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Pest Management Regulatory Agency

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Agence de réglementation de la lutte antiparasitaire

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EVALUATION REPORT

Fludioxonil

Scholar 50WP Fungicide

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OVERVIEW

Registration Decision for Scholar 50WP Fungicide

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*[1] and in accordance with the Pest Control Products Regulations, has granted conditional registration for the sale and use of Fludioxonil Technical Fungicide and Scholar 50WP Fungicide containing the technical grade active ingredient fludioxonil to control fungal diseases on stone and pome fruit after harvest.

Current scientific data from the applicant and relevant scientific reports were evaluated to determine if, under the proposed conditions of use, Scholar 50WP has value and does not present an unacceptable risk to human health or the environment.

This report summarizes the information evaluated and provides the results of the evaluation as well as the reasons for the conditional registration decision, with an outline of the additional scientific information required from the applicant. It also describes the conditions of registration that applicants must meet to ensure that the health and environmental risks as well as the value of these pest control products are acceptable for their intended use.

This overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on human health, environmental and value assessment of Fludioxonil Technical Fungicide and Scholar 50WP Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks[2] to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in

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1 As per subsection 28(1) of the *Pest Control Products Act*.

2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and ©) health, safety and environmental benefits and social and economic impact".

humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

What is Scholar 50WP Fungicide?

Scholar 50WP Fungicide contains the active ingredient fludioxonil to control fungal diseases on pome and stone fruit after harvest.

❖ Health Considerations

♦ Can Approved Uses of Scholar 50WP Affect Human Health?

Scholar 50WP is unlikely to affect your health when used according to the label directions.

People could be exposed to fludioxonil through diet (food and water) or when Scholar 50WP Fungicide is applied. When assessing health risks, the PMRA considers two key factors: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only the uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when products containing fludioxonil are used according to the label directions.

The technical grade active ingredient fludioxonil caused mild eye irritation in animals. Consequently, the statement "Caution—Eye Irritant" is required on the label. Fludioxonil did not cause cancer in animals and was not genotoxic[4]. There was also no indication that fludioxonil caused damage to the nervous system, and there were no effects on reproduction. The first signs of toxicity in animals given daily doses of fludioxonil over longer periods of time were effects on the liver. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

[4] Genotoxic chemicals are those capable of causing damage to DNA. Such damage can potentially lead to the formation of a malignant tumor, but DNA damage does not lead inevitably to the creation of cancerous cells.

When fludioxonil was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus was not any more sensitive to fludioxonil than the adult animal.

♦ Residues in Water and Food

Dietary risks from food and water are not of concern.

There is no acute reference dose or cancer potency factor established for fludioxonil. Chronic aggregate dietary intake estimates (food plus water) revealed that the general population will typically consume less than 14% of the acceptable daily intake for fludioxonil. Children from one to two years old, the subpopulation most sensitive to fludioxonil relative to body weight, are expected to be exposed to less than 40% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from fludioxonil is not of concern for all population subgroups.

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Each MRL value determines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Pesticide MRLs are established for the *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted in the United States on pome fruit and stone fruit treated with fludioxonil after harvest were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Report.

♦ Occupational Risks From Handling Scholar 50WP Fungicide

Occupational risks are not of concern when Scholar 50WP Fungicide is used according to the label directions, which include protective measures.

Direct skin contact can occur when workers mix, load or apply Scholar 50WP Fungicide or handle freshly treated fruit. Therefore, the label will specify that applicators and other handlers of Scholar 50WP Fungicide must wear a long-sleeved shirt, pants and chemical-resistant gloves. Taking into consideration these label requirements and that occupational exposure is expected to be of short- to intermediate-term, risk to applicators or workers is not a concern.

For the general population, the exposure is expected to be much less than that of workers, which is considered negligible. Therefore, health risks to bystanders are not of concern.

❖ Environmental Considerations

♦ What Happens When Scholar 50WP Fungicide is Introduced Into the Environment?

Only negligible amounts of fludioxonil are expected to be released into the environment because Scholar 50WP Fungicide is applied indoors. The PMRA has added a label statement to Scholar 50WP Fungicide to ensure waste water contaminated with fludioxonil is properly disposed of and to reduce any potential risk.

❖ Value Considerations

♦ What is the Value of Scholar 50WP Fungicide?

A single application of Scholar 50WP Fungicide effectively controls a wide range of diseases on pome and stone fruit after harvest.

The number of fungicides for controlling diseases in pome and stone fruit after fruit is harvested is limited. The active ingredient fludioxonil in Scholar 50WP Fungicide represents a new class of chemistry (phenylpyrrole) for this use. The addition of fludioxonil to manage diseases occurring after harvest could help reduce the reliance on other products, thereby lowering the potential for pome and stone fruit to develop resistance to current products.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Key Risk-Reduction Measures

- **Human Health**

Anyone mixing, loading or applying Scholar 50WP Fungicide must wear a long-sleeved shirt, pants and chemical-resistant gloves to protect their skin.

- **Environment**

The following statement has been added to the label to reduce any risk: “DO NOT allow fludioxonil contaminated waste water from processing plants to enter lakes, streams, ponds or other waters.”

