assuming a maximum application rate of 800 g a.i./ha applied 3 times with an interval of 7 days and a soil aerobic DT_{50} of 153 days.

5.9.2 Aquatic Systems

Drinking Water
Pyrimethanil has low to moderate mobility in soils and transforms in soil and aquatic environments to a series of minor transformation products and the primary transformation product, ZK 512723. The ZK 512723 transformation product is more persistent and mobile than the parent. For the purposes of the assessment, 50% conversion from the parent compound to the 2-amino-,6-dimethylpyramidine transformation product was assumed.

Pyrimethanil and ZK 512723 residues in potential drinking water sources (groundwater and surface water) were modelled using the parameters provided in Appendix III, Table 6. The maximum drinking water concentrations of pyrimethanil and ZK 512723 in groundwater sources as a result of leaching were estimated using the Leaching Estimation and Chemistry Model (maximum annual peak over 20 years; Appendix III, Table 7). Drinking water concentrations in surface water sources (reservoirs and dugouts) as a result of surface runoff were estimated using the linked Pesticide Root Zone Model/Exposure Analysis Modelling System models (90^{th} percentile of the yearly peak and yearly average over 50–75 years; Appendix III, Table 7). These values are considered to be “upper bound” concentrations in a drinking water source.

Direct Overspray in Surface Water
The maximum seasonal application rate is used to calculate the EEC of pyrimethanil from direct overspray in surface waters at 30-cm water depth. The EEC of pyrimethanil in water was estimated to be 0.77 mg a.i. /L, assuming a maximum application rate of 800 g a.i./ha applied 3 times with an interval of 7 days and an aerobic aquatic DT_{50} of 121 days.

5.9.3 Vegetation and Other Food Sources

The EECs of pyrimethanil in vegetation and food sources are calculated based on the maximum annual label rate of application for Scala SC of 800 g a.i./ha applied 3 times with an interval of 7 days. This did not account for any transformation of pyrimethanil on the foliage (as data were not available). Direct overspray scenario using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972), Kenaga (1973),

and modified according to Fletcher et al. (1994) for use in ecological risk assessment (Urban and Cook 1986) was used (Table 8 and Table 9 of Appendix III).

6.0 Effects on Non-target Species

6.1 Effects on Terrestrial Organisms

Pyrimethanil showed low toxicity to earthworms in acute studies. The 14-day no observed effect concentration (NOEC) was reported as 250 mg a.i./kg dw of soil, and the lowest observed effect concentration (LOEC) as 500 mg a.i./kg dw soil based on worm discolouration. The 14-day LC_{50} was 625 mg a.i./kg soil.

Pyrimethanil was not toxic to beekeepers after topical contact or oral uptake. The contact and oral LD_{50} values and the no observed effect level (NOEL) were all determined to be > 100 µg a.i./bee and 100 µg a.i./bee, respectively. Therefore, pyrimethanil is categorized as relatively non-toxic to honeybees in accordance with Atkins et al. (1981).

Different species of beneficial insects were exposed to pyrimethanil at a rate of 1 kg a.i./ha in the laboratory. The results showed that pyrimethanil was toxic to parasitic wasps (*Trichogramma cacoeciae*), to predacious mites (*Typhlodromus pyri*) as well as to lady bird beetles (*Coccinella septempunctata*) and was harmless to lacewings (*Chrysoperla carnea*). Semi-field tests were then conducted with those species where toxicity had been demonstrated in the laboratory. In the semi-field studies no adverse effects were seen with single applications of 1 kg a.i./ha (two studies) or with 5 applications of 445–475 g a.i/ha (one study). The conclusion to be drawn from these studies is that pyrimethanil is considered harmless to beneficial species at or below these application rates.

Pyrimethanil was of low acute oral toxicity to the bobwhite quail because a single dose of 2000 mg a.i./kg bw by gavage did not induce any clinical sign of toxicity or mortality. In the mallard duck, pyrimethanil induced vomiting at doses greater than 125 mg a.i./kg, but no other clinical signs or mortality were observed. Thus, pyrimethanil is not toxic up to doses of 125 mg a.i./kg, but no conclusion can be drawn from data at higher doses due the emetic responses at these doses. Therefore, pyrimethanil is categorized as practically non-toxic (LD_{50} > 2000 mg a.i./kg bw) to quails but moderately toxic to ducks (LD_{50} > 125 mg a.i./kg bw) on an acute oral basis in accordance with the USEPA descriptive categorization (USEPA 1985a). Similarly, pyrimethanil was of low short-term dietary toxicity because dietary exposure for 5 consecutive days caused no treatment-related mortality or clinical signs in either species at doses up to 5200 mg a.i./kg diet. Therefore, pyrimethanil is categorized as practically non-toxic (LD_{50} > 5000 mg a.i./kg diet) to birds on a short-term dietary basis in accordance with the USEPA descriptive categorization (USEPA 1985b). Dietary administration of pyrimethanil to adult mallard ducks for 21 weeks and to bobwhite quails for 23 weeks caused no treatment-related effects on reproductive endpoints such as the number of eggs laid per female and their hatchability up to concentrations of 640 mg a.i./kg diet in the duck and 1000 mg a.i./kg diet in the

quail. Therefore, the NOECs for reproductive toxicity are 640 mg a.i./kg and 1000 mg a.i./kg for mallard ducks and bobwhite quail, respectively.

The acute toxicity of pyrimethanil to small mammals was low. The LD_{50} in rats and mice was 5060 and 5000 mg/kg bw, respectively. No acute neurotoxicity was demonstrated in rats up to doses of 1000 mg a.i./kg bw. The lowest NOEC values for short-term dietary exposure were 800 and 900 mg a.i./kg diet in the rat and mouse, respectively. The NOAEL in a multigeneration study with rats was 400 mg a.i./kg diet for both the parents and the offspring.

Pre-emergent and postemergent screening tests exposing 13 terrestrial vascular plant species to pyrimethanil found no phytotoxic effects at rates up to 3 kg a.i./ha (maximum single application rate = 0.8 kg a.i./ha). Another screening study exposed 7 species of terrestrial vascular plants to the major transformation product, 2-amino-4,6-dimethylpyrimidine, and found some degree of phytotoxicity, but at rates that were 6–20 times the maximum seasonal application rate for the parent. This transformation product was never found at levels exceeding 15% of the parent; therefore, it is unlikely that levels of the transformation product would ever approach the rates used in the screening study.

The data related to the toxicity of pyrimethanil and relevant transformation products to terrestrial organisms is summarized in Table 10 of Appendix III.

6.2 Effects on Aquatic Organisms

Pyrimethanil is expected to be moderately toxic to freshwater invertebrates on both an acute and chronic basis. In studies with *Daphnia magna*, the acute and chronic concentrations resulting to a 50% effect (EC_{50}s) were 2.9 mg a.i./L and 1.87 mg a.i./L, respectively, and the corresponding NOECs were 1.5 and 0.97 mg a.i./L, respectively.

Pyrimethanil was found to be slightly toxic to freshwater fish on an acute basis. In acute studies with 3 species of freshwater fish, LC_{50} s ranged from 10.6 to 35.4 mg a.i./L, and NOECs ranged from 4 to 12.5 mg a.i./L. On a chronic basis, pyrimethanil had a reported NOEC of 1.6 mg a.i./L in a 21-day exposure study with rainbow trout. In an early-life stage exposure with rainbow trout the NOEC was 77 µg a.i./L.

Pyrimethanil was found to not be acutely toxic to the freshwater cyanobacteria *Aphanizamenon flos-aqua* or the diatom *Navicula pelliculosa* up the highest concentration tested (4.0 mg a.i./L). Pyrimethanil was acutely toxic to the green algae *Selenastrum capricornutum* where significant effects on growth rate and biomass were observed at all concentrations tested (NOEC < 0.33 mg a.i./L, E_rC_{50} for growth rate = 5.84 mg a.i./L and E_bC_{50} for biomass = 1.20 mg a.i./L).

Toxicity was also observed in the freshwater vascular plant, *Lemna gibba*, as evidenced by reduced frond number, weight, growth rate and biomass with an NOEC < 1.9 mg a.i./L for the most sensitive endpoint, frond weight.

Pyrimethanil was found to be moderately toxic to mysid shrimp on an acute as well as on a chronic basis with a 96-hour LC_{50} of 3.4 mg a.i./L (NOEC = 0.37 mg a.i./L) and a 28-day NOEC of 0.5 mg a.i./L. Pyrimethanil was also moderately toxic to the eastern oyster with a reported 96-hour EC_{50} of 3.9 mg a.i./L and a NOEC of 1.3 mg a.i./L, based on shell deposition.

Pyrimethanil is expected to be moderately toxic to marine fish based on the results of a 96-hour study with sheephead minnows. The 96-hour LC_{50} was estimated to be 2.8 mg a.i./L and the NOEC was 1.2 mg a.i./L.

Pyrimethanil significantly inhibited growth rates and biomass in the marine diatom *Skeletonema costatum*, and the 96-hour NOEC was 3.9 mg a.i./L. No EC_{50}s could be calculated because no concentration tested caused inhibition exceeding 50%.

The toxicity of pyrimethanil to aquatic organisms is summarized in Table 11 of Appendix III.

6.3 Effects on Biological Methods of Sewage Treatment

Data are not required.

6.4 Risk Characterization

6.4.1 Environmental Behaviour

Pyrimethanil is not expected to volatilize under field conditions (i.e., from dry and wet or moist surfaces), nor undergo photolysis or hydrolysis on soils or in aquatic environments. Biotransformation is expected to be an important route for the transformation of pyrimethanil under aerobic conditions in the aquatic and terrestrial environment. However, pyrimethanil is expected to be persistent under anaerobic conditions. In aquatic environments, pyrimethanil appears to be rapidly removed from water and is partitioned to sediments, which may act as a sink for this compound. Pyrimethanil and/or its transformation products will also bind strongly to soils and sediments over time, making them less available for biological uptake but also acting as a sink and potential source of residues over the long term. These bound residues may also be confounding the estimation of an accurate half-life because it is known that they consist of at least some parent compound. Some amount of mineralisation occurs during biotransformation whereby the parent is transformed to CO_2.

The predicted mobility of pyrimethanil was low to moderate on the basis of laboratory adsorption/desorption and soil column leaching studies. This was supported by terrestrial field studies that indicated that all of the parent and transformation compounds were found within the first 15-cm soil horizon. Overall, data from laboratory and field studies indicate that pyrimethanil and its transformation product, 2-amino-4,6-dimethylpyrimidine, have a limited potential for leaching to groundwater. However, as

already stated, bound residues may act as a potential source for the release of residues over an extended period.

6.4.2 Terrestrial Organisms

Earthworms
The estimated initial EEC for pyrimethanil based on the maximum allowable seasonal application is 1.0 mg a.i./kg soil. Based on the observed NOEC of 250 mg a.i./kg soil, the risk quotient (RQ) for earthworms is 4.0×10^{-3}. The risk of lethal and sublethal effects of pyrimethanil to earthworms is negligible with the application of pyrimethanil at the maximum label rate.

Honeybees
Products that are applied as sprays can be evaluated initially by considering the likely exposure of bees and the toxicity of the product. According to the classification by Atkins et al. (1981), pyrimethanil is classified as relatively non-toxic to honeybees as LD_{50}s were > 100 µg a.i./bee for oral and contact exposures, respectively. Using a conversion factor of 1.12 which is multiplied by the LD_{50} an endpoint of > 112 kg a.i./ha is calculated as the rate that would be equivalent to the LD_{50} (Atkins et al. 1981). This value is much larger than the proposed application rate; therefore, it is unlikely that the use of pyrimethanil will pose a significant risk to bees.

Other Arthropod Species
The risk of pyrimethanil to beneficial arthropods was assessed for five species of arthropods in laboratory test. Additional semi-field tests were conducted with those species that showed a toxic response in the laboratory. The rates used in the studies are not considered high enough to evaluate the potential risk for the grape use pattern, which has 3 applications of 0.8 kg a.i./ha. However, the rates were sufficient to evaluate the risk from the apple use pattern, which has single application maxima of 0.4 kg a.i./ha applied 4 times. For those use patterns using 0.4 kg a.i./ha single application maxima, the data suggest that the risk to beneficial arthropods is unlikely to be significant.

Birds
Wild upland game birds and waterfowl, as represented by bobwhite quail and mallard duck, respectively, could be exposed to pyrimethanil residues as a result of consumption of treated vegetation, contaminated prey or spray drift. The bobwhite diet may consist of approximately 30% small insects, 15% forage crops and 55% grain and seeds. Based on the maximum seasonal application rate (2400 g a.i./ha), the EEC in the bobwhite diet after the application of pyrimethanil is 420.2 mg a.i./kg dw diet. The mallard diet consists of approximately 30% large insects and 70% grain and seeds. The EEC in the mallard diet is 81.2 mg a.i./kg dw diet.

In the acute oral toxicity studies with pyrimethanil, the mean body weight per individual (BWI) of bobwhite quail and mallard duck in the control treatments was 0.024 kg bw/ind/day and 0.143 kg bw/ind, respectively, while the mean daily individual food consumption (FC) was 0.004 and 0.035 kg dw for the bobwhite quail and mallard duck,

respectively. The potential daily intake of pyrimethanil (FC × EEC) was calculated as 1.68 mg a.i./ind/day for the quail and 2.84 mg a.i./ind/day for the duck. The reported LD_{50}s and NOELs for the quail were > 2000 and 2000 mg a.i./kg bw, respectively, and > 125 and 125 mg a.i./kg bw, respectively, for the duck. Expressed on a per individual basis, the $LD_{50(ind)}$ (LD_{50} × BWI) was > 48.6 mg a.i./ind, and the $NOEL_{(ind)}$ (NOEL × BWI) was 48.6 mg a.i./ind for the quail. For the duck, the $LD_{50(ind)}$ and the $NOEL_{(ind)}$ were > 17.87 mg a.i./ind and 17.87 mg a.i./ind, respectively. Based on the daily intake, the $LD_{50(ind)}$ and the $NOEL_{(ind)}$, it would take a bobwhite quail and a mallard duck at least 28.9 and 6.29 days of continuous consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory by gavage that had no observable effect on the laboratory population. Therefore, pyrimethanil poses a negligible risk to bobwhite quail and mallard ducks when applied at the proposed maximum application rate.

The NOECs in bobwhite quail and mallard duck from dietary exposure were both 5200 mg a.i./kg diet, respectively, and the NOECs for reproductive effects were 1000 and 640 mg a.i./kg diet, respectively. For both sublethal and reproductive effects, the EECs were lower than the NOECs for both species. The resulting RQs for sublethal toxicity and reproductive effects from pyrimethanil were 0.08 and 0.42, respectively, in bobwhites and 0.02 and 0.13, respectively, in mallards. Therefore, pyrimethanil poses a negligible risk of lethal and sublethal effects and poses a low risk of reproductive effects in bobwhite quail and mallard duck when applied at the proposed maximum application rate.

Small Wild Mammals

Small wild mammals such as rats, mice and rabbits may be exposed to residues of pyrimethanil as a result of consumption of sprayed vegetation and/or contaminated prey. The EECs of pyrimethanil in the diet of rats, mice and rabbits of 1210.8, 1203.57 and 1810.5 mg a.i./kg dw diet are very conservative as they assume no transformation from food sources following repeated applications up to the maximum allowable annual application rate (800 g a.i./ha).

The following data on BWI and FC estimates developed by the USEPA (1988) were used to determine risk to small wild mammals:

Species	BWI (kg)	FC (kg dw/ind/day)
Rat	0.35	0.06
Mouse	0.033	0.006
Rabbit	2	0.08

The risk to small wild mammals from acute exposure to pyrimethanil is expected to be negligible. Acute exposure to pyrimethanil resulted in an LD_{50}s of 5000 and 5060 mg a.i./kg bw in mice and rats, respectively. Based on a daily intake (FC × EEC) for mice and rats of 7.22 and 72.6 mg a.i./ind/day, respectively, and mice and rats $LD_{50(ind)}$ (LD_{50} ×

BWI) values of 165.0 and 1771.0 mg a.i./ind, respectively, a mouse and rat would require 23 and 24 days of continuous feeding on contaminated food sources to reach dose equivalent to that administered in the laboratory by gavage that killed 50% of the test populations. Therefore, pyrimethanil poses a negligible risk to small wild mammals on an acute basis.

The risk to small wild mammals from chronic dietary exposure to pyrimethanil is expected to be moderate. Chronic exposure of pyrimethanil to mice and rats in the diet resulted in a NOEC of 900 and > 800 mg a.i./kg diet, respectively. The EECs of pyrimethanil in the mouse and rat diets are higher, resulting in RQs of 1.3 and 1.5, respectively. Therefore, pyrimethanil poses a moderate risk to small wild mammals from exposure through their diet.

The risk of neurotoxic effects in small mammals was evaluated using an NOAEL of 1000 mg a.i./kg bw seen in the rat. Based on a daily intake for rats of 72.6 mg a.i./ind/day and a $NOAEL_{(ind)}$ (NOAEL × BWI) of 350.0 mg a.i./ind, a rat would require 4.8 days of continuous feeding on contaminated food sources to reach the NOEL. Therefore, the risk of neurotoxicity in small wild mammals from pyrimethanil exposure is considered negligible.