What Additional Scientific Information Is Required?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

- **Value**
    - Two additional efficacy trials for mucor rot on pome fruit and rhizopus rot on stone fruit. The applicant must submit this information no later than 1 September 2007.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted[5], the PMRA will publish a consultation document when there is a proposed decision on the applications to convert the conditional registrations to full registrations or on the applications to renew the conditional registrations, whichever occurs first.

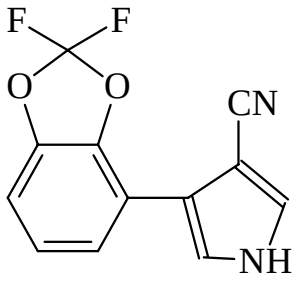
The test data cited in this Evaluation Report (i.e., the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra_infoserv@hc-sc.gc.ca).

[5] As per subsection 28(1) of the *Pest Control Products Act*.

SCIENCE EVALUATION

1.0 The Technical Grade Active Ingredient, its Properties and Uses

1.1 Identity of the Technical Grade Active Ingredient

Active substance		Fludioxonil
Function		Fungicide
Chemical name		
1.	International Union of Pure and Applied Chemistry (IUPAC)	4-(2,2-difluoro-1,3-benzodioxol-4-yl)pyrrole-3-carbonitrile
2.	Chemical Abstracts Service (CAS)	4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1*H*-pyrrole-3-carbonitrile
CAS number		131341-86-1
Molecular formula		$C_{12}H_6F_2N_2O_2$
Molecular weight		248.2
Structural formula		
Purity of the technical grade active ingredient		97.6% (limits: 94.7–100.0%)

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product — Fludioxonil Technical Fungicide

Property	Result	
Colour and physical state	Yellowish powder	
Odour	Odourless	
Melting point	199.8°C	
Boiling point or range	Not applicable	
Density at 20°C	1.54 g/cm^3	
Vapour pressure at 25°C	3.87 x 10^{-7} Pa	
Henry's law constant at 20°C	5.4 × 10^{-5} Pa m^3/mol (1/H = 4.56 × 10^7)	
Ultraviolet (UV)—visible spectrum	λ_{max}= 207 nm λ_{max}= 265 nm	
Solubility in water at 25°C	1.8 mg/L	
Solubility in organic solvents at 25°C (g/100 mL)	**Solvent** ethanol acetone toluene n-octanol hexane	**Solubility** 4.4 19 0.27 2.0 0.00078
n-Octanol–water partition coefficient (K_{ow})at 25°C	log K_{ow} = 4.12	
Dissociation constant (pK_a)	basic pKa < 0 acidic pKa = 14.1	
Stability (temperature, metal)	The product is stable to metals, temperature and light.	

End-Use Product —Scholar 50WP Fungicide

Property	Result
Colour	Off white powder
Odour	Sweet, soap-like
Physical state	Solid

Property	Result
Formulation type	Wettable powder
Guarantee	50.0% nominal (limits: 48.5%, 51.5%)
Container material and description	Low density polyethylene (LLDPE) pouches 793.8 g to 10 kg
Bulk Density	0.37 g/cm^3
pH of 1% dispersion in water	8.9 at 25°C
Oxidizing or reducing action	The product does not contain oxidizing or reducing agents.
Storage stability	The analytical data show 2% decomposition after storage for one year. The guarantee is within the certified limits.
Explodability	The product does not contain any components with explosive properties.

1.3 Directions for Use

Scholar 50WP Fungicide is a fungicide for control of various postharvest fungal diseases of stone and pome fruits. It can be applied as a dip or drench directly to the fruit after harvest at a rate of 227 g of product / 378 L of water.

1.4 Mode of Action

Scholar 50WP Fungicide is a protectant, contact fungicide and has little to no systemic activity. The active ingredient, fludioxonil, blocks a protein kinase that catalyses phosphorylation of a regulatory enzyme of glycerol synthesis. The fungicide remains on the fruit surface and inhibits spore germination and growth of germ tubes and mycelia on the fruit surface. Thus, Scholar 50WP Fungicide has a single site mode of action and resistance management practices are essential to ensure its long term usefulness.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Technical Grade of Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Fludioxonil Technical Fungicide have been validated and assessed to be acceptable.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the Scholar 50WP Fungicide formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with ultraviolet absorbance detector (HPLC-UV) (Methods AG-597B and AG-616B) and a gas chromatography method using a nitrogen phosphorous detector (GC-NPD) (Method AG-664) were proposed for data generation and enforcement purposes in plant and animal matrices (Appendix I, Table 2.3). These previously reviewed methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in pome fruit and stone fruit.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for fludioxonil. The database is complete, consisting of the full array of laboratory animal (in vivo) and cell culture (in vitro) toxicity studies currently required for health hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the toxicity of this pest control product.

Fludioxonil Technical Fungicide is of low acute toxicity by the oral and inhalation routes in Sprague-Dawley rats and of low acute dermal toxicity and slight acute inhalation toxicity in a Sprague-Dawley derived strain of rats. It is non-irritating to the skin in New Zealand White rabbits and non-sensitizing via the maximization method in Pirbright Guinea Pigs. It causes mild eye irritation in New Zealand White rabbits

Scholar 50WP Fungicide formulation is of low acute toxicity by the oral and inhalation routes in Sprague-Dawley rats and low acute dermal toxicity in New Zealand White rabbits. It was minimally irritating when applied to the skin and eyes of New Zealand White rabbits. Results of skin sensitization testing in guinea pigs using the Guinea Pig Maximisation method were negative.

Absorption and excretion of single (0.5, 100 mg/kg bw) oral doses of fludioxonil was rapid and relatively complete in both sexes of Tif:RAIf (SPF) rats, with 75–90% and 97% elimination of ^{14}C within 24 hours and 7 days, respectively. The bile was the primary route of elimination (> 67%), along with 10–30% urinary excretion. Kidney, liver, lungs and blood contained the highest concentrations of radioactivity, with a maximum level of 1 ppm in the kidneys of high-dose animals 7 days post-treatment. Previous exposure to fludioxonil did not alter the distribution of tissue residues (0.5 mg/kg bw/2 weeks) or the amount of material eliminated via the urine.

Three oxidative metabolites were identified. All phase I metabolites excreted in the bile were glucuronic and to a lesser extent sulphuric acid conjugates. The major route of fludioxonil degradation was oxidation at position 2 of the pyrrole ring, with hydroxylation of the phenyl ring yielding the corresponding phenol as an alternate degradation pathway. Conjugates excreted in

the bile are deconjugated in the intestinal tract leading to reactive exocons that, in turn, give rise to numerous artifacts including non-extractable feces residues. A coloured metabolite was identified in the urine and feces, which accounted for 1–2% of the administered dose at steady state. The coloured metabolite was found to be a dimer formed by autoxidation following deconjugation.

A short-term dermal study showed no skin irritation in any of the test groups after repeated applications of fludioxonil to an area of skin clipped of fur in albino rats. Indications of toxicity included increased clinical chemistry parameters, increased adrenal weights and an increased incidence of phagocytic cells in the thymus.

In subchronic and chronic toxicity studies, fludioxonil produced specific target organ toxicity in the liver, kidneys and bile duct. Generalized toxicity was observed in mice as decreased food efficiency, in rats as decreased body weight and in dogs as diarrhea in the short-term study only and decreases in body weight in the one-year study. In mice, liver weights were increased along with altered clinical chemistry values, liver histopathology changes (including liver necrosis), bile duct hyperplasia, kidney calcification and nephropathy. In rats, there were changes to liver histopathology, clinical chemistry changes and renal pathology. In dogs, there were changes to clinical chemistry and liver histopathology.

Eighteen-month and two-year studies in mice and rats, respectively, provided no evidence of treatment-induced oncogenicity at any dose level tested.

Fludioxonil did not cause point mutations or germ cell mutations. It was not associated with in vitro unscheduled DNA synthesis or with in vivo/in vitro unscheduled DNA synthesis or alteration of replicative DNA synthesis in rat hepatocytes. Although fludioxonil was negative in three in vivo chromosomal aberration assays (micronucleus test in mice, Chinese hamster ovary / bone marrow and dominant lethal study in mice), fludioxonil caused mitotic arrest in mammalian cells (Chinese hamster ovary) in vitro both in the presence and absence of metabolic activation. It was associated with the inhibition of replicative DNA-synthesis activity in mouse lymphoma cells in vitro and it was positive in the rat micronucleus/hepatocyte test in vivo, but under conditions of mitogenic (artificial) stimulation only. As there was no clear evidence of treatment-induced oncogenicity in mouse or rat long-term studies and as there was no association with heritable genetic defects, the concern for genotoxic effects in human adults is considered minimal.

Rat and rabbit developmental toxicity studies and a two-generation, one litter per generation reproduction study in rats indicated that fludioxonil was not teratogenic and that embryo-fetotoxicity and reproductive toxicity occurred only at doses that were maternally toxic as well. In both rat and rabbit teratology studies, maternal toxicity was observed as lower body-weight gains and decreased food consumption at higher doses. At the same doses at which decreased body weight in the dams was observed, embryo-fetotoxicity in the rat was seen as dilated renal pelvis. In a two-generation rat reproduction study, maternal toxicity was based on lower body weights and body-weight gains and offspring toxicity was based on lower F1 and F2 pup weights at the same dose. There were no other reproductive effects.

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account potential pre- and post-natal toxicity and completeness of the data with respect to the exposure of and toxicity to, infants and children. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, no additional studies are required at this time since extensive data are available on fludioxonil. The potential pre- and post-natal toxicity in rats and potential developmental toxicity in rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to in utero exposure to fludioxonil. There was no indication of increased susceptibility in the offspring compared to parental animals in the reproductive toxicity study. On the basis of this information, the 10X PCPA factor can be removed.

3.2 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for fludioxonil is 0.037 mg/kg bw/day, based on the calculation shown below. The rat chronic toxicity study was considered the most appropriate study to assess chronic dietary exposure. The NOAEL was 3.7 mg/kg bw/day, based on liver lesions at 37 mg/kg bw/day. The standard uncertainty factor (UF) of 100 has been applied to account for any intraspecies and interspecies variability in toxicological responses when exposed to a chemical substance. This ADI provides a protective factor commonly referred to as a margin of safety to cover off any other endpoints of concern that were observed in the fludioxonil toxicological database, including body weight changes and kidney nephropathy.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{3.7 \text{ mg/kg bw/day}}{100} = 0.037 \text{ mg/kg bw/day of fludioxonil}$$

3.3 Determination of Acute Reference Dose

Acute reference doses are not required because fludioxonil is considered unlikely to present an acute hazard.