A multigenerational reproduction study with rats reported an NOEC of 400 mg a.i./kg diet. The EEC in rat diets is 1210.8 mg a.i./kg diet. This results in an RQ of 3.03 and represents a moderate risk of reproductive effects from pyrimethanil exposure.

In summary, the risk to small wild mammals from exposure to pyrimethanil is expected to be moderate to negligible. The most sensitive endpoints were observed in the dietary studies with rats and mice that had RQs of 1.5 and 1.3, respectively, indicating a moderate risk to small mammals.

Terrestrial Plants

Screening studies with several species of terrestrial macrophytes found no evidence of phytotoxicity from pyrimethanil exposure and some evidence of phytotoxicity from the transformation product but at extremely high exposure rates. It is unlikely that these levels would be seen in the field, and the risk to terrestrial vascular plants is not likely to be significant.

Summary of the Risk to Terrestrial Organisms

The overall risk to terrestrial organisms exposed to pyrimethanil under field conditions is negligible to moderate. Pyrimethanil is not expected to pose a risk to terrestrial arthropods or terrestrial plants. Pyrimethanil may pose a low risk to birds and a moderate risk to small mammals.

The risk to terrestrial organisms associated with pyrimethanil use is summarized in Table 12 of Appendix III.

6.4.3 Aquatic Organisms

Although the proposed use does not include direct application to water, the possibility that aquatic organisms would be exposed to pyrimethanil cannot be ruled out. As with the terrestrial organisms, the degree of risk to aquatic organisms is assessed by determining RQs that compare the EEC in 30 cm of surface water as a result of direct overspray with toxicity endpoints (i.e., EEC ÷ NOEC). The EEC used in the calculation of all aquatic RQs was 0.77 mg a.i./L.

Non-target Freshwater Invertebrates
The acute and chronic NOECs for *Daphnia magna* are1.5 and 0.97 mg a.i./L, respectively. Therefore, the RQs are 0.51 and 0.79, indicating a low risk to freshwater invertebrates from both chronic and acute exposure to pyrimethanil.

Non-target Marine Invertebrates
The 96-hour acute NOECs for the mysid shrimp and oyster are 0.37 and 1.3 mg a.i./L , respectively, giving RQs of 2.1 and 0.59, indicating that pyrimethanil use poses a moderate and low acute risk to marine crustaceans and mollusks, respectively. The chronic NOEC for mysid shrimp is 0.50 mg a.i./L giving an RQ of 1.5. Therefore, chronic exposure to pyrimethanil poses a moderate risk to mysid shrimp.

Freshwater Fish
Pyrimethanil is slightly toxic on an acute basis to coldwater and warmwater fish. The NOECs for rainbow trout, mirror carp and bluegill sunfish are 4.0, 6.25 and 12.5 mg a.i./L, respectively. This means that pyrimethanil poses a low acute risk to rainbow trout (RQ = 0.19) and the mirror carp (RQ = 0.12) and a negligible risk to the bluegill sunfish (RQ = 0.06). The most sensitive endpoint in the chronic study is NOEC (1.6 mg a.i./L) for fish weight giving an RQ of 0.48, which indicates that chronic exposure to pyrimethanil use will pose a low risk to freshwater fish. In the early life-stage study, an NOEC of 0.077 mg a.i./L for body weight giving an RQ of 10.0, indicates that pyrimethanil will pose a high risk to the early life stages of freshwater fish.

Marine Fish
The sheepshead minnow has an acute NOEC of 1.2 mg a.i/L (mortality), giving an RQ of 0.64, indicating that acute exposure to pyrimethanil will pose a low risk to marine fish.

Freshwater Algae
The acute NOECs for diatoms and cyanobacteria were 3.9 and 3.8 mg a.i/L, respectively, resulting in RQs of 0.20 for both. No acute NOECs could be determined for green algae because there were effects at all treatment levels. Therefore, 1/10 of the EC_{50} for biomass was used (0.1 × 1.2 mg a.i/L) which results in an RQ of 6.4. Therefore, pyrimethanil will pose a low risk to freshwater diatoms and cyanobacteria, but will pose a moderate risk to freshwater green algae.

Marine Algae
The acute NOEC for marine algae is 3.9 mg a.i./L, giving an RQ of 0.2. These values indicate that pyrimethanil use will result in a low risk to marine algae.

Aquatic Vascular Plants
No NOEC value could be determined for aquatic vascular plants because effects were seen at all concentration tested. Therefore, 1/10 of the EC_{50} for dry weight (0.1 × 8.7 mg a.i./L) was used resulting in an RQ of 0.87 and meaning that pyrimethanil is expected to pose a low risk to freshwater vascular plants.

Summary of the Risk to Aquatic Organisms
Overall, pyrimethanil is expected to pose a low risk to freshwater invertebrates and aquatic vascular plants, a moderate risk to freshwater algae and a high risk to freshwater fish. Pyrimethanil is expected to pose a low risk to marine mollusks, fish and algae but a moderate risk to marine crustaceans.

The risk to aquatic organisms associated with pyrimethanil use is summarized in Table 13 of Appendix III.

6.5 Risk Mitigation

Based on the data submitted and on the existing data requirements for use-site categories 13 and 14, an assessment of the environmental safety associated with the use of pyrimethanil has been conducted. Application of the technical grade active ingredient pyrimethanil and the formulated end-use product Scala SC using a scenario of 3 applications at the maximum rate of 800 g a.i./ha has identified areas of concern, particularly with aquatic organisms (i.e., fish early life stage). Further mitigative label statements, as outlined hereafter, are required for the label of the manufacturing technical product and the end-use product for Scala SC Fungicide.

For Technical Pyrimethanil Fungicide Label

Add: "**ENVIRONMENTAL HAZARDS:**

This product is toxic to aquatic organisms. **DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

For End-Use Product Scala SC Fungicide Label

Delete the section entitled **ENVIRONMENTAL PRECAUTIONS.**

Add: "**ENVIRONMENTAL HAZARDS:**

This product is toxic to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to, heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g., compacted or fine-textured soils such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

DO NOT apply this product through any type of irrigation system."

Add to **DIRECTIONS FOR USE**:

"Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification.

Airblast application: **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

DO NOT apply by air.

Buffer zones: Based on the proposed application rates, the following buffer zones to protect sensitive aquatic habitats are required to mitigate risks.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands), and estuarine/marine habitats.

Method of Application	Buffer Zone (metres) for Protection of:	
	Freshwater Habitat	Estuarine/Marine Habitat
Field spray boom	1	0
Field sprayer with drift reducing spray shields (shroud, curtain)	0	0
Field sprayer with cone-shape shields	0	0
Airblast sprayer (early growth stage)	10	4
Airblast sprayer (late growth stage)	5	2

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture."

7.0 Efficacy

7.1 Effectiveness Against Target Organisms or with Respect to the Effect Achieved

7.1.1 Intended Use

Scala SC is proposed for the control of the following specific foliar and fruit diseases:

- scab (*Venturia inaequalis*, *Venturia pirina*) on apples and pears;
- *Botrytis* and *Penicillium* storage diseases on apples;
- Botrytis bunch rot (*Botrytis cinerea*) on grapes;
- Botrytis grey mould (*Botrytis cinerea*) on strawberries; and
- early blight (*Alternaria solani*) on potatoes.

The proposed application rates range from 0.75 to 2.0 L/ha (300 to 800 g a.i./ha), applied from 1 to 6 times per season per disease, while PHIs range from 1 to 72 days. Minimum proposed application volumes are 300 L/ha for vegetable crops and 1000 L/ha for fruit crops.

7.1.2 Mode of Action

Pyrimethanil is a member of the anilinopyrimidine family of fungicides, and its mode of action is to inhibit fungal enzyme secretion. Pyrimethanil prevents a fungus from degrading and digesting plant host tissues, thereby controlling the infection process of disease development.

This active ingredient has been classified by the FRAC as a Group 9 Fungicide, which also includes the active ingredients cyprodinil and mepanipyrim. Group 9 fungicides are rated as having a medium risk of resistant strains developing if restrictions are not placed on their use. Resistance to Group 9 fungicides has been documented in strains of *Botrytis* and *Venturia*.

7.1.3 Crops

Scala SC has been proposed for use on apples, pears, grapes, strawberries and potatoes.

7.1.4 Effectiveness Against Pest

7.1.4.1 Apple and Pear—Scab (*Venturia inaequalis, Venturia pirina*)

The proposed use pattern for this claim is a maximum of 4 applications per season for scab alone, applied at 300–400 g a.i./ha. Apply early in the season, from green tip to petal drop. Fifteen field orchard trials were conducted in Ontario, Quebec, Nova Scotia, Michigan, New York, Pennsylvania, North Carolina and California. Thirteen of these trials tested apple, and two tested pear.

For the apple trials, most were rejected for one or more of the following reasons:

- treatments did not follow the proposed label rate or were tank-mixed with another product that is already registered for scab control;
- disease assessments were made weeks after Scala SC applications or after a registered scab protectant (captan or mancozeb) was applied, and it was not possible to distinguish between the effects of Scala SC and the other product (this occurred in most trials);
- disease pressure was unacceptably low (2% disease incidence); or
- the experimental set up and fungicide application protocols were not clear, and the applicant could not clarify the details of the trial when contacted.

Three apple trials were reviewed to evaluate the scab claim. For these, Scala SC was applied consecutively (3–5 applications) as initial prebloom applications, followed by applications of other scab-control fungicides. When trees were assessed for scab on the leaves (within 18, 25 and 1 day of the last Scala SC application), the data show that Scala SC at 200 g a.i./ha rate provided low disease control (33%), compared to the 400 g a.i./ha rate (77% control). In addition under good disease pressures, in the trial that directly compared the 300 to the 400 g a.i./ha rate, there were no differences in the level of disease control (75% control for the 300 g rate and 69% for the 400 g rate). When the 286 g a.i./ha Scala SC rate was tested, results indicate that it provided acceptable disease control (79%), but this was considerable lower than what the commercial standards provided (92–96%).

Apple scab assessments were made later on in the growing season after the Scala SC applications had ceased, and other scab control products were applied. Because the duration of effectiveness of Scala SC had elapsed when the fruit assessments were made, it is difficult to determine the effectiveness of Scala SC for control of fruit scab. Two of

the trials compared different rate of Scala SC made for the initial (early season) applications, followed by the same alternate fungicides applied afterwards, allowing a relative comparison for the Scala SC rates. Results indicate that the 200 g a.i./ha rate was ineffective in controlling apple scab later in the season (14% control), while the 400 g a.i./ha rate was as effective (79% control) as the commercial standards Dithane, Nova and Maestro (~81% control). For the remaining trial, results were consistent; the 300 g a.i./ha rate resulted in moderate fruit scab control (52%), while the 400 g a.i./ha rate provided acceptable (78%) control.

For the pear trials, the California study was rejected because the trial did not follow the proposed application rates or directions and the scab pressures were low. In addition, Scala SC was applied alone for two applications, then in a tank mix with Nova (three applications), and Nova is registered for scab control.

The second pear trial demonstrated low disease incidence (3%) on the leaves and fruit at the time of first disease assessment and received three applications of Scala SC. At the time of the second assessment, disease incidence increased to 25% for the untreated leaves and 15% for the untreated fruit. Scala SC applied 4 times at 400 g a.i./ha provided good disease control, (96% on leaves and 87% on fruit). Scala SC performance was compared to Syllit (dodine), a product not registered in Canada. There were no differences between these two products in terms of control of scab incidence.

Data support the claim that under light apple and pear scab pressures, the 300 g a.i./ha rate will provide acceptable scab control, while under heavier disease pressures, the 400 g a.i./ha rate is required. Apply early in the season starting at green tip, then every 7 to 12 days, for a maximum of four yearly applications for scab control. Do not apply postbloom.

7.1.4.2 Apple—*Botrytis cinerea* and *Penicillium* spp. Storage Diseases

The proposed use pattern is one Scala SC application made two weeks before harvest at 800 g ai/ha.

Three orchard trials were conducted in British Columbia. Disease pressures for both pathogens were acceptable to assess the two disease claims. All three trials were performed according to the use directions on the proposed label claim. The fruit were treated, then harvested and stored for three or six months. After storage, the fruit were inoculated with either *Botrytis cinerea* or *Penicillium* spp. and incubated for a further 5–7 days. Disease incidence ratings were conducted for each disease and treatment.

After a preharvest application, then 3, 4 or 6 months of storage, followed by injury and inoculation, Scala SC at 600 and 800 g a.i./ha significantly reduced both the mean *Botrytis* rot diameter and the percent disease incidence by 94–98% compared to the untreated check. There were no significant differences in the level of disease control between the 600 and 800 g a.i./ha rates. In addition, Scala SC performed as well or better than the commercial standard, Vanguard. Similar results were found for *Penicillium*,

when Scala SC was assessed after 3 and 6 months. In side by side trials where applications of 600 g a..i./ha and 800 g a.i./ha were compared, no statistical differences were seen in the degree of control. However, it was noted that the higher (800 g a.i./ha) rate provided numerically greater disease incidence control (86–98%) than the 600 g a.i./ha rate (66–84%). Therefore, it is recommended that Scala SC be applied at a range of 600–800 g a.i./ha, applied once, 2 weeks before harvest for the control of *Botrytis cinerea* and *Penicillium* storage diseases. It should be applied at the higher rate if there is a history of high disease pressures in the storage facility.

7.1.4.3 Grape—Bunch Rot *(Botrytis cinerea)*

The proposed use pattern is 800 g a.i./ha, applied at early bloom if needed, then followed with applications from berry touch to bunch closure. An application can also be made from fruit ripening through to harvest during frequent wet conditions (conducive to infection) or when symptoms of infection are evident. Thorough coverage of bunches is essential. Apply a maximum of three applications, and a PHI of seven days.

Sixteen field trials were conducted in British Columbia, Ontario, New York, Michigan, California, France and Spain. Three of these trials demonstrated low disease pressures and were not assessed. Trails tested Scala SC at different application rates, including 280 g, followed by 3 applications at 421 g a.i./ha, at 400 and 800 g a.i./ha, and a tank mix of Scala SC at 400 g a.i./ha + Rovral.

Results demonstrate that under low to high disease pressure, Scala SC applied at 800 g a.i./ha consistently provided acceptable to good control (29–82% range) of Botrytis bunch rot. In addition, Scala SC provided similar or better levels of disease control than the commercial standards, Rovral and Vanguard. Scala SC at 400 g a.i./ha provided similar levels of disease control as the 800 g a.i./ha rate; however, the disease pressures in the trial were very low. In addition, the trial that assessed Scala SC at the 280 and 421 g a.i./ha rates demonstrated low disease pressures. Regardless, results indicate that acceptable disease control at these lower rates was still achieved, with Scala SC outperforming the commercial standard Vanguard. It is believed that Scala SC rates lower than 800 g a.i./ha would provide acceptable level of disease control under low and moderate disease pressures; however, additional data would be necessary to confirm this.

To assess for the appropriate application timing, Scala SC was tested with an initial application made at either prebloom or postbloom, followed by additional applications at berry touch, cluster closure, veraison or preharvest. While there was variation between trials, trends suggest that a prebloom application resulted in lower bunch rot later in the growing season. Applications closer to preharvest also demonstrated good late-season control of bunch rot. This confirms that the directions on the proposed Scala SC label to apply at prebloom (if necessary) and that if conditions warrant it, late season applications (preharvest) may be appropriate.

The claim that Scala SC Fungicide applied at 800 g a.i./ha at early bloom if needed, then follow with a second application from berry touch to bunch closure will control Botrytis

bunch rot, is supported. Applications should be at least 7 days apart. Data also support the claim that veraison and/or preharvest applications can also be made during frequent wet conditions (conducive to infection) or when symptoms of infection are evident. A maximum of three yearly applications can be made.

Because there are known resistant strains of *Botrytis* to Group 9 fungicides, each application of Scala SC must be followed by two applications of fungicides with a different mode of action before making the next Scala SC application.

7.1.4.4 Strawberry: Grey Mould (*Botrytis cinerea*)

Proposed use directions state apply 800 g a.i./ha at prebloom, then every 7–10 days for a maximum of 3 applications. Nine field trials were conducted in Ontario, Nova Scotia, British Columbia and Spain during 2001 and 2002. Three of these trials demonstrated unacceptably low disease pressures and were not reviewed. In the remaining trials, Scala SC was tested at 400 or 800 g a.i./ha, with 2 to 5 sequential applications, before being assessed.

Results demonstrate that under moderate to low disease pressures, Scala SC provided good control of *Botrytis* on both the plant and berries. There were no significant differences in disease control between the 400 and 800 g a.i./ha rates (83–100% control for the 400 g rate and 90–100% for the 800 g rate). However, it is noted that none of the trials assessed demonstrated high disease pressures. Therefore, it is unknown if either rate would maintain good disease control under high disease pressures. When Scala SC was compared to the commercial standards Rovral or Elevate, it performed at least as well at both the 400 and 800 g a.i./ha rates. It should be noted that when berries were assessed for *Botrytis* development during postharvest storage, under high disease pressure, Scala SC provided a moderate degree of control after 3–6 days storage.

Based on FRAC guidelines regarding the maximum number of yearly applications that can be made for control of *Botrytis* by any anilinopyrimidine-based product (including Scala SC), it is recommended that each Scala SC application be followed by two applications of registered fungicides with a different mode of action before making the next Scala SC application.