Results of the acute and chronic tests conducted on laboratory animals with fludioxonil and its associated end-use product Scholar 50WP Fungicide as well as the toxicological endpoints selected for the human health risk assessment are summarized in Tables 2, 3 and 4 of Appendix I.

3.4 Occupational and Bystander Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure is characterized as short to intermediate term and is predominantly by the dermal and inhalation routes. For fludioxonil, the oral route reproduction study was considered

the most appropriate for short and intermediate exposures with a NOAEL of 20 mg/kg bw/day. This endpoint should be used for both short and intermediate term dermal and inhalation exposures. An MOE of 100 is recommended to account for intra– and inter–species differences.

3.4.2 Dermal Absorption

An in vivo dermal absorption study in rats was submitted in support of Switch 62.5 WG containing 25% fludioxonil and 37.5% cyprodinil (See Regulatory Note for Switch 62.5 WG Fungicide, REG2006-08). Two groups of 4 male rats were administered nominal doses of fludioxonil (3.75 and 667 µg/cm^2 of skin) in an aqueous liquid formulation and monitored up to 48 hours post-dosing. The total recovery ranged from 90.5% to 96.44%. Total amounts of radioactivity in samples were reported as a percentage of the total dose. All rats were washed after 6 hours of exposure and groups were sacrificed at 6, 24 and 48 hours. Dermal absorption was higher at the lowest dose. A dermal absorption value of 13.6% was considered appropriate for use in a risk assessment for Switch 62.5 WG. This value included skin bound residues (approximately 8.5% of the applied dose).

3.4.3 Worker Exposure

3.4.3.1 Mixer, Loader and Applicator Exposure and Risk Assessment

Workers are expected to be exposed to fludioxonil for a short to intermediate term duration through the dermal and inhalation routes while mixing and loading the water soluble pouches of Scholar 50WP Fungicide to the mixing tank. The maximum proposed application rate is 227 g Scholar 50WP Fungicide (113.5 g fludioxonil) to treat 90 000 kg of pome/stone fruit or 11 500 kg of cherries. This is equivalent to 0.00126 g ai/kg for pome/stone fruit and 0.00987 g ai/kg for cherries. Data provided by the applicant indicates that for large stone/pome fruits, 400 bins containing 363 kg of fruit may be treated in one day. For cherries, 45 350 kg of fruit may be treated per day. This is based on information provided to the applicant by the Ontario Ministry of Agriculture, Food & Rural Affairs, the B.C. Ministry of Agriculture and Lands and Dendy Orchards Ltd. in Kelowna, B.C. As such the amount of fludioxonil handled per day is equivalent to 183 g ai/day for large pome/stone fruits and 448 g ai/day for cherries.

Exposure estimates for mixer/loaders are based on data from the Pesticide Handlers Exposure Database (PHED). PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. To estimate exposure for each use scenario, appropriate subsets of A and B grade data were created from the wettable powder, closed mix/load database files of PHED. The quality of this data set is of low confidence. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part.

Table 3.4.3.1.1 PHED Unit Exposure Values for Workers Mixing/Loading Scholar 50WP Fungicide

Crop	kg ai handled/day	PHED Unit Exposure (µg/kg ai handled)[a]		
		Dermal	Inhalation	Total
Large Pome/Stone Fruit	0.183	46.16	0.18	46.34
Cherries	0.448	46.16	0.18	46.34

[a] Based on a clothing scenario of single layer, no gloves

Table 3.4.3.1.2 Exposure and Risk Estimates for Workers Mixing and Loading Scholar 50WP Fungicide

Crop	Exposure (mg/kg bw/day)		MOEs[b]		
	Dermal[a]	Inhalation	Dermal	Inhalation	Total
Large Pome/Stone Fruit	1.6×10^{-5}	4.7×10^{-7}	1250000	42600000	1200000
Cherries	4.0×10^{-5}	1.1×10^{-6}	500000	18000000	490000

[a] Based on a dermal absorption value of 13.6% from a rat in vivo dermal absorption study

[b] Based on a NOAEL of 20 mg/kg bw/day from a 2 generation rat reproduction study. The target MOE is 100.

Risk estimates for workers mixing and loading Scholar 50WP Fungicide for treatment of large pome and stone fruit as well as cherries are well above the target MOE of 100 and are therefore considered to be acceptable.

3.4.3.2 Postapplication Worker Exposure and Risk

Workers may be exposed to residues of fludioxonil on treated fruit during sorting/culling, stacking boxes of treated fruit, loading trucks using a forklift and while cleaning treated areas. The highest exposure is expected to occur during sorting/culling activities. Exposure is expected to be mainly via the dermal route and to be mainly to the hands. Several approaches were considered to estimate exposure to workers sorting/culling treated fruit including the approach taken by EPA for postharvest treatment of fruit with thiabendazole. A quantitative approach to estimate exposure was considered unnecessary since exposure is mainly to the hands and workers performing sorting/culling activities are expected to wear cotton gloves which would further limit exposure. As such, risk to workers sorting/culling treated fruit is considered to be acceptable.