The claim that Scala SC, applied at 800 g a.i./ha starting at prebloom, followed by additional applications 7 to 10 days later, will control Botrytis grey mould is supported. A yearly maximum of three applications can be made. Each Scala SC application be followed by two applications of registered fungicides with a different mode of action before making the next Scala SC application.

Additional trials are required to refine the lowest effective rate (LER). Scala SC must be tested to compare the 400, 600 and 800 g a.i./ha rate under high disease pressures.

7.1.4.5 Potato—Early Blight (*Alternaria solani*)

The proposed use pattern is to apply Scala SC Fungicide in a tank mix with Bravo 500 Fungicide. Apply 300 g a.i./ha Scala SC plus Bravo 500 at 1.5 L/ha. Apply when plants are 15 to 20 cm high or when disease threatens. Repeat applications at 7 to 10 day intervals or as necessary to maintain disease control. If severe disease conditions exist, use a shorter spray interval. Ensure that the area to be treated is covered uniformly.

Efficacy data from 12 trials conducted in Canada, United States and Australia were submitted to support the use of Scala SC on potatoes for control of early blight. All seven trials from Australia were not reviewed because it compared Walabi (chlorothalonil + pyrimethanil) to Bravo Plus, a product not registered in Canada and composed of two fungicide active ingredients, chlorothalonil and cyproconazole (a demethylation inhibitor Group 3 Fungicide). One trial in the United States was not reviewed because of low disease pressures. Four trials were reviewed to support this claim. These trials tested a tank mix of Scala SC and Bravo or used Walabi, a co-formulation of chlorothalonil and pyrimethanil.

Results from the Walabi trials showed that under increasing disease pressure through the growing season and at the proposed rate (300 g a.i./ha pyrimethanil + 750 g a.i./ha chlorothalonil), Walabi maintained good (76–81%) disease severity control compared to the untreated plants. The level of disease control was equal or better than when compared to Bravo applied alone. When the timing of application for Walabi was compared (7–10 day vs 10–14 days), there were no significant differences between the level of disease control on any of the 5 assessment days. The Maine trial directly compared 8 applications of Walabi at 300 g a.i./ha pyrimethanil + 750 g a.i./ha chlorothalonil, to 3 applications of Bravo alone (625 g chlorothalonil), followed by 5 applications of a tank mix of Scala SC (300 g pyrimethanil) and Bravo (625 g pyrimethanil). Four days after the last application, 1% disease severity assessment was made, and differences between these two treatments were not significant (88% for the tank mix and 98% for Walabi). These results suggest that while there may be some differences between the tank mix and the preformulated mixture of the two active ingredients, these differences are small in terms of efficacy against potato early blight.

The last two trials compared Bravo applied alone to a tank mix of Scala SC and Bravo (300 g pyrimethanil + 630 g chlorothalonil). It is noted that the tank mix rate for chlorothalonil is lower (by 120 g chlorothalonil) than what is proposed on the Scala SC label. Results from these trials were consistent with the previous potato early blight trials. Under low to moderate disease pressures during the growing season, Scala SC and Bravo provided acceptable disease control (88–100%). For a single assessment made under high disease pressures, Scala SC and Bravo provided 77% disease severity control and were similar to Bravo applied alone at 1260 g a.i./ha.

The applicant was contacted with regards to the maximum number of applications for this claim, and the response was six. There is no limit on the Bravo label with regards to maximum applications for control of early blight on potato. In addition, it is

recommended to apply Bravo 500 not just at the 1.5 L /ha rate, but at registered label rates, which may be necessary when high late blight disease pressures exist. The data support the label claim that 300 g a.i./ha Scala SC and Bravo 500 at label rates in a tank mix will control potato early blight when applied on a 7–14 day schedule, at a maximum of 6 applications per year.

7.1.5 Total Spray Volume

The proposed guidelines for application carrier volumes, a minimum of 1000 L/ha for fruit crops and 300 L/ha for vegetable crops, is supported based on the efficacy trials submitted for review. Exact application volumes were not stated in the proposed label, as there is variation in size of plants to be treated, such as orchard fruit. Recommendations regarding to coverage were provided on the label, such as apply the product in sufficient water for good coverage.

7.2 Phytotoxicity to Target Plants or Target Plant Products

No phytotoxicity (recognized as 100% of trials reporting no adverse effects) was reported for grape, apple, pear, strawberry and potato. It was noted that for some crops, limited data on Scala SC applied alone was provided, and the phytotoxicity assessment was based on applications of Walabi SC, which contains pyrimethanil, but is a separate product and formulation.

7.3 Impact on Succeeding Crops, Adjacent Crops and on Treated Plants or Plant Products Used for Propagation

Not applicable.

7.3.1 Impact on Succeeding Crops

Not applicable.

7.3.2 Impact on Adjacent Crops

Not applicable.

7.3.3 Impact on Seed Viability

Not applicable.

7.4 Economics

Not applicable.

7.5 Sustainability

7.5.1 Survey of Alternatives

7.5.1.1 Non-chemical Control Practices

The proposed claims for Scala SC Fungicide are for control of diseases affecting the foliage and fruit. Non-chemical disease control practices for these diseases include the following:

- the use of resistant or tolerant varieties;
- the use of certified, clean seed;
- disease avoidance by altering planting date;
- rotation of crop with non-host crops;
- removal of infested debris; and
- sanitation of equipment and enclosed (storage) structures.

Management of the crop canopy by planting, thinning, mowing, irrigation or pruning can also contribute to the reduction of the leaf wetness or humidity that favour disease development.

7.5.1.2 Chemical Control Practices

Table 7.5.1.2.1 Alternative Fungicide Active Ingredients for Control or Suppression of the Proposed Disease Listed on the Scala SC Label and the FRAC Fungicide Group They Belong to

Disease Claim	FRAC Group	Technical Grade Active Ingredient
Control of scab on apples and/or pears	M[2]	Sulphur
	M[3]	Ferbam
		Mancozeb
		Ziram
		Zineb
		Metiram
	M[4]	Captan
	M[7]	Dodine
	1	Thiophanate-methyl
	9	Cyprodinil

Disease Claim	FRAC Group	Technical Grade Active Ingredient
Control of *Botrytis* and/or *Penicillium* storage diseases on apple	1	Thiabendazole
	N/A	Sodium hypochlorite (chlorine)
Control of Botrytis bunch rot on grapes	2	Iprodione
	9	Cyprodinil
	17	Fenhexamid
Control of Botrytis grey mould on strawberries	M[2]	Chlorothalonil
	M[4]	Captan
	1	Thiophanate-methyl
	2	Iprodione
	2	Vinclozolin
	7	Boscalid
Control of early blight on potatoes	M[2]	Mancozeb
		Metiram
	M[3]	Zineb
	M[5]	Chlorothalonil
	M[8]	Anilazine
	4	Metalaxyl-M
	7	Boscalid
	11	Fenamidone
		Azoxystrobin
		Pyraclostrobin

7.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Scala SC Fungicide is compatible with the current non-chemical integrated pest management practices and with other chemical fungicides registered for the same disease claims. There are currently no other Group 9 Fungicide registered for control of Botrytis rot on strawberries or early blight on potatoes, which allows users greater flexibility in managing these diseases.

7.5.3 Contribution to Risk Reduction

Pyrimethanil is in a class of fungicides with modern chemistries. As such, less quantities of product are generally required for similar efficacy when compared to fungicides with older chemistries. In addition, registering a product with a new chemistry allows for alternation of application of existing chemical products, thus leading to less chance of resistance developing in susceptible pathogens.

7.5.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The anilinopyrimidines (AP or Group 9 Fungicide) are active against a wide spectrum of fungal pathogens. There is no known cross-resistance with fungicides from other fungicide groups. Evidence from lab and field trials have shown that there is a medium risk of resistance developing against AP fungicides in strains of *Botrytis* and *Venturia*, and there are known strains of Group 9 resistant *Botrytis* and *Venturia*. Therefore, limitations on the use of any fungicide within this class are necessary.

FRAC guidelines for AP fungicides for use against *Botrytis* are as follows.

- When two treatments per season are generally made for a particular crop, a maximum of one Group 9 Fungicide may be made.
- When up to six *Botrytis* treatments are made per crop and season, a maximum of two applications may be made.
- In specific situations where seven or more *Botrytis* treatments are made per crop per season, a maximum of three applications may be made.
- When different products from the Group 9 Fungicide class are used in one season, the cumulative number of applications may not exceed the above maxima.

FRAC guidelines for AP fungicides for use against *Venturia* are as follows.

- When applied alone (not in a tank mix), Group 9 Fungicide products can be applied to a maximum of four times per season.
- When applied in a tank mix with another product also registered for scab control, a maximum of five tank mix applications may be made.

- Where different Group 9 Fungicide products are applied in one season, the cumulative number of applications for all AP fungicides may not exceed the above maxima.

7.6 Conclusions

7.6.1 Summary

Table 7.6.1.1 Summary of Proposed and Accepted Claims Based on Efficacy Data

	Proposed	Supported (based on value assessment)	Comments
Claim 1			
Crop	Apple, pear	Apple, pear	
Disease	Scab (*Venturia* spp.)	Scab (*Venturia* spp.)	
Rate	0.75–1.0 L/ha	0.75–1.0 L/ha	
Application Timing	Apply in early season, from green tip to petal drop. For scab control do not apply postbloom.	Apply in early season, from green tip to petal drop. For scab control do not apply postbloom.	
Max. No. of Applications	4	4	
Carrier Volume	Minimum of 1000 L/ha	Minimum of 1000 L/ha	
PHI	14 days for apples, 72 for pears	*72 for apples and pears	*Note that for scab control, Scala SC applications should not be made postbloom. Therefore, a 14-day PHI is not applicable for this disease.
Claim 2			
Crop	Apple	Apple	

	Proposed	Supported (based on value assessment)	Comments
Disease	*Botrytis cinerea* and *Penicillium* spp. storage diseases	*Botrytis cinerea* and *Penicillium* spp. storage diseases	
Rate	2.0 L/ha	1.5–2.0 L/ha. Apply the higher rate if severe disease conditions exist in the field or a history of high disease in the storage facility.	Addition of a rate range.
Application Timing	Apply 2 weeks before harvest	Apply 2 weeks before harvest	
Max. No. of Applications	1	1	
Carrier Volume	Minimum of 1000 L/ha	Minimum of 1000 L/ha	
PHI	14 days	14 days	
Claim 3			
Crop	Grape	Grape	
Disease	Botrytis bunch rot	Botrytis bunch rot	
Rate	2.0 L/ha	2.0 L/ha	LER data must be submitted.

	Proposed	Supported (based on value assessment)	Comments
Application Timing	Begin applications at early bloom if needed. Then, follow with applications from berry touch to bunch closure. An application can also be made from fruit ripening through to harvest during frequent wet conditions (conducive to infection) or when symptoms of infection are evident. Thorough coverage of bunches is essential.	Begin applications at early bloom if needed. Then, follow with applications from berry touch to bunch closure. An application can also be made from fruit ripening through to harvest during frequent wet conditions (conducive to infection) or when symptoms of infection are evident. A minimum of 7 days between applications must be observed. Thorough coverage of bunches is essential. Each application of Scala SC must be followed by two applications of fungicides with a different mode of action before making the next Scala SC application.	Note addition of use directions for minimum application interval (7 days). Alternation with non-Group 9 fungicides is necessary, as there are known Group 9 resistant *Botrytis* strains.
Max. No. of Applications	3	3	
Carrier Volume	Minimum of 1000 L/ha	Minimum of 1000 L/ha	
PHI	7 days	7 days	
Claim 4			
Crop	Strawberry	Strawberry	
Disease	Botrytis grey mould	Botrytis grey mould	
Rate	2.0 L/ha	2.0 L/ha	LER data must be submitted.

	Proposed	Supported (based on value assessment)	Comments
Application Timing	Make first application at the white bud stage (prebloom) and repeat applications as required at 7–10 day intervals.	Make first application at the white bud stage (prebloom) and repeat applications as required at 7–10 day intervals. Each application of Scala SC must be followed by two applications of fungicides with a different mode of action before making the next Scala SC application.	Alternation with non-Group 9 fungicides is necessary as there are known Group 9 resistant *Botrytis* strains.
Max. No. of Applications	3	3	
Carrier Volume	Minimum of 1000 L/ha	Minimum of 1000 L/ha	
PHI	1 day	1 day	
Claim 5			
Crop	Tuberous and corm vegetables (potatoes)	Potatoes	Must delete all label reference to "Tuberous and corm vegetables" and replace with "Potatoes".
Disease	Early blight	Early blight	
Rate	Tank mix of Scala SC at 0.75 L/ha plus Bravo 500 at 1.5 L/ha.	Tank mix of Scala SC at 0.75 L/ha plus Bravo 500 at registered label rates.	Replace proposed "1.5 L Bravo 500" tank mix rate, with "registered label rates".

	Proposed	Supported (based on value assessment)	Comments
Application Timing	Apply when plants are 15–20 cm high or when disease threatens. Repeat applications at 7–10 day intervals or as necessary to maintain disease control. If severe disease conditions exist, use a shorter spray interval. Ensure that the area to be treated is covered uniformly.	Apply when plants are 15–20 cm high or when disease threatens. Repeat applications at 7–14 day intervals or as necessary to maintain disease control. If severe disease conditions exist, use a shorter spray interval. Ensure that the area to be treated is covered uniformly.	Longer application interval supported (7–14 days).
Max. No. of Applications	6	6	
Carrier Volume	Minimum of 1000 L/ha	Minimum of 1000 L/ha	
PHI	7 days	7 days	

8.0 Toxic Substances Management Policy Considerations

During the review of technical grade active ingredient pyrimethanil and its associated end-use product Scala SC Fungicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1], has followed its Regulatory Directive DIR99-03[2] and has concluded the following:

- Pyrimethanil does meet the criteria for persistence in anaerobic soil and sediments, which are ≥ 182 days for soil and ≥ 365 days for sediments.

- Pyrimethanil has an *n*-octanol–water partition coefficient (log K_{ow}) of 2.84, which is below the TSMP Track 1 cut-off criterion of ≥ 5.0.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1-800-267-6315 within Canada or 613-736-3799 outside Canada (long distance charges apply); fax: 613-736-3758; e-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca.

- Pyrimethanil (technical grade) does not contain any byproduct or microcontaminant that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The formulated end-use product is not known to contain any USEPA inert List 1 or 2 formulant or any known TSMP Track 1 substance.

- There are insufficient data to determine if the major transformation product, 2-amino-4,6-dimethylpyrimidine, meets the TSMP criteria of toxicity, persistence and bioaccumulation.

- The toxicity of Pyrimethanil is summarized in sections 3 and 6.

9.0 Regulatory Decision

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value. The Agency has concluded that the use of pyrimethanil and the associated end-use product Scala SC Fungicide for control of apple and pear scab, *Botrytis cinerea* and *Penicillium* spp. storage diseases on apples, Botrytis bunch rot on grapes, *Botrytis cinerea* on strawberries and early blight on potatoes, in accordance with the label has merit and value consistent with the Pest Control Product Regulations and does not entail an unacceptable risk of harm. Therefore, based on the considerations outlined above, the use of the reduced-risk products pyrimethanil and the associated end-use product Scala SC Fungicide for control of apple and pear scab, *Botrytis cinerea* on strawberries and early blight on potatoes has been granted temporary registration, under the Pest Control Products Regulations, and subject to the provisions of required, confirmatory data and of label amendments.

Bayer CropScience Inc. will be required to submit the following confirmatory data:

- additional data on the toxicological properties of the environmental metabolite 2-amino-4,6-dimethylpyrimidine;
- additional information on the analytical methodology for livestock matrices;
- data on the storage stability of working solutions;
- freezer storage stability data for processed foods, milk and livestock tissues;
- a supervised residue trial on apples;
- a study to determine the n-octanol-water partition coefficient (log K_{ow}) of the transformation product 2-amino-4,6-dimethylpyrimidine;
- a chronic freshwater sediment toxicity study;
- small-scale efficacy studies on strawberries and grapes; and
- confirmatory bridging studies on potatoes.

List of Abbreviations

^{125}I	radioisotope
λ_{max}	wavelength of peak absorbance
a.i.	active ingredient
ADI	acceptable daily intake
AN2	2-(4-hydroxyanilino)-4,6-dimethylpyrimidine (AE C614276)
AN3	2-anilino-4,6-dimethylpyrimidin-5-ol (AE C614277)
AN4	6-methyl-2-(phenylamino)-4-pyrimidinemethanol (AE C614278)
AN5	AE C621312
AN7	2-amino-4,6-dimethylpyrimidine
AP	anilinopyrimidines
AR	applied radioactivity
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
atm	atmosphere
BBCH	BASF, Bayer, Ciba-Geigy and Hoechst
bw	body weight
BWI	body weight per individual
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CO_2	carbon dioxyde
DAT	days after treatment
DFR	dislodgeable foliar residue
DNCB	dinitrochlorobenzene
DT_{50}	decline time 50%
dw	dry weight
E	overall effect
EC_{50}	effect concentration 50%
EEC	expected environmental concentration
EROD	ethoxyresorufin-O-deethylase
F_0	parental animals
F_1	1^{st} generation offspring
F_2	2^{nd} generation offspring
FC	food consumption
FOB	functional observational battery
FRAC	Fungicide Resistance Management Action Committee
FSD	full scale deflection
fw	fresh weight
g	gram
GC-MS	gas chromatography with mass spectrometric detection
GC-MS/MS	gas chromatography with ion trap mass spectrometer
GGT	gamma glutamyl transferase
ha	hectare
HCl	hydrochloric acid
Hg	mercury

HGPRT	hypoxanthine-guanine phosphoribosyl transferase
HPLC	high performance liquid chromatography
IARC	International Agency for Research on Cancer
IC_{50}	inhibition concentration 50%
ILV	independent laboratory validation
ind	individual
IUPAC	International Union of Pure and Applied Chemistry
K	Henry's law constant
kg	kilogram
K_{oc}	organic carbon adsorption coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LER	lowest effective rate
ln	natural log
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantitation
LSS	Laboratory Services Subdivision
MAS	maximum average score
m	metre
m/z	mass to charge ratio
mg	milligram
mL	millilitre
MIS	maximum irritation score
MOE	margin of exposure
MOS	margin of safety
MRID	master record identifier
MRL	maximum residue limit
MRM	multiresidue method
MTDB	maximum theoretical dietary burden
NAFTA	North American Free Trade Agreement
ng	nanogram
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand white
OECD	Organisation for Economic Co-operation and Development
P_1	1st generation parental animals
P_2	2nd generation parental animals
PAM	*Pesticide Analytical Manual*
PAS	periodic acid Schiff

PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRDD	proposed registration decision document
PROD	pentoxyresorufin-O-dealkylase
RAC	raw agricultural commodity
ROC	residue of concern
RQ	risk quotient
rrt_c	relative retention time
rT3	reverse tri-iodothyronine
SC	suspension concentrate
SD	Sprague Dawley
Std. Dev.	standard deviation
T3	tri-iodothyronine
T4	thyroxine
TC	transfer coefficient
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMD	trimethylsilyl diazomethane
TSMP	Toxic Substances Management Policy
µg	microgram
µL	microlitre
UDPGT	uridine diphosphoglucuronyl transferase
USEPA	United States Environmental Protection Agency
UV	ultraviolet
UV-VIS	UV-visible
v/v	volume/volume
w/v	weight/volume
ZK 512723	2-amino-4,6-dimethylpyrimidine

Appendix I Toxicology

METABOLISM

Pyrimethanil is rapidly absorbed, distributed and excreted; the primary excretion routes are through urine and feces. Almost all of the pyrimethanil administered in a single dose is excreted within 24 hours. In general, there were no major sex-related differences in the metabolism or excretion of pyrimethanil. Distribution is widespread but pyrimethanil is found at the highest levels in blood and blood-bearing organs such as liver and kidney. Metabolism essentially consists of hydroxylation of the methyl or ring structures at the site of least steric hindrance, followed by conjugation with sulphate or glucuronide. The two-ring configuration is retained. There is no evidence to indicate that the metabolic products produced by rat or lactating cow metabolism will be more or less toxic than the parent.

Rat: Absorption and excretion of single (10, 11.8 or 800 mg/kg bw) or repeated (10, 11.8 or 800 mg/kg bw/day/2 weeks, 10 mg/kg bw/day/28 days) oral doses of pyrimethanil was very rapid in rats. The majority of the administered dose was absorbed and excretion was almost complete, with urine as the principle route of clearance (72–76%) and the feces the secondary route of excretion (15–23%). Within 24 hours, > 90% of the administered low dose and > 63–67% of the high dose was detected in the urine and feces, suggesting a saturation of excretion. The liver, the carcass and the gastrointestinal tract of one male rat still had detectable levels of pyrimethanil 96 hours after a single low dose. A single dose of 10 mg/kg was distributed primarily to the lachrymal glands, Harderian gland (female only), kidney, liver and white fat, but was present in all other tissues 45 minutes postdose. The residues quickly cleared thereafter, falling an order of magnitude within 6 hours. At the high dose, peak concentrations occurred at 3–6 hours and 6–12 hours in males and females, respectively. A single high dose produced detectable residue levels in liver, kidney, blood and plasma. For the 14-day study, the highest detectable residue levels 24 hours after the final dose were in liver and kidney, at 0.371 mg/kg and 0.152 mg/kg, respectively. Repeated dosing does not affect the major route or excretion of pyrimethanil or the magnitude of the residue concentration in tissues. **Mouse:** The excretion of pyrimethanil is almost complete (> 95%) with 24 hours after a single dose. The major route of excretion is via urine (86–92%), the remainder via feces (17–24%). Only the carcass, liver, kidney and whole blood contained detectable levels of pyrimethanil 96 hours after a single dose of 10 mg/kg, at 0.035, 0.01, 0.003 and 0.016 mg/kg, respectively. **Dog:** In dogs administered a single oral dose of 10 mg/kg bw pyrimethanil, > 70% was excreted within 24 hours. The major elimination pathway was via the fecal route (53–59%); urinary excretion accounted for 29–38% of total excretion. Maximum residue levels were detected in plasma within 2 hours postdose. The terminal half-lives were 11.57 and 13.48 hours in males and females, respectively. Residue levels were detectable in the adrenals, liver and thyroid and in the female gastrointestinal tract and male spleen.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES—TECHNICAL			
Oral (pyrimethanil, 98.4%)	Rat, Sprague-Dawley 5/sex/dose at 0, 800, 1600, 3200 or 6400 mg/kg bw	LD_{50} = 4149 mg/kg bw (♂) LD_{50} = 5971 mg/kg bw (♀) LD_{50} = 5060 mg/kg bw (♂ and ♀)	**LOW toxicity** ≥ 1600 mg/kg bw: reduced activity, reduced muscle tone, ataxia and prostration.
Oral (pyrimethanil, 98.4%)	Mouse, Crl:CD-1(ICR)BR 5/sex/dose at 0, 1250, 2500 or 5000 mg/kg bw	LD_{50} = 4665 mg/kg bw (♂) LD_{50} = 5359 mg/kg bw (♀) LD_{50} = 5000 mg/kg bw (♂ and ♀)	**LOW toxicity** = 5000 mg/kg bw: prostration and cool to touch. ≥ 2500 mg/kg bw: reduced activity, reduced muscle tone ≥ 1250 mg/kg bw: reduced activity, reduced muscle tone (♀ only)

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Dermal (pyrimethanil, 98.4%)	Rat, Sprague-Dawley 5/sex at 5000 mg/kg bw, limit test	LD_{50} > 5000 mg/kg bw (♂) LD_{50} > 5000 mg/kg bw (♀) LD_{50} > 5000 mg/kg bw (♂ and ♀)	**LOW toxicity** = 5000 mg/kg bw: very slight focal erythema in 2/5 ♂, very slight sloughing of the superficial dermis in 3/5 ♀
Inhalation (pyrimethanil, 96.4%)	Rat, Sprague-Dawley 5/sex at 1.98 mg/L for 4 hours (nose only), limit test	LC_{50} > 1.98 mg/L (♂) LC_{50} > 1.98 mg/L (♀) LC_{50} > 1.98 mg/L (♂ and ♀)	**LOW toxicity** = 1.98 mg/L: no mortalities and no treatment-related clinical observations
Skin irritation (pyrimethanil, 98.4%)	Rabbit, NZW 1 ♂ and 2 ♀, 0.5 g moistened in distilled water	MAS = 0.0 MIS = 0.0	**Non-irritating** No erythema or edema was observed during the study.
Eye irritation (pyrimethanil, 98.4%)	Rabbit, NZW 3 ♀, 0.1 mL, all eyes unwashed	MAS (unwashed) = 0.0 MIS (unwashed) = 0.3 (1 hour)	**Non-irritating** Very slight conjunctival redness at 1 hour in one animal that resolved within 24 hours. No corneal opacity or iritis was noted during the study.
Skin sensitization (pyrimethanil, 99.7%) (Buehler Method)	Guinea pig, Dunkin-Hartley 10 ♀/group, 60% w/v in Alembicol "D" fractionated coconut oil for induction and challenge, positive control: 1% dinitrochlorobenzene (DNCB) w/v in 70% ethanol for the induction phase and 0.05% DNCB w/v in 70% ethanol used in the challenge phase	Negative	**Not a dermal sensitizer** Slight erythema (grade 1) was noted in 3/10 test animals following the first and second induction treatments. No dermal reactions were noted in any of the test animals following the third induction treatment. There were no dermal reactions seen in any of the test animals at 24, 48 or 72 hours following the challenge treatment. The positive control substance, 0.05% w/v DNCB, produced the appropriate response.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Skin sensitization (pyrimethanil, 96.5%) (Guinea Pig Maximization Test)	Guinea pig, Hartley-derived albino 10/group, intradermal injection of 20% w/w in paraffin oil for induction followed by topical application of 50% w/w in paraffin oil for challenge, positive control: 0.05% DNCB w/w in paraffin oil for the induction phase and 0.5 or 1% DNCB w/w in paraffin oil used in the challenge phase.	Negative	**Not a dermal sensitizer** There were no clinical signs or mortalities. Body-weight gain was normal when compared to that of the control animals. The positive control substance, 0.05% w/w DNCB, produced the appropriate response.
ACUTE STUDIES—FORMULATION (Scala SC Fungicide)			
Oral (pyrimethanil, 380.9 g/L a.i.)	Rat, Sprague-Dawley 5/sex at 5000 mg/kg bw, limit test	LD_{50} > 5000 mg/kg bw (♂) LD_{50} > 5000 mg/kg bw (♀) LD_{50} > 5000 mg/kg bw (♂ and ♀)	**LOW toxicity** > 5000 mg/kg bw: clinical signs of toxicity included hypokinesia, sedation and lateral recumbency in most animals and dyspnea in 1 ♂ and 2 ♀. One ♂ was severely moribund after 2 and 4 hours postdosing. Clinical signs of toxicity were noted within 15 minutes postdosing and were completely resolved by day 4.
Dermal (pyrimethanil, 380.9 g/L a.i.)	Rat, Sprague-Dawley 5/sex, 4000 mg/kg, limit test	LC_{50} > 4000 mg/kg bw (♂) LC_{50} > 4000 mg/kg bw (♀) LC_{50} > 4000 mg/kg bw (♂ and ♀)	**LOW toxicity** > 4000 mg/kg bw: no mortality and no treatment-related clinical observations. One ♀ lost 12 g body weight between days 1 and 5, but body-weight gain appeared normal thereafter.
Inhalation (pyrimethanil, 401.9 g/L a.i.)	Rat, Sprague-Dawley (Crl: CD BR), 5/sex at 1.26 mg/L for 4 hours (nose only), limit test	LC_{50} > 1.26 mg/L (♂) LC_{50} > 1.26 mg/L (♀) LC_{50} > 1.26 mg/L (♂ and ♀)	**Slightly toxic** > 1.26 mg/L: no mortality and no treatment-related clinical observations.
Skin irritation (pyrimethanil, 410 g/L a.i.)	Rabbit, NZW, 6 ♀, 0.5 mL	MAS = 0.0 MIS = 0.33 (1 hour)	**Minimally irritating** Barely perceptible erythema (grade 1) was noted in 2/6 animals at approximately 1 hour postexposure. This was completely resolved by 24 hours of postexposure. Edema was not observed in any animal at any time point. The study was terminated after 72 hours.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Skin irritation (pyrimethanil, 380.9 g/l a.i.)	Rabbit, NZW 3 ♂, 0.5 mL	MAS = 1.11 MIS = 2.0 (1 hour)	**Mildly irritating** Well-defined erythema (grade 2) was noted in all animals at 1 hour. In one animal this was downgraded to very slight (grade 1) by 24 hours and resolved by 48hours. In a second animal, this was downgraded to very slight by 24 hours and resolved by 96 hours. This animal also exhibited desquamation at 96 hours. In the remaining animal, erythema remained well-defined up to 72 hours, was downgraded to very slight by 96 hours and resolved by 120 hours. This animal also exhibited desquamation at 72 and 96 hours. All dermal reactions were resolved by 120 hours. Edema was not observed in any animal at any time point. The study was terminated after 120 hours.
Eye irritation (pyrimethanil, 410 g/l a.i.)	Rabbit, NZW 6 ♀, 0.1 mL, unwashed	MAS (unwashed) = 0.33 MIS (unwashed) = 3.0 (30 minutes, 1 hour)	**Minimally irritating** In the first animal, conjunctival redness (grades 1–2) was noted immediately following and up to 24 hours postinstillation. Chemosis (grade 1) was also noted from 30 minutes up to 4 hours postinstillation. 3/5 remaining animals exhibited conjunctival redness only (grade 1) immediately after and up to 4 hours, while 2/5 animals exhibited conjunctival redness and chemosis (grade 1) immediately after and up to 24 hours. All signs were resolved by 48 hours. There were no corneal or iridial changes observed in any animal.
Eye irritation (pyrimethanil, 380.9 g/L a.i.)	Rabbit, NZW 3 ♂, 0.1 mL, unwashed	MAS (unwashed) = 0.0 MIS (unwashed) = 0.0 (30 min, 1 hour)	**Non-irritating** No ocular irritation was observed in any animal at any observation time. The study was terminated after 72 hours.
Skin sensitization (pyrimethanil, 380.9 g/L a.i.) (Buehler Method)	Guinea pig, Hartley-derived albino 5/sex/group, 0.5 mL during initiation and challenge, no naive or positive control	Negative	**Not a dermal sensitizer** There were no signs of dermal irritation in any of the treated animals during the induction phase or at 24 or 48 hours following challenge treatment. No positive control data were provided. **This study is unacceptable.**

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Skin sensitization (pyrimethanil, 389.7 g/L a.i.) (Magnusson-Kligman maximization method)	Guinea pig, Dunkin-Hartley albino 10/sex/test group, 5/sex/control group, intradermal injection of 25% w/w in Freund's complete adjuvant. Topical induction was either via 0.9% w/v NaCl or undiluted test substance (treated) following treatment with 10% (w/w) sodium lauryl sulphate in vaseline. All test and control animals received a dermal application of 75% (w/w) test substance in the vehicle for the challenge phase.	Negative	**Not a dermal sensitizer** There were no signs of dermal irritation in any of the treated animals during the induction phase or at 24 or 48 hours following challenge treatment. The positive control substance, 0.5% (w/w) DNCB, produced the appropriate response.
SHORT-TERM TOXICITY			
28-day dietary (pyrimethanil, 95.3–98.1%)	Mouse, CD-1 5/sex/dose in diet at dose levels of 0, 1000, 3000, 10 000 or 30 000 ppm (0, 167, 567 or 1960 mg/kg bw/day in ♂ and 0, 236, 667 or 2357 mg/kg bw/day in ♀)	NOAEL = 3000 ppm (♂ 567 mg/kg bw/day and ♀ 667 mg/kg bw/day) LOAEL = 10 000 ppm (♂ 1960 mg/kg bw/day and ♀ 2357 mg/kg bw/day)	**≥ 3000 ppm (♂ 529 mg/kg bw/day and ♀ 626 mg/kg bw/day):** ↓ food consumption
90-day dietary (pyrimethanil, 95.3–98.1%)	Rat, Crl:CD(SD)BR 10/sex/dose, 0, 80, 800 or 8000 ppm (0, 5.4, 55 and 529 mg/kg bw/day in ♂ and 0, 6.8, 67 and 626 mg/kg bw/day in ♀) in diet for 13 weeks	NOAEL = 800 ppm (♂ 55 mg/kg bw/day and ♀ 67 mg/kg bw/day) LOAEL = 8000 ppm (♂ 529 mg/kg bw/day and ♀ 626 mg/kg bw/day)	**≥ 8000 ppm (♂ 529 mg/kg bw/day and ♀ 626 mg/kg bw/day):** ↓ body weight, body-weight gain and food consumption. Urinalysis findings and histopathological findings in the thyroid in one or both sexes were also reported. Histopathological findings in the thyroid included an increased incidence and severity of follicular epithelial hypertrophy, accumulation of lipofuscin in the follicular epithelium and a slight increased incidence of colloid depletion in the follicular cells in both sexes. ↑ relative liver weights and minimal centrilobular hepatocellular hypertrophy (not considered to be adverse).