3.4.4 Residential Exposure and Risk

There are no domestic class products, therefore, a residential handler assessment was not required.

3.4.5 Postapplication Exposure and Risk

Postapplication exposure to treated fruit is expected to be negligible because the amount of fruit handled will be small.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is fludioxonil. The residue definition in animal products for enforcement purposes is fludioxonil. The data gathering/enforcement analytical methodology, a high-performance liquid chromatography method with ultraviolet absorbance detector (HPLC-UV) and a gas chromatography method using a nitrogen phosphorous detector (GC-NPD), are valid for the quantification of fludioxonil residues in pome fruit and stone fruit. Residues of fludioxonil are stable in pome fruit and stone fruit under frozen storage conditions for the maximum storage duration for each study. Raw agricultural commodities were processed into apple juice and wet pomace. Residues of fludioxonil concentrated in apple pomace (6.6-fold) and decreased by 0.1-fold in apple juice. Supervised residue trials conducted throughout the United States using end-use products containing fludioxonil at proposed label rates on apples, pears, peaches, cherries and plums are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.0), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

Acute Dietary Exposure Results and Characterization
As acute reference dose (ARfD) toxicological endpoints have not been established for fludioxonil, an acute dietary exposure assessment was not conducted.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for fludioxonil consists of exposure from food (including pome fruit, stone fruit, imported commodities, animal commodities and milk) and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on chronic endpoints. There was no acute endpoint identified for the general population, including infants and children.

3.5.4 Maximum Residue Limits

Table 3.5.4.1 Maximum Residue Limits

MRLs (ppm)	Foods
5	Pome fruit* Stone fruit*

** See Appendix III for all commodities included within the above named crop groups.*

For additional information on Maximum Residue Limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data and the acute and chronic dietary risk estimates are summarized in Tables 1, 5 and 6 in Appendix I.

4.0 Impact on the Environment

Only negligible release of fludioxonil to the environment is expected to occur with the indoor pome and stone fruit processing use of Scholar 50 WP Fungicide. A label statement has been added to mitigate potential release of fludioxonil through effluent disposal. The data required for indoor use of fludioxonil were previously reviewed for the registration of fludioxonil as a seed treatment and there were no data gaps. Further data were submitted to the PMRA for the registration of a foliar use (Regulatory Note for *Switch 62.5 WG Fungicide*, REG2006-08). This information was also included in this risk assessment.

4.1 Fate and Behaviour in the Environment

Fludioxonil is persistent and generally immobile in soils. However despite the immobile nature of fludioxonil, studies have shown that vertical soil erosion may move it deeper into the soil than would be expected. Fludioxonil does phototransform in water, however, it is expected to be persistent in aquatic ecosystems and to primarily be found in sediment. Release to the environment, based on the use pattern, is expected to be negligible.

4.2 Effects on Non-Target Species

To estimate risk of potential adverse effects on non-target species, a quotient method is used. The risk quotient (RQ) is calculated by dividing the exposure estimate by a value representing a toxicity endpoint. A screening-level risk assessment is initially performed using the expected environmental concentrations (EECs) for a worst-case scenario (e.g., direct overspray of a body of water) and the most sensitive toxicity endpoint. Low risk is predicted if the risk quotient is less than the trigger value of one. In these cases, no further assessment is done. For those groups of organisms for which the RQ is greater than one, a refined assessment is undertaken. A refined assessment takes into consideration more realistic exposure scenarios (e.g., drift to non-target habitats and runoff to water bodies) and may consider different toxicity endpoints.

4.2.1 Effects on Terrestrial Organisms

Fludioxonil has a low toxicity to beneficial insects, birds and mammals. The toxicity to earthworms is unknown. Exposure and risk to terrestrial organisms from indoor pome and stone fruit processing will be negligible.

4.2.2 Effects on Aquatic Organisms

Fludioxonil is highly toxic to freshwater organisms and is toxic to freshwater algae and marine species. Fludioxonil will not bioaccumulate in fish. Exposure and risk to aquatic organisms from the indoor pome and stone fruit processing will be negligible.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Pome Fruit

Blue Mold (*Penicillium expansum*): Results from 10 trials (nine on apple and one on pear) demonstrated that after long term storage, both dip and drench applications at the rates of 0.6 and 1.2 g Scholar 50WP Fungicide /L (227 and 454 g Scholar/378 L water) provided consistent control of the incidence of blue mold compared to the inoculated check and the commercial standard (Mertect). Percent control varied from 75–100%. However, in most cases no significant difference in the percent control was noted between the rates of 0.6 g/L (227 g Scholar/378 L water) and 1.2 g/L (454 g Scholar/378 L water). Therefore the lowest effective rate for control of blue mold is 227 g Scholar/378 L water to treat 90,000 kg fruit for both dip and drench applications of apples and pears.

Gray Mold (*Botrytis cinerea)*: Results from four trials (three on apple and one on pear) demonstrated that after long term storage, both dip and drench applications at the rates of 0.3 g Scholar/L provided good control of gray mold as measured by disease incidence and was comparable to rates of 0.6 and 1.2 g/L. Percent control varied from 40–100%.