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
90-day dietary (pyrimethanil, 97.7–97.9%)	Mouse, Crl:CD-1(ICR)BR 20/sex/dose, 0, 80, 900 or 10000 ppm (0, 12, 139 and 1864 mg/kg bw/day in ♂ and 0, 18, 203 and 2545 mg/kg bw/day in ♀) in diet for 13 weeks	NOAEL = 900 ppm (♂ 139 mg/kg bw/day and ♀ 203 mg/kg bw/day) LOAEL = 10 000 ppm (♂ 1864 mg/kg bw/day and ♀ 2545 mg/kg bw/day)	**≥ 10 000 ppm (♂ 1864 mg/kg bw/day and ♀ 2545 mg/kg bw/day):** ↓ body weight, body-weight gain and food efficiency, clinical chemistry findings, ↑ liver weights, gross pathological and/or histopathological findings in the urinary bladder, kidneys, liver and thyroid gland in one or both sexes. In the bladder, uroliths were detected in both sexes with ♀ also exhibiting hyperplasia of the urinary bladder epithelium. Slight tubular dilatation was noted in the kidneys of ♂. Glycogen depletion was noted in the liver in both sexes. Slight to severe exfoliative necrosis of the thyroid follicular cells was noted in ♂. Minimal exfoliative necrosis of the follicular cells was also noted in one ♀.
90-day dietary (pyrimethanil, 97.7–97.9%)	Dog, Beagle 4/sex/dose, 0, 6, 80 or 1000 mg/kg bw/day in 0.5% w/v methylcellulose via gavage for 13 weeks. Animals at 1000 mg/kg bw/day were reduced to 800 mg/kg bw/day after 6 days.	NOAEL = 6 mg/kg bw/day LOAEL = 80 mg/kg bw/day	**≥ 80 mg/kg bw/day:** ↑ incidence of vomiting, salivation, diarrhea, discolouration of the feces, reduced activity and decreased water consumption in one or both sexes. There were no treatment-related ophthalmoscopic, electrocardiography, hematology, clinical chemistry, organ weight, gross pathology or histopathological findings.
12-month gavage (pyrimethanil, 96.3–96.9%)	Dog, Beagle 4/sex/dose, 0, 2, 30 or 400 mg/kg bw/day in 0.5% w/v methylcellulose via gavage for 52 weeks. Animals at 400 mg/kg bw/day were reduced to 250 mg/kg bw/day after 8 days.	NOAEL = 30 mg/kg bw/day LOAEL = 250 mg/kg bw/day	**≥ 250 mg/kg bw/day:** ↑ vomiting, salivation, diarrhea, discolouration of the feces, decreased body weight, body-weight gain, food consumption, food efficiency and water consumption in one or both sexes.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY			
80-week dietary (pyrimethanil, 96.0–97.3%)	Mouse, Crl:CD-1(ICR)BR 51/sex/dose, at dose levels of 0, 16, 160 and 1600 ppm (0, 2.0, 20.0 and 210.9 mg/kg bw/day, ♂; 0, 2.5, 24.9 and 253.8 mg/kg bw/day, ♀) in diet for 80 weeks.	NOAEL = 160 ppm (♂ 20 mg/kg bw/day and ♀ 24.9 mg/kg bw/day) LOAEL = 1600 ppm (♂ 210.9 mg/kg bw/day and ♀ 253.8 mg/kg bw/day)	**≥ 1600 ppm (♂ 210.9 mg/kg bw/day and ♀ 253.8 mg/kg bw/day):** ↑ urogenital tract lesions in ♂, ↑ in the percentage of total deaths before 56 weeks, but not the number of total deaths No evidence of carcinogenicity.
2-year dietary (pyrimethanil, 95.5–97.6%)	Rat, Sprague-Dawley 70/sex/dose, at dose levels of 0, 32, 400 or 5000 ppm (0, 1.3, 17 or 221 mg/kg bw/day, ♂, 0, 1.8, 22, 291 mg/kg, ♀) in diet for 52 weeks (interim sacrifice) or 104 weeks (main study)	NOAEL = 400 ppm (♂ 17 mg/kg bw/day and ♀ 22 mg/kg bw/day) LOAEL = 5000 ppm (♂ 221 mg/kg bw/day and ♀ 291 mg/kg bw/day)	**Non-neoplastic** **≥ 5000 ppm (♂ 210.9 mg/kg bw/day and ♀ 253.8 mg/kg bw/day):** ↑ serum cholesterol (♀) and g-glutamyl transferase (GGT) levels (♂), ↑ absolute liver weights (♂), ↑ relative liver/body weight ratios, ↑ centrilobular hepatocellular hypertrophy and eosinophilic foci,↓ body-weight gains and food consumption **Neoplastic** **≥ 5000 ppm (♂ 210.9 mg/kg bw/day and ♀ 253.8 mg/kg bw/day):** ↑ incidence in thyroid follicular cell adenomas Pyrimethanil appears to be tumorigenic in rats.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Multigeneration (pyrimethanil, 96.2–97.2%)	Rat, Sprague-Dawley Crl:CD(SD)BR (30/dose/sex, F_0; 25/dose/sex, F_1) at dose levels of 0, 32, 400 or 5000 ppm (equal to 0, 1.9, 23.1 and 294 mg/kg bw/day for P_1/P_2 ♂, respectively, during premating; 0, 2.2, 27.4, 343 for P_1/P_2 ♀, respectively, during premating, gestation and lactation periods).	**Parental** NOAEL = 400 ppm (♂ 23.1 mg/kg bw/day and ♀ 27.4 mg/kg bw/day) LOAEL = 5000 ppm (♂ 294 mg/kg bw/day and ♀ 343 mg/kg bw/day) **Offspring** NOAEL = 400 ppm (♂ 17 mg/kg bw/day and ♀ 22 mg/kg bw/day) LOAEL = 5000 ppm (♂ 221 mg/kg bw/day and ♀ 291 mg/kg bw/day) **Reproductive** NOAEL = 5000 ppm (♂ 221 mg/kg bw/day, ♀ 291 mg/kg bw/day)	**Parental** **≥ 5000 ppm:** ↓ body weights and body-weight gains **Offspring** **≥ 5000 ppm:** ↓ pup body weights at lactation day 21
Developmental toxicity (pyrimethanil, 96.3–97.0%)	Rat, Sprague-Dawley 30 ♀/dose, at 0, 7, 85, 1000 mg/kg bw/day via gavage for gestation days 6–15	**Maternal** NOAEL = 85 mg/kg bw/day LOAEL = 1000 mg/kg bw/day **Developmental** NOAEL = 85 mg/kg bw/day LOAEL = 1000 mg/kg bw/day	**Maternal** **≥ 1000 mg/kg bw/day:** ↓ body weight, body-weight gain and food consumption **Developmental** **≥ 1000 mg/kg bw/day:** ↓ mean litter and fetal weight No evidence of teratogenicity. There were no treatment-related external, visceral or skeletal findings.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
Developmental toxicity (pyrimethanil, 97.1%)	Rabbit, NZW 18–19 ♀/dose at 0, 7, 45, 300 mg/kg bw/day via gavage for gestation days 7–19	**Maternal** NOAEL = 45 mg/kg bw/day LOAEL = 300 mg/kg bw/day **Developmental** NOAEL = 45 mg/kg bw/day LOAEL = 300 mg/kg bw/day	**Maternal** **≥ 300 mg/kg bw/day:** reduced and/or no feces and small fecal pellets, body-weight loss gestation days 7–9, ↓ body-weight gain and food consumption **Developmental** **≥ 300 mg/kg bw/day:** ↓ mean fetal weights, ↑ incidence of runted fetuses No evidence of teratogenicity. There were no treatment-related external, visceral or skeletal findings.

STUDY	SPECIES and STRAIN or CELL TYPE and CONCENTRATIONS or DOSES	RESULTS
GENOTOXICITY		
Gene mutations in bacteria (pyrimethanil, 98.7%)	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 0–1500 µg/plate; with and without activation	Negative
Gene mutations in bacteria (pyrimethanil, 98.7%)	*E. coli* CM881 WP2 trp *uv* and CM891 WP2 trp *uvr*A 0–1500 µg/plate; with and without activation	Negative
Gene mutations in mammalian cells in vitro (pyrimethanil, 97.2%)	CHO cells (HGPRT locus) 0–240 µg/mL without activation 0–280 µg/mL with activation	Negative
Chromosome aberrations in vitro (pyrimethanil, 97.4%)	Human lymphocytes 0, 1, 2, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250 or 500 µg/mL with and without activation	Negative
Unscheduled DNA synthesis in vivo	Primary rat hepatocytes (♂ SD rats) 100, 300 or 1000 mg/kg bw (single oral dose; hepatocytes harvested 2 and 14 hours postdosing)	Negative
Micronucleus assay (in vivo)	♂ and ♀ CD-1 (ICR) mice 0, 225, 450 and 900 mg/kg bw (single oral dose; bone marrow harvested 24, 48 and 72 hours postdosing)	Negative

STUDY	SPECIES and STRAIN or CELL TYPE and CONCENTRATIONS or DOSES	RESULTS	
SPECIAL STUDIES			
Acute neurotoxicity (pyrimethanil, 99.8%)	Rat, Sprague-Dawley(CD), 12/sex/dose, single dose of 0, 30, 100 or 1000 mg/kg bw, 16-day observation period	**Systemic** NOAEL = 100 mg/kg bw LOAEL = 1000 mg/kg bw **Neurotoxicity** NOAEL = 1000 mg/kg bw	**Systemic** **1000 mg/kg bw:** ataxic gait, dilated pupils, ↓ hindlimb grip strength, ↓ body temperature and ↓ motor activity in one or both sexes on day 1. These effects were no longer present by the next testing date (day 8). There was no evidence of neurotoxicity. The FOB observations were not corroborated with treatment-related gross pathological findings or neuropathological findings in the CNS or PNS. Therefore, systemic effects were not considered due to neurotoxicity.
13-week neurotoxicity study (pyrimethanil, 99.8%)	Rat, Sprague-Dawley, 12/sex/dose, at 0, 60, 600 or 6000 ppm (0, 4, 38.7 or 392 mg/kg bw, ♂, 0, 4.6, 44.3 or 430 mg/kg bw, ♀) in diet for 13 weeks	**Systemic** NOAEL = 600 ppm (38.7 mg/kg bw/day, ♂, 44.3 mg/kg bw/day, ♀) LOAEL = 6000 ppm (392 mg/kg bw/day, ♂, 430 mg/kg bw/day, ♀) **Neurotoxicity** NOAEL = 6000 ppm (392 mg/kg bw/day, ♂, 430 mg/kg bw/day, ♀)	**≥ 6000 ppm (392 mg/kg bw/day, ♂, 430 mg/kg bw/day, ♀):** ↓ body weight, body-weight gain and food consumption No evidence of neurotoxicity.
Hepatic enzyme induction (pyrimethanil, 99.4%)	Rat, Sprague-Dawley, 6 ♂ at 0,100 or 200 mg/kg bw twice daily via gavage for 4 days	No treatment-related increase in lauryl acid hydroxylase activity (no peroxisome proliferation) (CYP450 4A), ↑ EROD activity (CYP450 1A), ↑ PROD activity (100 mg/kg bw/day only) (CYP450 2B6), ↑ CYP b5 activity, CYP 450 content was not significantly increased	
Hormone and enzyme induction (pyrimethanil, 96.2%)	Rat, Sprague-Dawley, 10 ♂/dose at 0 or 379 mg/kg bw/day in diet for 14 days	↑ TSH (215%) and UDPGT (446%) activity at 15 days, TSH activity returned to control values 2 weeks after cessation of treatment, ↓ T3 and T4 with ↑ TSH activities at Day 4, ↑ absolute and relative liver weights at Day 15, ↓ absolute and relative thyroid weights	
Thyroid function (perchlorate discharge) (pyrimethanil, 96.2%)	Rat, Sprague-Dawley, 6 ♂ Crl:CD(SD)BR/ group with 0, pyrimethanil (509 mg/kg bw/day), propylthiouracil (177 mg/kg bw/day) or phenobarbital (109 mg/kg bw/day) in diet for 7 days	↑ ^{125}I uptake (150%), but no significant increase in perchlorate-induced discharge of ^{125}I. Pyrimethanil effects are similar to phenobarbital (indirectly affects thyroid via liver enzyme activation).	

STUDY	SPECIES and STRAIN or CELL TYPE and CONCENTRATIONS or DOSES	RESULTS
Compound-Induced Mortality **Mouse 80-week Study:** Increase in deaths at the high dose up to week 56 (14/21 deaths in the high-dose group occurred before week 56, no dose-related increase in total deaths). **Mouse Micronucleus Assay:** One ♂ after single gavage dose at 900 mg/kg (cause not determined) **Rabbit Developmental Study:** Three dams became moribund at 300 mg/kg bw/day and were sacrificed.		
Recommended ARfD: 1 mg/kg/day (acute rat neurotoxicity study NOAEL = 100, SF = 100×)		
Recommended ADI: 0.17 mg/kg/day (chronic rat study NOAEL = 17 mg/kg bw/day, SF 100×) **MOE for thyroid tumours:** 100 **MOE for maternal toxicity (rabbit):** 265 **MOS for developmental toxicity (rabbit):** 1765 **MOS for long-term toxicity (♂ mouse):** 100 **MOS for long-term toxicity (♀ mouse):** 129 **Occupational Endpoints** **Short-term/intermediate:** NOAEL = 30 mg/kg bw/day (1-year dog study) **Long-term:** NOAEL = 17 mg/kg bw/day (2-year rat study)		

Appendix II Residues

Table 1 Integrated Food Residue Chemistry Summary

Direction for Use						
Crop	**Formulation Type**	**Interval (days)**	**Rate (g a.i./ha)**	**Application/ season**	**Maximum Rate (kg a.i./ha)**	**PHI (days)**
Apple	SC	7–12	400	4	1.6	72
		N/A	800	1	0.8	14
Pear	SC	7–12	400	4	1.6	72
Grape	SC	7	800	3	2.4	7
Strawberry	SC	7–10	800	3	2.4	1
Potato	SC	7–14	300	6	1.8	7
	Apply in tank mix with BRAVO 500 (750 g chlorothalonil/ha).					
Label restrictions: **A plantback interval restriction of 30 days for wheat and of 130 days for all the other crops must be added to the Scala SC Fungicide label.**						
United States Label						
Field tomato	SC	7–10	302	5	1568	1

Physicochemical Properties	
Water solubility at 20°C (mg/L)	99 at pH 10 160 at pH 4
Solvent solubility (g/100g)	Acetone 38.88 Ethyl acetate 61.69 Methanol 17.59 Dichloromethane 100.02 *n*-hexane 2.37 Toluene 41.23
n-octanol–water partition coefficient (log K_{ow}) at 25°C	2.84
Dissociation constant (p*K*a) at 20°C	3.52
Vapour pressure (Pa) at 20°C	1.13×10^{-3}
Density	1.15
Melting point (°C)	96.3
UV/visible absorption spectrum	λ_{max} (in methanol): 271 nm

Analytical Methodology	
Parameters	**Plant Matrices**
Method ID	DGM C05/98-0
Type	Data-gathering and enforcement method
Analyte	Pyrimethanil
Instrumentation	GC-MS
LOQ	0.05 ppm
Standard	Internal standardization using pentachlorobenzene as a GC marker compound.
ILV	Successfully validated by an independent laboratory.
Extraction/ Clean-up	Extraction with acetone followed by filtration, liquid partition and solid-phase extraction clean-up (silica cartridge).
Multiresidue Methods	MRM Protocol D of the PAM Vol. I is **suitable** for the analysis of pyrimethanil in non-fatty crop matrices.
Parameters	**Livestock Matrices**
Method ID	RAM AN/01/01 Version 2 (superseded by RAM AN/01/02)
Type	Data-gathering and enforcement method
Analytes	Pyrimethanil and the metabolites AN2 (AE C614276) and AN3 (AE C614277).
Instrumentation	GC-MS/MS
LOQ	0.01 ppm in milk for each of the analytes 0.05 ppm in livestock tissues for each of the analytes
Standard	An external standard method was used as a marker for retention time, response and calibration.
ILV	Method RAM AN/01/01 Version 2 was successfully validated at the third attempt using milk and marginally successful at the third attempt using muscle.
Extraction/ Clean-up	Extraction: Fat: acetonitrile under reflux conditions (1 hour) Muscle, liver and kidney: acetonitrile/0.6M HCl (92:8, v/v) Milk: conc. HCl/acetonitrile (1:50, v/v), further extracted with pH 7 phosphate buffer/acetonitrile (1:1, v/v) and extracted once more with acetonitrile. Clean-up: 1. All sample extracts: following extraction, partitioning into hexane, evaporation, re-constitution into methanol. 2. Additional step for milk and kidney only: enzyme hydrolysis, partitioning into ethyl acetate, evaporation, reconstitution into acetone. 3. All sample extracts: derivatization (methylation with TMSD)
Multiresidue methods	MRM Protocols A through G of the PAM Vol. I **are not suitable** for the analysis of the metabolites AN2 and AN3 in livestock matrices.

Nature of the Residue in Grape	
Radiolabel	U-Phenyl-^{14}C pyrimethanil
Test site	Greenhouse
Treatment	Fruits and leaves of grape vines were painted twice (45 and 21 days before harvest).
Rate	1.6 kg a.i./ha
PHI	21 days

In grapes (fruits), TRRs ranged from 20.5 to 36.2 ppm (mean of 29.5 ± 7.0 ppm; n = 4) corresponding to 76.8% of the AR. Identification of the TRRs in grapes indicated that the parent and metabolite AN4 comprised up to 93% (up to 31.5 ppm) and 0.5% (up to 0.17 ppm) of the TRRs, respectively. Three other metabolites (M1, M2 and M4) were characterized; however, no single metabolite comprised greater than 0.5% (0.08 ppm) of the TRRs. Minimal degradation of the parent compound was observed in grapes.

In grape leaves, TRRs ranged from 9.5 ppm to 45 ppm (mean of 23.2 ± 15.5 ppm; n = 4) corresponding to 20% of the AR. Identification of the TRRs in leaves indicated that the parent and unknown M1 were the predominant components (average of 31.1% of the TRRs, 3.91 ppm for pyrimethanil and of 16.8% of the TRRs, 2.07 ppm for M1). AN4 was observed in leaves (1.7–3.9% of the TRRs, 0.16–0.54 ppm). Two other unidentified metabolites (M2 and M4) were obtained in concentrations ranging from 1 to 3.5% of the TRRs. Significant metabolism of pyrimethanil was observed in leaves. Leaves do not constitute a food or feed item; therefore, the unidentified TRRs are not of concern.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel	Phenyl-^{14}C Pyrimethanil	
Grapes—fruits	Pyrimethanil	Metabolite AN4 (AE C614278)
Grapes—leaves	Pyrimethanil M1 (Unidentified)	Metabolite AN4 (AE C614278)

Nature of the Residue in Apple	
Radiolabel	U-Phenyl-^{14}C pyrimethanil or 2-^{14}C-pyrimidyl pyrimethanil
Test site	Under outdoor conditions
Treatment	Apple trees were streaked with 1000 µL/leaf and 100 µL/fruit of formulated product. A total of 4 applications were made at PHIs of 77, 67, 56 and 42 days.
Rate	~1.8 kg a.i./ha/season
PHI	42 days

In apple leaves, TRRs were 856 ppm (pyrimidyl label) and 864 ppm (phenyl label), and in apple fruits. TRRs were 9.2 ppm (pyrimidyl label) and 12.0 ppm (phenyl label). Pyrimethanil was not extensively metabolized accounting for ~72% of the TRRs in fruits and 53% of the TRRs in leaves. The results observed for the two radiolabels (phenyl and pyrimidyl) were similar both qualitatively and quantitatively; thus, indicating that cleavage of the diaryl amine linkage between the phenyl and the pyrimidyl rings of the parent compound was not a significant pathway in apples. The major metabolic pathway in apples occurred primarily via methyl hydroxylation processes yielding AN4 (AE C614278) and AN5 (AE C621312) followed by conjugation with glucose (or other C-6 sugars).

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	U-Phenyl-^{14}C pyrimethanil and 2-^{14}C-pyrimidyl pyrimethanil	
Apple fruits (flesh and peel)	Pyrimethanil	AN4 (free and glucoside conjugate) AN5 (free and glucoside conjugate)
Apple leaves	Pyrimethanil AN5 (free and glucoside conjugate)	AN4 (free and glucoside conjugate)
Nature of the Residue in Tomato		
Radiolabel	U-Phenyl-^{14}C pyrimethanil or 2-^{14}C-pyrimidyl pyrimethanil	
Test site	Tomato plants were grown hydroponically in climate controlled growth chamber.	
Treatment	Test compound was applied using a micropipette to either foliage or fruit. A total of 4 applications were made at 4, 3, 2, and 1 weeks prior to harvest.	
Rate	3.2 kg a.i./ha/season	
PHI	7 days	

In tomato leaves, for the phenyl and pyrimidyl labels, TRRs were 586.3 ppm and 2486.8 ppm in the surface wash, respectively; and TRRs were 113.3 ppm and 343.9 ppm in the rinsed leaves (homogenate), respectively. In tomato fruits (peel and flesh), TRRs were 63.05 ppm (phenyl label) and 59.1 ppm (pyrimidyl label).

In tomato fruit, for both radiolabels, the majority (96.9%–97.6%) of the TRRs were found in the peel. A total of 88.2%–90.9% of the TRRs were removed from the peel by a surface wash using dichloromethane. In whole fruits, 7.3%–8.7% of the TRRs were not removed by the surface wash. Only 0.47%–0.49% of the TRRs were unextractable. In all fractions (wash, organo- and aqueous-soluble fractions for peel, pulp or whole fruit), parent was identified by comparative retention times (with MS confirmation) as the major component (96%–97% of the TRRs).

In both tomato fruits and leaves, the major residue observed was pyrimethanil. Minor metabolites (< 2% of the TRRs) were identified as hydroxylated derivatives of pyrimethanil conjugated to sugars.

Based on the information presented (enzymatic hydrolysis released AN2 and AN4), the parent underwent hydroxylation to form metabolites AN2 and AN4 followed by conjugation with C-6 sugars.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel	U-Phenyl-^{14}C pyrimethanil and 2-^{14}C-pyrimidyl pyrimethanil	
Tomato fruits	Pyrimethanil	AN2 and AN4 glycoconjugates
Tomato leaves	Pyrimethanil	AN2 and AN4 glycoconjugates
Nature of the Residue in Lettuce		
Radiolabel	2-^{14}C-pyrimidyl pyrimethanil	
Test site	Under outdoor conditions.	
Treatment	Hand sprayer (2 applications; 32 and 21 days before harvest).	
Rate	1.6 kg a.i./ha/season	

PHI	0, 18, and 32 days after the **first** application.

TRRs were 98.9 ppm in day 0 lettuce, 18.0 ppm in day 18 lettuce and 4.2 ppm in day 32 lettuce (final harvest; PHI 21 days). The results demonstrated that the proportional amount of radiolabelled material contained in the surface decreased with time. A corresponding increase in material was observed in the extract of the homogenized tissue. In all cases the predominant residue was the parent (44–92% of the TRRs, 1.8–91 ppm). In addition to parent, small amounts of hydroxylated metabolites (AN2 and AN3 + their glycoconjugates; ≤ 7.9% of the TRRs, ≤ 0.3 ppm for each metabolite) were observed.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel	2-^{14}C-pyrimidyl pyrimethanil	
Day 0 lettuce	Pyrimethanil	None
Day 18 lettuce	Pyrimethanil	AN2 and AN3 (free and glucoside conjugate)
Day 32 lettuce	Pyrimethanil	AN2 and AN3 (free and glucoside conjugate)

Nature of the Residue in Carrot	
Radiolabel	2-^{14}C-Pyrimidyl Pyrimethanil
Test site	Under outdoor conditions.
Treatment	The formulation was applied twice either to soil or as foliar treatments to carrot plants at growth stages BBCH 43 (when leaves have fully developed and roots are expanding) and BBCH 47 (21 days before the crop was mature).
Rate	Either 1.6 kg a.i./ha/season or 4.8 kg a.i./ha/season.
PHI	Whole carrot plants were harvested 1 day and 21 days after each application.

TRRs were calculated from a sum of the radioactivity present in the solvent extracts (extracted ^{14}C-residues) and the radioactivity present in the extracted solids (unextracted ^{14}C-residues). TRRs in foliar treated (1.60 kg a.i./ha) carrot roots were 0.444 ppm at the first harvest, 0.436 ppm at the second harvest, 0.359 ppm at the third harvest and 0.829 ppm (Replicate A) and 0.662 ppm (Replicate B) at maturity (fourth harvest) and in soil treated carrot roots were 0.233 ppm at the second harvest and 0.181 ppm (Replicate A) and 0.169 ppm (Replicate B) at maturity. TRRs in foliar treated (1.60 kg a.i./ha) carrot foliage were 26.536 ppm at the first harvest, 5.138 ppm at the second harvest, 52.820 ppm at the third harvest and 9.134 ppm (Replicate A) and 12.220 ppm (Replicate B) at maturity (fourth harvest) and in soil treated carrot foliage were 0.300 ppm at the second harvest and 0.582 ppm (Replicate A) and 0.888 ppm (Replicate B) at maturity.

The predominant residue was the parent compound (45–98% of the TRRs, 0.31–26 ppm) in carrot roots and foliage harvested at the different time points during the study. Minor metabolites observed in roots and foliage included AN2(< 0.1–1% of the TRRs, 0.001–0.02 ppm) and AN4 (< 0.001–1.3% of the TRRs, 0.004–0.07 ppm). The metabolite AN7 was observed in carrot foliage only (0.2–1% of the TRRs, 0.095–0.115 ppm).

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (< 10% TRRs)
Radiolabel	2-^{14}C-Pyrimidyl Pyrimethanil	
Carrot roots Foliar treated Fourth harvest Maturity (PHI of 21 days)	Pyrimethanil	β-O-glucoside conjugate of AN4
Carrot roots Soil treated Fourth harvest Maturity (PHI of 21 days)	Pyrimethanil	Malonyl-β-O-glucoside conjugate of AN4 β-O-glucoside conjugate of AN2 Malonyl-β-O-glucoside conjugate of AN2 β-O-glucoside conjugate of AN4
Carrot foliage Foliar treated Fourth harvest Maturity (PHI of 21 days)	Pyrimethanil Malonyl-β-O-glucoside conjugate of AN4	AN2 AN4 AN7 β-O-glucoside conjugate of AN2 Malonyl-β-O-glucoside conjugate of AN2 β-O-glucoside conjugate of AN4
Carrot foliage Soil treated Fourth harvest Maturity (PHI of 21 days)	Pyrimethanil	Malonyl-β-O-glucoside conjugate of AN4 β-O-glucoside conjugate of AN2 Malonyl-β-O-glucoside conjugate of AN2 β-O-glucoside conjugate of AN4
Confined Rotational Crop Study—Lettuce, Radish and Wheat		
Radiolabel	2-^{14}C-pyrimidyl pyrimethanil	
Test site	Outdoor field cages	
Treatment	Formulation applied once to bare soil (sandy loam).	
Rate	2.4 kg a.i./ha	
Plantback interval	Soil was aged for 30, 130 and 300 days following treatment. Crops were harvested at maturity.	

TRRs accumulated at levels greater that 0.01 ppm in all the rotational crop matrices planted 30, 130 and 300 days after treatment. TRRs at the 30 days after treatment interval were 0.628 ppm (lettuce), 0.872 ppm (radish tops), 0.231 ppm (radish roots), 2.428 ppm (wheat forage), 0.411 ppm (wheat grain) and 8.201 ppm (wheat straw). TRRs dropped significantly between the 30 and 130 day intervals. In the 130 day crops, TRRs ranged from 0.012 ppm to 0.082 ppm and in the 300 day crops, from 0.009 ppm to 0.152 ppm.

In addition to pyrimethanil, several related degradates were present at low levels (< 10% TRRs) with the most significant being AN2, AN3, AN4, AN6, AN7 and AN8. The only metabolite that exceeded 10% TRRs was AN5 in 30-day lettuce and wheat forage.

Pyrimethanil (and possibly the degradates AN7 and AN8) were taken up by the roots of the rotational crops to subsequently be translocated throughout the whole plant. Metabolism of pyrimethanil in rotational crops occurred primarily via hydroxylation processes. Another degradation route was also observed consisting of cleavage of the diaryl amine linkage between the phenyl and the pyrimidyl rings of the parent molecule or of compound AN2 to release the metabolite AN7.

The magnitude of the residues in the rotational crops from the confined crop rotation study **triggered** a need for field accumulation studies.

Metabolite AN5 **was not seen in the rat** metabolism study and accordingly it cannot be assumed that AN5 would be less toxic than the parent. On this basis, **the ROC in rotational crops (secondary plants) will be defined as pyrimethanil and the metabolite AN5 (AE C621312).**

Field Accumulation Rotational Crop Study—Wheat

Pyrimethanil, (Scala 40SC, containing 400 g a.i./L) was applied to potatoes, planted as the primary crop, at a rate of 2.40 kg a.i./ha/season (3 foliar broadcast applications at a rate of 800 g a.i./ha with a retreatment interval of 7 days). Following the last application, the primary crop (potato) was destroyed. Winter wheat was planted 30 days after the last treatment. Wheat forage was harvested at two time points: when plants were 8 inches tall and later at the flag leaf growth stage corresponding to PHIs of 128 to 197 days and of 135 to 232 days, respectively. Wheat hay was sampled at PHIs of 149 to 239 days and wheat straw and grain were collected at normal maturity (PHIs of 190 to 239 days).

No measurable residues of pyrimethanil at or above the LOQ (0.05 ppm) of the enforcement method were found in/on forage, hay, straw and grain. Residues of AN5 (which was the predominant metabolite identified in the confined rotational crop study) were all below the method LOD of 0.015 ppm in all the wheat matrices.

The data support a plantback interval of 30 days for wheat and of 130 days for all other crops not on the label.

Nature of the Residue in Lactating Cow

Species	Radiolabel	Dose Level	Length of Dosing	Sacrifice
British Friesian cow	Radiolabelled position not reported	10 ppm	7 consecutive days	~16.5 hours

Pyrimethanil was absorbed and predominantly excreted in urine (total of ~136 ppm over the 7-day period). The amount of radioactivity excreted in feces was not reported. ^{14}C-residues in milk and tissues were low. TRRs in tissues were 0.017 ppm in muscle, 0.036 ppm in renal fat, 0.249 ppm in kidney and 0.363 ppm in liver. TRRs in bile amounted to 1.771 ppm. Residues in milk increased biphasically, reaching 0.0645 ppm by the second day (47 hours), and then peaking again by the 5th day (119 hours) to 0.0688 ppm.

It should be noted that no residue of parent was found in any matrix. In muscle, 52.9% (0.009 ppm) of the TRRs were organosoluble (hexane and methanol) and 47.1% of the TRRs (0.008 ppm) were unextractable. As each of the extracts were less than 0.01 ppm, these were not analyzed further. In kidney, the major residue was the metabolite AN2 (46% of the TRRs, 0.115 ppm) and minor metabolites observed were AN3 (6.8% of the TRRs, 0.017 ppm) and AN6 (5.4% of the TRRs, 0.013 ppm). In liver, most of the radioactivity was incorporated into peptides and amino acids.

Metabolic Pathway in Livestock

In summary, pyrimethanil was extensively metabolized in cows as no parent molecule was observed in any matrix. The main route of metabolism of pyrimethanil in cattle was by hydroxylation at the 4-position of the phenyl ring yielding the metabolite AN2. In kidney, other hydroxylation products were seen in minor amounts: AN3 and AN6. In order to facilitate elimination via the urine, the phenolic compounds were further conjugated as glucuronide or sulfate conjugates. In liver, conjugation to peptides and amino acids occurred. Little accumulation in muscle, milk or fat was observed. The primary metabolic route (oxidation to phenol) in rat was similar to that found in cattle. The minor routes of metabolism in cattle were also observed in the rat.

Metabolites Identified	Major Metabolites (> 10% TRRs)	Minor Metabolites (<10% TRRs)
Radiolabel	Not Specified	
Milk	AN2 (sulfate or glucuronide conjugates) (AN2 was misidentified; the predominant metabolite was actually AN3)	None
Urine	AN2 (sulfate or glucuronide conjugates)	AN3 and AN6 (sulfate or glucuronide conjugates)
Kidney	AN2 (sulfate or glucuronide conjugates)	AN3 and AN6 (sulfate or glucuronide conjugates)
Liver	Radioactivity has been conjugated into peptides and small proteins of liver.	

Nature of the Residue in Laying Hen

Not required for the petitioned uses.

Crop Field Trials for Domestic Registration

Crop Field Trials—Potato

Sixteen trials were conducted in the United States in Zones1, 2, 3, 5, 5A, 9, 10 and 11 during the 1999 growing season. Although these were not representative of the Canadian growing zones (as per DIR98-02), residues of pyrimethanil in treated potato tubers were consistent within each region and from one region to another.

Commodity	**Rate (kg a.i./ha)**	**PHI (days)**	**Pyrimethanil Residue Levels (ppm)**						
			n	**Min.**	**Max.**	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Potato tubers (data from the United States)	1.5	7	32	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	0

Crop Field Trials—Strawberry

Ten field trials were conducted in the NAFTA representative growing zones 1, 2, 3, 5, 5A, 5B, 10 and 12 during the 1999 and 2001 growing seasons.

Commodity	Rate (kg a.i./ha)	PHI (days)	Pyrimethanil Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Strawberries (data from Canada and the United States)	2.4	1	20	0.58	2.44	2.33	0.97	1.07	0.48

Crop Field Trials—Grape

Twelve field trials were conducted in the United States in Zones 1, 10 and 11 during the 1999 growing season. Two field trials were conducted in Canada in Zone 5 during the 2001 growing season. The supervised residue trials submitted did not satisfy the Canadian zonal requirements (as per DIR98-02). However, when the whole database for pyrimethanil residues in/on grapes is considered, no additional residue trials were required.