Mucor Rot (*Mucor piriformis*): One trial on apple was conducted to assess Scholar 50WP Fungicide for control of Mucor rot. The results demonstrated good control (84–96%) at a rate of 0.6 g Scholar/L water. However, for a new disease at least three trials are required to demonstrate consistency in efficacy results, therefore, this use is conditionally supported. Additional trial results are required to demonstrate consistency.

It should be recognized that these trials were conducted under controlled conditions. Perishable fruit in storage and on the shelf are susceptible to severe bruising and disease development during handling. It is important, therefore, to ensure that fruit are adequately protected. In addition, producers generally treat for several postharvest diseases at one time, therefore one rate for control of all diseases is important in postharvest disease management.

For these reasons the rate of 0.6 g Scholar 50WP Fungicide/L (227 g Scholar/378 L) which gives consistent control of all three diseases is recommended. Increasing the rate of Scholar 50WP Fungicide to 1.2 g product/L provided only a slight increase in the level of disease control. Therefore the lowest effective rate is 227 g Scholar/378 L water for dip and drench applications of all diseases on pome fruit.

5.1.1.2 Stone Fruit

Brown Rot (*Monilinia fructicola*): Results from six trials (two on cherry, one on nectarine, two on peach and one on plum) demonstrated that after long term storage, dip application at the rate of 0.6 g Scholar/L provided good control (60–100%) of Brown Rot as measured by disease incidence and was comparable to 1.2 g Scholar/L, the inoculated check and the commercial standard (Mertect).

Blue Mold (*Penicillium spp*): Results from one trial on cherries demonstrated that after long term storage, dip application at the rate of 0.6 g Scholar/L provided good control (97%) of blue mold as measured by disease incidence and was comparable to 1.2 g Scholar/L. Although only one trial was submitted in support of blue mold on stone fruit, the blue mold trials for pome fruit were used to support the stone fruit use, as disease development is similar in both crop types.

Gray Mold (*Botrytis cinerea*): Results from 5 trials (four on peach and one on plum) demonstrated that after long term storage, one dip application at the rate of 0.6 g Scholar/L resulted in good control (50–100%) of gray mold as measured by disease incidence, compared to the inoculated check and the commercial standard (Mertect).

Rhizopus Rot (*Rhizopus spp*): One trial on peaches was conducted to assess the product for control of Rhizopus rot and demonstrated good control (100%) at a rate of 0.6 g Scholar/L water. However, for a new disease at least three trials are required to demonstrate consistency. Therefore, this use is conditionally supported. Additional trial results are required to demonstrate consistency.

It should be recognized that these trials were conducted under controlled conditions. Perishable fruit in storage and on the shelf are susceptible to severe bruising and disease development during handling. It is important, therefore, to ensure that fruit are adequately protected. In addition, producers generally treat for several postharvest diseases at one time. Therefore, one rate for control of all diseases is important in postharvest disease management.

For these reasons the rate of 0.6 g Scholar 50WP Fungicide (227 g Scholar/378 L) which gives consistent control of all four diseases is recommended. Increasing the rate of Scholar 50WP Fungicide to 1.2 g/L provided only a slight increase in control. Therefore the lowest effective rate is 227 g Scholar/378 L water for dip applications of stone fruit.

5.1.1.3 Treatment of Bulk Fruit (Pome and Stone)

In the commercial trial where pears and apples were treated in bulk, the amount of Scholar 50WP Fungicide applied was 227 g in 378 L water/90 000 kg fruit. The results showed control

comparable to the small scale trials. Pome fruit and stone fruit (except cherries) are approximately the same size and have a similar surface area per kg fruit. Hence the amount of product per kg is the same. Therefore, the amount (90 000 kg) of bulk fruit treated by 227 g Scholar/378 L water is supported for both pome and stone fruit. Cherries, however are smaller and have a larger surface area per kg of fruit, hence, 227 g Scholar 50WP Fungicide can only treat 11 500 kg of cherries.

According to the registrant the measurement of 90 000 kg was chosen since this is the amount of fruit that the water volumes listed on the label for each application type typically treat with commonly used application equipment. The commercial trial on 90 000 kg of apple and pear fruit supports the rate of 227 g Scholar/ 378 L water.

Therefore, based on the information provided the following claims can be supported:

a) the claim that Scholar 50WP Fungicide at 227 g product applied in 378 L water can be used to treat 90 000 kg of pome and stone fruit (except cherries)

b) the claim that Scholar 50WP Fungicide at 227 g product applied in 378 L water can be used to treat 11 500 kg of cherries.

5.1.1.4 Summary

- Based on the data provided and for the reasons cited above, the rate of 0.6 g Scholar/L (227 g Scholar/378 L) is supported for control of blue mold, gray mold and mucor rot on apples (varieties Empire, Gala, Pink Lady, Delicious) and pears (varieties Bosc and d'Anjou). This rate is also supported for control of brown rot, blue mold, gray mold and Rhizopus Rot on peaches (Loring, Redhaven), nectarine (variety Harblaze), plums (varieties Shiro, Laroda) and cherries (varieties Brooks, Staccato).

- No difference in efficacy between dip and drench application methods was noted and as a result both application methods are supported for use on pome fruit and stone fruit.

- Crop Grouping:

  As Scholar 50WP Fungicide was tested on several different varieties of apples and pears and as postharvest diseases can develop similarly on different types of pome fruit, this use is extended to include the other commodities listed in the pome fruit crop group (apples, crabapple, loquat, mayhaw pear, oriental pear and quince).