Grapes	Rate (kg a.i./ha)	PHI (days)	Pyrimethanil Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Data from the United States	1.6	7	24	0.12	2.56	2.46	0.89	1.07	0.71
Data from Canada	2.4	7	4	1.04	2.67	2.20	1.95	1.9	0.69
French label: one application at a maximum rate of 1.0 kg a.i./ha and a PHI of 35 days.									
France (1990–1993)	0.8–1.0	28–42	14	< 0.05	1.98	–	0.43	0.56	0.46
	0.8–1.0	50–121	46	< 0.05	2.93	–	0.35	0.52	0.61
	2.4	19–56	9	0.59	2.5	–	1.5	1.55	0.58
	3.0–3.2	19–56	18	0.42	3.55	–	1.60	1.68	0.81
	4.0	19–30	12	0.26	4.59	–	1.90	2.87	3.09
German label: one application at a maximum rate of 1.0 kg a.i./ha and a PHI of 28 days.									
Germany (1990–1992)	0.6	18–103	11	< 0.05	1.5	–	0.1	0.36	0.45
	0.8–1.0	0–14	10	0.85	3.9	–	1.85	1.82	0.94
		28–30	6	0.40	1.30	–	0.77	0.78	0.30
		42–99	15	0.05	0.80	–	0.32	0.33	0.19
	2.4	0–67	39	0.30	7.20	–	1.8	2.28	1.57
Italian label: one application at a maximum rate of 0.8 kg a.i./ha and a PHI of 21 days.									
Italy (1990–1992)	0.8	20–22	4	1.30	3.20	–	1.9	2.08	0.89
	1.5–2.4	17–35	7	1.5	3.70	–	2.70	2.47	0.75

Spanish label: one application at a maximum rate of 0.9 kg a.i./ha and a PHI of 21 days.									
Spain (1991)	0.8	77	1	0.70	–	–	–	–	
	0.85	106	1	1.20	–	–	–	–	
	0.97	33	1	2.30	–	–	–	–	
Australian label: one application at a maximum rate of 0.8 kg a.i./ha and a PHI of 7 days.									
Australia (1993–1995)	0.8	0	8	1.04	1.59	–	1.39	1.36	0.22
	1.6		9	2.38	5.70	–	2.49	3.01	1.09
	0.8	7	8	1.33	1.65	–	1.42	1.46	0.13
	1.6		21	0.32	4.00	–	2.14	1.78	1.04
	0.8	11–17	8	0.17	2	–	1.35	1.22	0.70
	1.6		34	0.08	3.25	–	0.60	0.95	0.88
	3.2		4	0.31	0.44	–	0.36	0.37	0.06
	0.8	20–28	13	0.01	2.92	–	1.24	1.01	0.81
	1.6		66	0.04	2.92	–	0.56	0.81	0.78
	3.2		8	0.15	0.33	–	0.24	0.24	0.07
	0.8	34–116	10	0.02	0.06	–	0.05	0.04	0.02
	1.6		78	0.02	4.05	–	0.21	0.45	0.59
	3.2–3.6		7	0.07	0.20	–	0.15	0.14	0.04
	5.4	49–82	3	0.99	4.29	–	1.6	2.29	1.76
New Zealand label: one application at a maximum rate of 0.9 kg a.i./ha and a PHI of 28 days.									
New Zealand (1995)	0.8	49–130	6	< 0.05	3.23	–	0.12	0.63	1.28
	1.6	49–94	12	0.13	4.80	–	0.23	1.16	1.59
	2.4	30–59	10	0.51	5.13	–	0.90	1.88	1.77
	3.2	0–22	7	1.18	3.25	–	1.74	1.95	0.78
		63–93	7	0.16	0.83	–	0.40	0.43	0.22
	5.4	27–59	7	0.57	3.86	–	1.27	1.79	1.12
South African label: one application at a maximum rate of 0.96 kg a.i./ha and a PHI of 56 days.									
South Africa (1994–1995)	0.34–0.68	34–119	11	< 0.02	0.53	–	0.06	0.12	0.16
	1.02	57	2	0.06	0.07	–	–	0.07	–
	1.36	91	2	0.17	0.21	–	–	0.19	–
Chilean label: one application at a maximum rate of 1.02 kg a.i./ha and a PHI of 21 days.									
Chile (1995)	1.57–1.64	3	20	1.03	9.02	–	1.99	3.52	2.71
	1.55–1.65	21	20	0.99	4.58	–	1.51	2.14	1.25

Crop Field Trials—Apple

Twelve field trials were conducted in the United States in Zones 1, 2, 5, 9, 10 and 11 in the growing season of 1999. Apple trees were treated with 4 broadcast foliar applications of Scala SC at a rate of 450 g a.i./ha/application with a retreatment interval of 7 days for a total seasonal rate of 1800 g a.i./ha. Mature apple fruits were harvested 72 days after the last application of Scala SC.

Eight field trials were conducted in Canada in Zones 1A, 5, 5B and 11 in the growing season of 2001. Each trial site consisted of three plots. Plot A received an early season application, Plot B received a combination of early and late season applications and Plot C received a late season application. Apple trees in Plot A were treated with 4 broadcast foliar applications of Scala SC at a rate of 400 g a.i./ha/application with retreatment intervals of 4–7 days for a total seasonal rate of 1600 g a.i./ha. Mature apples were harvested 65–72 days after the last application. Apple trees in Plot B were treated with 5 broadcast foliar applications of Scala SC. The first 4 applications were made at a rate of 400 g a.i./ha/application with retreatment intervals of 4–7 days. The 5th application was made 14 days prior to harvest at a rate of 800 g a.i./ha. The total seasonal rate for this plot was 2400 g a.i./ha. Apple trees in Plot C were treated with a single broadcast foliar application of Scala SC at a rate of 800 g a.i./ha, and mature apples were harvested 14 days later. The number and location of the trials receiving the early season application were in accordance with DIR98-02, while the number and location of the trials receiving a combination of the early and late season applications and the single late season application were not in accordance with DIR98-02.

Commodity	Rate (kg a.i./ha)	PHI (days)	Pyrimethanil Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Apple	1.8 (United States)	72	24	< 0.05	0.16	0.155	0.05	0.08	0.04
	1.6 (Canada)	65–72	16	< 0.05	0.11	0.105	0.06	0.07	0.02
	2.4	14	16	0.11	0.57	0.54	0.28	0.3	0.13
	0.8	14	16	0.09	0.44	0.43	0.16	0.19	0.11

Crop Field Trials—Pear

Six field trials were conducted in the United States in Zones 1, 10 and 11 in the growing season of 1999. The number and location of the field trails were not in accordance with DIR98-02. However, based on a weight of evidence approach, the apple residue data (early season application) were used as bridging data.

Commodity	Rate (kg a.i./ha)	PHI (days)	Pyrimethanil Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	Std. Dev.
Pear (data form the United States)	1.8	72	12	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	0

Crop Field Trials for Promulgation of MRLs in/on Imports									
Crop Field Trials—Field Tomatoes									
Sixteen field trials were conducted in the representative zones of the United States (1, 2, 3, 5 and 10) during the 1999 growing season.									
Commodity	**Rate (kg a.i./ha)**	**PHI (days)**	**Pyrimethanil Residue Levels (ppm)**						
			n	**Min.**	**Max.**	**HAFT**	**Median**	**Mean**	**Std. Dev.**
Tomato (data from the United States)	1.5	1	32	< 0.05	0.38	0.37	0.14	0.16	0.01

Residue Decline					
Zone	**Crop/Variety**	**Commodity or Matrix**	**Total Rate (kg a.i./ha)**	**PHI (days)**	**Pyrimethanil (ppm)**
10	Grape/ Pinot Blanc	Fruit	1.6	1 7 14 21 28	0.60, 0.42 0.46, 0.52 0.43, 0.36 0.29, 0.28 0.24, 0.16
10	Strawberry/ Lido	Fruit	2.4	0 1 2 3 7 14 21	1.23, 1.43 1.15, 0.98 0.82, 0.91 1.48, 1.12 0.45, 0.18 0.43, 0.27 0.20, 0.18
2	Potato/ Red Pontiac	Tuber	1.5	0 7 14 21 28	< 0.05, < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05
10	Potato/ Red Chieftan	Tuber	1.5	0 7 14 21 28	< 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05
2	Field tomato / Celebrity	Fruit	1.5	0 1 7 14 21	0.14, 0.09 0.09, 0.10 < 0.05, < 0.05 < 0.05, < 0.05 < 0.05, < 0.05
3	Field Tomato / Heat Wave	Fruit	1.47	0 1 7 14 21	0.16, 0.13 0.12, 0.13 0.07, 0.06 < 0.05, < 0.05 < 0.05, < 0.05

Proposed Maximum Residue Limits (ppm)	
Apple	0.6*
Pear	0.2*
Strawberry	2.5*
Crop subgroup 1C	0.05*
Tomato	0.5*
Milk	0.02**
Meat of cattle, goats, hogs and sheep	0.1***
Liver of cattle, goats, hogs and sheep	0.1***
Fat of cattle, goats, hogs and sheep	0.1***
Meat byproducts (except liver) of cattle, goats, hogs and sheep	0.15**

* Pyrimethanil
** Pyrimethanil and the metabolite AN3
*** Pyrimethanil and the metabolite AN2

Processing Studies—Grape

The processing study was conducted with grapes treated at 4 kg a.i./ha (California, United States) and at 2.4 kg a.i./ha (Germany).

Fraction	Mean Residue Levels (ppm)	Calculated Concentration Factor
California, United States		
Grape	0.51	—
Juice	0.34	0.66
Wet Pomace	1.18	2.3
Dry Pomace	3.31	6.5
Raisin	0.8	1.6
Raisin Waste	9.25	18.1
Germany		
Grape	0.84	—
Juice	0.23	0.3

Processing Studies—Potato

The processing study was conducted with potato treated at 7.5 kg a.i./ha.

Fraction	Mean Residue Levels (ppm)	Calculated Concentration Factor
Potato	< 0.05	—

Processed fractions not analyzed

Processing Studies—Apple

The processing study was conducted with apple treated at 8.8 kg a.i./ha; 3.7-fold the recommended label rate.

Fraction	Mean Residue Levels (ppm)	Calculated Concentration Factor
Apples	0.17	—
Wet pomace	0.7	4.1
Juice	0.06	0.4

Processing Studies—Tomato		
The processing study was conducted with tomato treated at 7.6 kg a.i./ha; 3.7-fold the recommended label rate.		
Fraction	**Mean Residue Levels (ppm)**	**Calculated Concentration Factor**
Tomato	1.35	—
Puree	0.45	0.3
Paste	1.57	1.2

Livestock Feeding

Dairy Cow

Pyrimethanil was administered once daily orally by gelatin capsule to 14 Holstein dairy cows for 28 consecutive days. Dosing was made at 20.7, 64.7, 234.0 and 1120.0 mg a.i./day, which corresponded to 1, 3, 10, 50 ppm in diet, equivalent to 0.4×, 1.2×, 4× and 20× the maximum theoretical dietay burden (MTDB) of 2.49 ppm for beef cattle based on a diet consisting of wet apple pomace and potato culls and processed waste. For dairy cattle, the feeding levels were equivalent to 0.7×, 2×, 7× and 36× the MTDB of 1.40 ppm based on a similar diet. Cows were milked twice daily, milk samples were composited, and samples collected on days 1, 4, 8, 11, 15, 18, 22, 25 and 27. Subsamples of day-27 whole milk (50 ppm dose group) were separated into milk fat and skim milk by centrifugation.

Residue data for pyrimethanil in milk and tissues were reported at the method LOD or LOQ (non detectable or quantifiable) across all the dose groups. Residues of the metabolite AN2 in beef liver, muscle and fat were all below the limit of quantitation (< 0.01 ppm in milk and < 0.05 ppm in tissues) for the 50-ppm dose group. In kidney, residues of AN2 were measurable in the 3 ppm, 10 ppm and 50 ppm dose groups and averaged to 0.07 ± 0.01 ppm, 0.12 ± 0.02 ppm and 0.63 ± 0.35 ppm, respectively. In milk, residues consisted almost entirely of metabolite AN3. Maximum residues in milk were attained on day 22 at 0.025 ppm for the 10-ppm dose group and on day 27 at 0.088 ppm for the 50-ppm dose group. AN3 residues in milk fat were 0.031 ppm and in skim milk were 0.064 ppm. The milk fat and skim milk data demonstrated that residues do no concentrate in fat.

Anticipated residues of pyrimethanil and the metabolite AN3 in whole milk amounted to 0.02 ppm (LOQ [0.01 ppm] + LOQ [0.01 ppm]). In beef muscle, liver and fat, combined residues of pyrimethanil and the metabolite AN2 were 0.1 ppm (combined LOQs of 0.05 ppm) and were 0.13 ppm (LOQ of 0.05 ppm [pyrimethanil] + 0.08 ppm AN2]) in kidney.

Laying Hen

The requirement for a poultry feeding study was not triggered because pyrimethanil is not registered on any crop fed to poultry.

Storage Stability

Plant Matrices

Based on the results presented, the data indicate that residues of pyrimethanil are stable under deep freeze conditions for up to 844 days in apple, 912 days in peach and 12 months in grape, lettuce, carrot and tomato.

Processed Commodities

The freezer storage stability of pyrimethanil residues in apple processed commodities over the freezer storage interval of 200 days **was not demonstrated.**

Livestock Matrices

Storage stability data depicting the stability of pyrimethanil and the two metabolites AN2 (AE C614276) and AN3 (AE C614277) in livestock milk and tissues as per DIR98-02 for samples that were stored for more than 30 days **were not demonstrated**.

Table 2 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
ROC FOR ENFORCEMENT **Primary Crops** **Rotational Crops**	 Pyrimethanil Pyrimethanil and the metabolite AN5 (AE C621312)
ROC FOR RISK ASSESSMENT **Primary Crops** **Rotational Crops**	 Pyrimethanil Pyrimethanil and the metabolite AN5 (AE C621312)
METABOLIC PROFILE IN DIVERSE CROPS	Similar in grape, apple, tomato, lettuce and carrot
ANIMAL STUDIES	
ANIMALS	Ruminant
ROC FOR ENFORCEMENT	Pyrimethanil and the metabolite AN2 (AE C614276) in livestock tissues. Pyrimethanil and the metabolite AN3 (AE C614277) in milk.
ROC FOR RISK ASSESSMENT	Pyrimethanil and the metabolite AN2 (AE C614276) in livestock tissues. Pyrimethanil and the metabolite AN3 (AE C614277) in milk.
METABOLIC PROFILE IN ANIMALS	Similar in ruminants and rat.
FAT SOLUBLE RESIDUE	No

Dietary Risk from Food and Water			
Chronic Non-Cancer Dietary Risk **ADI = 0.17 mg/kg bw** **EEC (Level II; Groundwater) = 0.1895 ppm**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (refined)	**Food + EEC (refined)**
	All infants < 1 year old	12.60	20.30
	Children 1–2 years	53.60	57.10
	Children 3–5 years	40.70	43.90
	Children 6–12 years	24.40	26.60
	Youth 13–19 years	15.60	17.30
	Adults 20–49 years	10.70	12.90
	Adults 50+ years	11.10	13.40
	Females 13 to 49 years	11.80	14.00
	Total Population	15.50	17.90
Acute Dietary Exposure Analysis, 95th Percentile	**POPULATION**		
		Food (refined)	**Food + EEC (refined)**
ARfD = 1 mg/kg bw **EEC (Level II; Groundwater) = 0.1953 ppm**	**Total Population**	13.00	13.33

Appendix III Environmental Assessment

Table 1 Physical and Chemical Properties of the Active Ingredient Relevant to the Environment

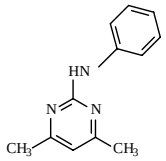
Property	Value	Comments
Chemical structure		
IUPAC name:	N-(4,6-dimethylpyrimidin-2-yl) aniline	
Empirical formula:	$C_{12}H_{13}N_3$	
Water solubility	121.0 mg/L at 25°C, pH = 6.1	This active ingredient is classified as very soluble in water.
Vapour pressure	2.2×10^{-3} Pa (= 1.65×10^{-5} mmHg), at 25°C	From LSS report, Part 2. According to the classification of Kennedy and Talbert (1977), the active ingredient has low volatility.
Henry's law constant (1/H)	$K = 3.58 \times 10^{-8}$ atm m^3/mol or $1/H = 6.84 \times 10^5$	The active ingredient is non-volatile from water or moist soil. Calculated by the reviewer.
Log K_{ow}	2.84	From LSS report, Part 2. There is a low potential for the active ingredient to bioaccumulate.
pK_a	3.52 at 20°C	At environmentally relevant pHs the molecule will be neutral
UV–visible absorption	No absorption observed from 300 to 800 nm	The active ingredient has a low potential for light-induced phototransformation under normal environmental conditions.

Table 2 Fate and Behaviour in the Terrestrial Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	Pyrimethanil	Half-life at: pH 5—stable pH 7—962 day pH 9—722 day	Not an important route of transformation in the environment
Phototransformation on soil	Pyrimethanil	Half-life: dark—stable irradiated—stable	Based on the scientific rationale of a submitted waiver request Not a route of transformation in the environment
Phototransformation in sir	Pyrimethanil	Not required –not volatile	
Biotransformation			
Biotransformation in Aerobic soil	Pyrimethanil	Half-life: loamy sand: 72 days sandy loam: 25 days loam: 70 days	Slightly to moderately persistent in soil A number of unidentified and unidentified transformation products observed, none of which exceeded 10% of the AR
Biotransformation in Anaerobic soil	Pyrimethanil	> 300 days	Persistent 2-amino-4,6-dimethylpyrimidine is a major transformation product
Mobility			
Adsorption/desorption in soil	Pyrimethanil	Adsorption K_{oc}: 438—686	Low to moderate mobility in soil
Column leaching	Pyrimethanil	Significant penetration into soil column (> 20 cm)	Supports adsorption desorption findings
Volatilization	Pyrimethanil	Not volatile based on vapour pressure	

Property	Test Material	Value	Comments
Field Studies			
Field dissipation (Canadian sites)	Pyrimethanil	DT_{50}: 75–153 days	No residues below 15 cm depth Moderately persistent 2-amino-4,6-dimethylpyrimidine is a transformation product

Table 3 Transformation Products in the Terrestrial Environment

Fate Process	Test Material		Major Transformation Products	Minor Transformation Products
Hydrolysis	Pyrimethanil		None identified	None identified
Phototransformation on soil	N/A		N/A	N/A
Biotransformation in aerobic soil	Pyrimethanil		Unidentified compound (U2) at 6.6% of AR	2-amino-4,6-dimethylpyrimidine 4,6-dimethyl-2(4-nitroanilino)-pyrimidine 2-anilino-4,6-dimethylpyrimidine-1oxide 4,6-dimethyl-2(2-nitroanilino)-pyrimidine 2-hydroxy-4,6-dimethylpyramidine and unidentified compounds.
	2-amino-4,6-dimethylpyrimidine		None identified	4 unidentified compounds
Biotransformation in anaerobic soil (flooded soil)	Pyrimethanil		2-amino-4,6-dimethylpyrimidine at 13.6% of AR	2-hydroxy-4,6-dimethylpyramidine
Field dissipation	Scala SC	Ontario	None identified	2-amino-4,6-dimethylpyrimidine

Table 4 Fate and Behaviour in the Aquatic Environment

Property	Test Material	Value	Comments
Abiotic Transformation			
Hydrolysis	Pyrimethanil	Half-life at: pH 5–Stable pH 7–962 day pH 9–722 day	Not an important route of transformation in the environment
Phototransformation in water	Pyrimethanil	Half-life: dark–stable irradiated–stable at environmentally relevant pHs	Not a route of transformation in the environment
Biotransformation			
Biotransformation in aerobic water/sediment	Pyrimethanil	DT_{50} of 40–121 days (system)	Partitions rapidly to sediments Slightly to moderately persistent in aquatic systems 2-amino-4,6-dimethylpyrimidine is the major transformation product
Biotransformation in anaerobic water/sediment	Pyrimethanil	DT_{50} of 566 days (total system)	Rapidly partitions to sediments Persistent in total system No major transformation products

Table 5 Transformation Products in the Aquatic Environment

Fate Process	Test Material	Major Transformation Products	Minor Transformation Products
Hydrolysis	Pyrimethanil	None identified	None identified
Phototransformation in water	Pyrimethanil	None identified	None identified
Biotransformation in aerobic water systems	Pyrimethanil	2-amino-4,6-dimethylpyrimidine at 10.4% of the AR	2-hydroxy-4,6-dimethylpyramidine 4,6-dimethyl-2(4-nitroanilino)-pyrimidine 2-anilino-4,6-dimethylpyrimidine-1-oxide
Biotransformation in anaerobic water systems	Pyrimethanil	None identified	4,6-dimethyl-2(4-nitroanilino)-pyrimidine

Table 6 Major Groundwater and Surface Water Model Inputs for Level 1 Assessment of Pyrimethanil and its Transformation Products

Type of Input	Parameter	Value
Application information Apple	Maximum allowable application rate per year (kg a.i./ha)	2.4
	Maximum rate for each application (kg a.i./ha)	4 × 0.4 kg a.i./ha early season plus 1 × 0.8 kg a.i./ha late season
	Maximum number of applications per year	See above
	Minimum interval between applications (days)	7
	Method of application	Airblast
Application information Grape	Maximum allowable application rate per year (kg a.i./ha)	2.4
	Maximum rate each application (kg a.i./ha)	0.8
	Maximum number of applications per year	3
	Minimum interval between applications (days)	7
	Method of application	Airblast
Environmental fate characteristics—**pyrimethanil**	Hydrolysis half-life at pH 7 (days)	962
	Photolysis half-life in water (days)	Stable
	Adsorption K_{oc} (mL/g)	337
	Aerobic soil biotransformation half-life (days)	82
	Aerobic aquatic biotransformation half-life (days)	121
	Anaerobic aquatic biotransformation half-life (days)	566

Type of Input	Parameter	Value
Environmental fate characteristics—**2-amino-4,6-dimethylpyramidine**	Hydrolysis half-life at pH 7 (days)	No data (assume stable)
	Photolysis half-life in water (days)	No data (assume stable)
	Adsorption K_{oc} (mL/g)	39.6
	Aerobic soil biotransformation half-life (days)	146
	Aerobic aquatic biotransformation half-life (days)	Assume stable
	Anaerobic aquatic biotransformation half-life (days)	Assume stable

Table 7 Estimated Environmental Concentrations of Pyrimethanil and its Transformation Product in Potential Drinking Water Sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
Pyrimethanil	25.3	24.5	68.45	19.16	115.6	77.3
2-amino-4,6-dimethylpyrimidine[5]	170	165	16.96	10.18	554.2	550.2

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations
5 Aquatic transformation rates could not be estimated for 2-amino-4,6-dimethylpyrimidine, and it was assumed to be stable for modelling purposes. This is a major contributor to its high dugout EECs.

Table 8 Maximum EEC of Pyrimethanil in Vegetation and Insects after a Direct Overspray of Scala SC

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/Dry Weight Ratios	EEC (mg a.i./kg dw)
Short range grass	513.6	3.3[b]	1694.9
Leaves and leafy crops	268.8	11[b]	2956.8
Long grass	235.2	4.4[b]	1034.9
Forage crops	288.0	5.4[b]	1555.2
Small insects	124.8	3.8[c]	474.2
Pods with seeds	25.7	3.9[c]	100.2
Large insects	21.4	3.8[c]	81.2
Grain and seeds	21.4	3.8[c]	81.2
Fruit	32.2	7.6[c]	244.4

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994)

[b] Fresh/dry weight ratios from Harris (1975)

[c] Fresh/dry weight ratios from Spector (1956)

Table 9 Maximum EEC of Pyrimethanil in Diets of Birds and Mammals after a Direct Overspray of Tribute 2.25 SC or Tribute 35 DF

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	420.2
Mallard duck	30% large insects 70% grain	81.2
Rat	70% short grass 20% grain/seeds 10% large insects	1210.8
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	1203.5
Rabbit	25% short grass 25% long grass 25% forage crops 25% leaves and leafy crops	1810.5

Table 10 Effects on Terrestrial Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Invertebrates				
Earthworm	Acute	Pyrimethanil (95.1%)	NOEC = 250 mg a.i./kg dw soil	N/A
Bee	Oral	Pyrimethanil (95.9%)	LD_{50} > 100µg a.i./bee NOEL = 100µg a.i./bee	Relatively non-toxic
	Contact	Pyrimethanil (95.9%)	LD_{50} > 100µg a.i./bee NOEL = 100µg a.i./bee	Relatively non-toxic
Parasitic wasp	Contact	End-use product 406.2 g a.i./L	100% mortality at 1 kg a.i./ha	Acutely toxic
Predaceous mite	Contact	End-use product 393.4 g a.i./L	47 ± 15.1% mortality at 1 kg a.i./ha E = 68.0%	Classified as slightly harmful for overall effect (E)
Lacewings	Contact	End-use product 398.7 g a.i./L	23.5% mortality at 1 kg a.i./ha E = 39.0%	Classified as harmless for overall effect (E)
Ladybird beetle	Contact	End-use product 398.7 g a.i./L	87.2% mortality at 1 kg a.i./ha E = 22.6%	Classified as harmless for overall effect (E) but acutely toxic
Ladybird beetle	Semi-field	End-use product 418 g a.i./L	No significant reduction in numbers at 1 kg a.i./ha	N/A
Parasitic wasp	Semi-field	End-use product 418 g a.i./L	No significant effect at 1 kg a.i./ha	N/A
Predatory mites	Semi-field	End-use product 400 g a.i./L	No significant effect at 475 kg a.i./ha × 5	N/A
Birds				
Bobwhite quail	Acute	Pyrimethanil (97.8%)	NOEL = 2000 mg a.i./kg bw LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic
	Dietary	Pyrimethanil (97.8%)	NOEC = 5200 mg a.i./kg diet LC_{50} > 5200 mg a.i./kg diet	Practically non-toxic

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
	Reproduction	Pyrimethanil (95.9–97.1%)	NOEC = 1000 mg a.i./kg bw	Unlikely to cause reproductive effects
Mallard duck	Acute	Pyrimethanil (97.8%)	NOEL = 125* mg a.i./kg bw LD_{50} > 125* mg a.i./kg bw	Moderately toxic. * Highest non-emetic dose
	Dietary	Pyrimethanil (97.8%)	NOEC = 5200 mg a.i./kg diet LC_{50} > 5200 mg a.i./kg diet	Practically non-toxic
	Reproduction	Pyrimethanil (95.9–97.1%)	NOEL = 640 mg a.i./kg bw	Unlikely to cause reproductive effects

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Mammals				
Rat	Acute	Pyrimethanil (98.4%)	LD_{50} = 5060 mg a.i./kg bw (combined)	Low toxicity
	Dietary	Pyrimethanil (95.3–98.1%)	NOAEL > 800 mg a.i./kg diet	N/A
	Acute neurotoxicity	Pyrimethanil (99.8%)	**Systemic** NOAEL = 100 mg a.i./kg bw LOAEL = 1000 mg a.i./kg bw **Neurotoxicity** NOAEL = 1000 mg a.i./kg bw	N/A
	Reproduction (multigeneration dietary)	Pyrimethanil (96.2–97.2%)	**Parental, offspring, and reproductive:** NOAEL = 400 ppm LOAEL = 5000 ppm	N/A
Mouse	Acute	Pyrimethanil (98.4%)	LD_{50} = 5000 mg a.i./kg bw (combined)	Low toxicity
	Dietary	Pyrimethanil (97.7–97.9%)	NOAEL = 900 mg a.i./kg diet LOAEL = 1000 mg a.i./kg diet	N/A
Vascular Plants				
Vascular plant	Pre-emergence and postemergence screening	Pyrimethanil	No effect to 3 kg a.i./ha	Not phytotoxic at recommended application rate
	Pre-emergence and postemergence screening	2-amino-4,6-dimethylpyrimidine	Some negative effects at 6–20 times maximum application rate for parent	Not expected to be phytotoxic at recommended application rate

[a] Atkins et al. (1981) for bees and the USEPA classification for others, where applicable.

Table 11 Effects on Aquatic Organisms

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater Species				
Daphnia magna	Acute	Pyrimethanil (98.9% a.i)	48 hour EC_{50} = 2.9 mg a.i./L NOEC =1.5 mg a.i./L	Moderately toxic
	Chronic	Pyrimethanil (98.9% a.i)	21 day EC_{50} = 1.87 mg a.i./L NOEC = 0.97 mg a.i./L	Moderately toxic
Rainbow trout	Acute	Pyrimethanil (99.4% a.i)	96 hour LC_{50} = 10.56 mg a.i./L NOEC = 4.0 mg a.i./L	Slightly toxic
	Chronic	Pyrimethanil (98.3% a.i)	NOEC = 1.6 mg a.i./L	N/A
	Early life stage	Pyrimethanil (99.4% a.i)	NOEC = 77 µg a.i./L	N/A
Mirror carp	Acute	Pyrimethanil (99.4% a.i)	96 hour LC_{50} = 35.36 mg a.i./L NOEC = 6.25 mg a.i./L	Slightly toxic
Bluegill sunfish	Acute	Pyrimethanil (99.4% a.i)	96 hour LC_{50} = 29.0 mg a.i./L NOEC = 12.5 mg a.i./L	Slightly toxic
Freshwater green alga	Acute	Pyrimethanil (95.5% a.i)	96 hour E_rC_{50} = 5.84 mg a.i./L (growth) 96 hour E_bC_{50} = 1.20 mg a.i./L (biomass) NOEC< 0.33 mg a.i./L	N/A
Freshwater diatom	Acute	Pyrimethanil (99.4% a.i)	96 hour IC_{50} > 3.9 mg a.i./L NOEC = 3.9 mg a.i./L	N/A

Organism	Exposure	Test Substance	Endpoint Value	Degree of Toxicity[a]
Freshwater cyanobacteria	Acute	Pyrimethanil (99.4% a.i)	96 hour IC_{50} > 3.8 mg a.i./L NOEC = 3.8 mg a.i./L	N/A
Vascular plant	Dissolved	Pyrimethanil (99.4% a.i)	7 day E_rC_{50} > 30.0 mg a.i./L (growth) 7 day E_bC_{50} = 15.3 mg a.i./L (biomass) 7 day EC_{50} = 8.7 mg a.i./L (dry weight) NOEC< 1.9 mg a.i./L	N/A
Marine Species				
Crustacean	Acute	Pyrimethanil (99.4% a.i)	96 hour LC_{50} = 3.4 mg a.i./L NOEC = 0.37 mg a.i./L	Moderately toxic
	Chronic	Pyrimethanil (99.4% a.i)	NOEC = 0.5 mg a.i./L	N/A
Mollusk	Acute	Pyrimethanil (99.4% a.i)	96 hour EC_{50} = 3.9 mg a.i./L NOEC = 1.3 mg a.i./L	Moderately toxic
Fish	Acute	Pyrimethanil (99.4% a.i)	96 hour LC_{50} = 2.8 mg a.i./L NOEC = 1.2 mg a.i./L	Moderately toxic
Marine alga	Acute	Pyrimethanil (99.4% a.i)	96 hour E_rC_{50} > 6.6 mg a.i./L (growth) 96 hour E_bC_{50} > 6.6 mg a.i./L (biomass) NOEC = 3.9 mg a.i./L	N/A

[a] USEPA classification, where applicable

Table 12 Risk to Terrestrial Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute	250 mg a.i./kg	1.0 mg a.i./kg soil	4.0×10^{-3}	Negligible risk
Bee	Oral and contact	> 112 kg a.i./ha equivalent to > 100 µg a.i./bee	2.4 kg a.i/ ha	N/A	Unlikely to pose a significant risk
Parasitic wasp	Contact	N/A	N/A	N/A	See semi-field test
Predaceous mite	Contact	N/A	N/A	N/A	See semi-field test
Lacewings	Contact	N/A	N/A	N/A	Unlikely to pose a significant risk at rates equal to or less than 0.4 kg/ha
Ladybird beetle	Contact	N/A	N/A	N/A	See semi-field test
Ladybird beetle	Semi-field	N/A	N/A	N/A	Unlikely to pose a significant risk at rates equal to or less than 0.4 kg/ha
Predaceous mite	Semi-field	N/A	N/A	N/A	Unlikely to pose a significant risk at rates equal to or less than 0.4 kg/ha
Parasitic wasp	Semi-field	N/A	N/A	N/A	Unlikely to pose a significant risk at rates equal to or less than 0.4 kg/ha

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Birds					
Bobwhite quail	Acute	48.6 mg a.i/ind	420.2 mg a.i./kg diet	28.9 days to consume dose equivalent to NOEC	Negligible risk
	Dietary	5200 mg a.i./kg diet	420.2 mg a.i./kg diet	0.08	Negligible risk
	Reproduction	1000 mg a.i./kg diet	420.2 mg a.i./kg diet	0.42	Low risk
Mallard duck	Acute	7.87 mg a.i/ind	81.2 mg a.i./kg diet	6.3 days to consume dose equivalent to NOEC	Negligible risk
	Dietary	5200 mg a.i./kg diet	81.2 mg a.i./kg diet	0.02	Negligible risk
	Reproduction	640 mg a.i./kg diet	81.2 mg a.i./kg diet	0.13	Low risk
Mammals					
Rat	Acute	1771.0 mg a.i./ind	1210.8 mg a.i./kg dw diet	24 days to consume dose equivalent to LD_{50}	Negligible risk
	Dietary	> 800 mg a.i./kg diet	1210.8 mg a.i./kg diet	1.5	Moderate risk
	Neurotoxicity	350.0 mg a.i./ind	1210.8 mg a.i./kg diet	4.8 days to consume dose equivalent to NOEC	Negligible
	Reproduction	400 mg a.i./kg diet	1210.8 mg a.i./kg diet	3.03	Moderate risk
Mouse	Acute	165 mg a.i./ind	1203.57 mg a.i./kg dw diet	23 days to consume dose equivalent to LD_{50}	Negligible risk
	Dietary	900 mg a.i./kg diet	1203.57 mg a.i./kg dw diet	1.3	Moderate risk
Vascular Plants					

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Vascular plant	Pre-emergence and postemergence screening with pyrimethanil	N/A	3 kg a.i./ha	N/A	No significant risk expected
	Pre-emergence and postemergence screening with 2-amino-4,6-dimethyl-pyrimidine	N/A	56 and 11.2 kg a.i./ha	N/A	No significant risk expected

Table 13 Risk to Aquatic Organisms

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Freshwater Species					
Daphnia magna	Acute	1.5 mg a.i./L	0.77 mg a.i./L	0.51	Low
	Chronic	0.97 mg a.i./L	0.77 mg a.i./L	0.79	Low
Rainbow trout	Acute	4.0 mg a.i./L	0.77 mg a.i./L	0.19	Low
	Chronic	1.6 mg a.i./L	0.77 mg a.i./L	0.48	Low
	Early life stage	0.077 mg a.i./L	0.77 mg a.i./L	10	High
Mirror carp	Acute	6.25 mg a.i./L	0.77 mg a.i/L	0.12	Low
Bluegill sunfish	Acute	12.5 mg a.i./L	0.77 mg a.i./L	0.06	Negligible
Freshwater green algae	Acute	0.12 mg a.i/L[a]	0.77 mg a.i./L	6.4	Moderate
Freshwater diatom	Acute	3.8 mg a.i./L	0.77 mg a.i./L	0.2	Low
Freshwater cyanobactera	Acute	3.9 mg a.i/L	0.77 mg a.i./L	0.2	Low
Vascular plant	Dissolved	0.87 mg a.i/L[a]	0.77 mg a.i./L	0.88	Low

Organism	Exposure	Endpoint Value	EEC	RQ	Risk
Marine Species					
Crustacean	Acute	0.37 mg a.i./L	0.77 mg a.i./L	2.1	Moderate
	Chronic	0.50 mg a.i./L	0.77 mg a.i./L	1.5	Moderate
Mollusk	Acute	1.3 mg a.i./L	0.77 mg a.i./L	0.59	Low
Fish	Acute	1.2 mg a.i/L	0.77 mg a.i./L	0.64	Low
Marine alga	Acute	3.9 mg a.i./L	0.77 mg a.i./L	0.2	Low

[a] Indicates that 1/10 of the EC_{50}/LC_{50} was used.

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