  As Scholar 50WP Fungicide was tested on several different varieties of stone fruits and as postharvest diseases can develop similarly on different types of stone fruit, this use is extended to include the other commodities listed in the stone fruit crop group (apricot, nectarine, peach, plum(including Chickasaw, Damson and Japanese), plumcot, prune (fresh) as well as other cultivars of these, cherry (sweet), cherry (tart as well as cultivars and hybrids of cherries).

Table 5.1 Postharvest Disease Claims Supported for Scholar 50 WP Fungicide

Crops	Pests	Product Rate	
		Drench Application	**Dip Application**
Pome fruits: Apple, Crabapple, Loquat, Mayhaw, Pear, Pear (oriental), Quince	Blue Mold (*Penicillium expansum)* Gray Mold *(Botrytis cinerea)* Mucor Rot *(Mucor piriformis)*	Mix 227 g of product in 378 L of water for the crop being treated. Can treat up to 90 000 kg of fruit.	Mix 227 g of product in 378 L of water for the crop being treated. Dip for approximately 30 seconds and allow fruit to drain. Can treat up to 90 000 kg of fruit.
Stone Fruits: Apricot, Nectarine, Peach, Plum (including Chickasaw, Damson, and Japanese), Plumcot, Prune (fresh) as well as other cultivars of prunes.	Blue Mold (*Penicillium expansum)* Gray Mold *(Botrytis cinerea)* Brown Rot *(Monilinia fructicola)* Rhizopus Rot *(Rhizopus spp)*	Mix 227 g of product in 378 L of water for the crop being treated. Can treat up to 90 000 kg of fruit.	Mix 227 g of product in 378 L of water for the crop being treated. Dip for approximately 30 seconds and allow fruit to drain. Can treat up to 90 000 kg of fruit.
Cherries: Cherry (sweet), Cherry (tart as well as other cultivars and hybrids of cherries)	Blue Mold (*Penicillium expansum)* Gray Mold *(Botrytis cinerea)* Brown Rot *(Monilinia fructicola)* Rhizopus Rot *(Rhizopus spp)*	Mix 227 g of product in 378 L of water. Can treat up to 11 500 kg of cherries.	Mix 227 g of product in 378 L of water. Dip for approximately 30 seconds and allow fruit to drain. Can treat up to 11 500 kg of cherries.

5.2 Phytoxicity to Host Plants

No phytotoxicity was reported in any of the pome fruit or stone fruit trials.

5.3 Impact on Succeeding Crops

This is not applicable to postharvest treatments.

5.4 Economics

Crop	Acres	Farm Gate (000)	Shrinkage[1]	Value of Shrinkage
Apples	60595	$157 103	20%	$ 31 421
Pears	3765	$ 10 571	10%	$ 1 057
Total Pomes	64360	$167 674		$ 32 478
Sweet Cherries	3257	$ 16 265	10%	$ 1 627
Peaches	8055	$ 32 110	12%	$ 3 853
Plums and Prunes	1930	$ 2 915	N/A	N/A
Apricots	580	$ 1 415	N/A	N/A
Total Stone	13882	$ 52 705		$ 5 480
Total Market	78182	$220,379		$ 37,957

[1] Shrinkage is a measure of postharvest loss.

5.5.1 Survey of Alternatives

Crop	Chemical Name	FRAC Fungicide Group Number
Pome Fruits	fenhexamid	17
	thiabendazole	1
Stone Fruits	tebuconazole	3
	fenhexamid	17
	boscalid; pyraclostrobin	7, 11

Fludioxonil, the active ingredient in Scholar 50WP Fungicide, is the only available registered fungicide from the phenylpyrrole chemical class for postharvest use on fruit. The addition of a new class of fungicide for this use will help reduce the reliance on the few registered products available and thus diminish the potential for development of resistance to current products.

5.5.2 Compatibility with Current Management Practices

This product should complement current management practices based on the relatively low use rates and broad spectrum fungal disease control.

5.5.3 Resistance Management

Fludioxonil is the only phenylpyrrole on the market and there is no cross-resistance with other fungicide groups. There is a low to medium risk of resistance developing in *Botrytis cinerea* populations. However, fludioxonil has a single site mode of action and resistance management practices, such as rotation with fungicides of different chemistry, are essential to minimize the development of resistance. The resistance management recommendations on the label adequately address this concern.

5.5.4 Contribution to Risk Reduction and Sustainability

The low use rate and broad spectrum of activity of fludioxonil will add to current postharvest fungal disease management practices in pome and stone fruit. In addition, the new class of chemistry of Scholar 50WP Fungicide will help defer the risk of development of disease resistance.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, fludioxonil was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of fludioxonil were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in the end-use product, Scholar 50WP Fungicide. The PMRA has reached the following conclusions:

- Fludioxonil does meet the criteria for persistence. Its values for half-life in soil (up to 494 days) is above the TSMP Track 1 cut-off criteria for soil (≥182 days). Values in water are unknown. Although data on the persistence in air were not available, the vapour pressure and Henry's law constant indicate that fludioxonil will not volatilize from water or moist soil under field conditions; therefore, long-range atmospheric transport of fludioxonil is not likely to occur. Fludioxonil does not bioaccumulate. Fludioxonil does not meet all Track 1 criteria; therefore, it is not classified as a Track 1 substance.

- Fludioxonil may form major transformation products that meet the TSMP Track 1 criteria. The PMRA has requested additional information on the major transformation products of fludioxonil (Regulatory Note for *Switch 62.5 WG Fungicide*, REG2006-08). However, the indoor use of Scholar 50WP Fungicide is not expected to result in release of major transformation products to the environment.

Therefore, the use of 50WP Fungicide is not expected to result in the entry of Track 1 substances into the environment.

Fludioxonil does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

The end-use product Scholar 50WP Fungicide does not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted is adequate to define the majority of toxic effects that may result from human exposure to fludioxonil. In subchronic and chronic studies on laboratory animals, target organs included the liver, kidneys and bile duct. There was no evidence of any carcinogenicity and no evidence of increased susceptibility of the young in teratology studies. Fludioxonil is not considered to be a neurotoxicant.

The nature of the residue in plants is adequately understood for the purposes of this registration. The residue definition is fludioxonil. The proposed postharvest use of fludioxonil on pome fruit and stone fruit does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The PMRA recommends that the following maximum residue limits be specified under the authority of the *Pest Control Products Act*:

residues of fludioxonil in and on pome fruit (5 ppm);
residues of fludioxonil in and on stone fruit (5 ppm).

Mixer, loader, applicators and workers handling treated fruit are not expected to be exposed to levels of fludioxonil that will result in unacceptable risk when Scholar 50WP Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers and no additional personal protective equipment is required.

7.2 Environmental Fate

Only negligible release of fludioxonil to the environment is expected to occur with the indoor pome and stone fruit processing use of Scholar 50WP Fungicide. A label statement has been added to mitigate potential release of fludioxonil through effluent disposal.

7.3 Environmental Risk

As this is an indoor use, risk to organisms in the environment is negligible. A label statement has been added to mitigate potential release of fludioxonil through effluent disposal.

7.4 Value

- The rate of 0.6 g Scholar/L (227 g Scholar / 378 L) is supported for control of blue mold, gray mold and mucor rot on apples and pears. This rate is also supported for control of brown rot, blue mold, gray mold and Rhizopus Rot on peaches, nectarine, plums and cherries.

- The dip and drench application methods are supported for use on pome fruit and stone fruit.

- The accepted use is extended to include the other commodities listed in the pome fruit crop group (apples, crabapple, loquat, mayhaw pear, oriental pear and quince) and stone fruit crop group (apricot, nectarine, peach, plum, plum (chickasaw), plum (damson), plum (japanese), plumcot, prune (fresh) as well as other cultivars of prunes, cherry (sweet), cherry (tart as well as cultivars and hybrids of cherries)).

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and in accordance with the Pest Control Products Regulations, has granted conditional registration for the sale and use of technical grade active ingredient and the end-use product Scholar 50WP Fungicide to control fungal diseases in stored pome fruit and stone fruit. An evaluation of current scientific data from the applicant and scientific reports has resulted in the determination that, under the approved conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been determined to be acceptable when all risk-reduction measures are followed, as a condition of these registrations, the following additional scientific information is required from the applicant as a result of this evaluation.

Two additional efficacy trials for Mucor Rot on pome fruit and Rhizopus Rot on stone fruit are required. The applicant is required to submit this information no later than 1 September 2007.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARfD	acute reference dose
ASE	accelerated solvent extraction
atm	atmoshpheres
bw	body weight
CAS	chemical abstracts service
cm	centimetres
DACO	data code
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in the test population)
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EEC	estimated environmental concentration
ER_{25}	effective rate for 25% of the population
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
km	kilometre
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
mg	milligram
mL	millilitre
MAS	maximum average score

MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
m/z	mass to charge ratio
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OECD	Organisation for Economic Cooperation and Development
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
R/F	residue-to-feed ratio
RSD	relative standard deviation
RQ	risk quotient
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Methods for Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	AG-597 (enforcement)	Fludioxonil	HPLC-UV	0.02 ppm	potato tubers, sorghum grain, corn fodder.	1163343, 1170253
				0.02 ppm	pome fruit, apple juice, stone fruit	1036130, 1036131, 1036132, 1036133
				0.04 ppm	apple pomace	1036130
	AG-664 (data gathering)	Fludioxonil	GC-NPD	0.1 ppm	peaches	1178270
Animal	AG-616 (enforcement)	Fludioxonil	HPLC-UV	0.01 ppm	milk, muscle	1190942, 1190943
				0.05 ppm	fat, liver, kidney, eggs	1190942, 1190943

Table 2 Acute Toxicity of Fludioxonil Technical Fungicide and Its Associated End-Use Product (Scholar 50WP Fungicide)

Study Type	Species	Result	Comment
Acute Toxicity of Fludioxonil Technical Fungicide			
Oral	Rat/Sprague-Dawley	LD_{50} > 5000 mg/kg bw	LOW TOXICITY
Dermal	Rat/Tif:RAIf (SPF)	LD_{50} > 2000 mg/kg bw	LOW TOXICITY
Inhalation, 4-hour nose	Rat/Tif:RAIf (SPF)	LC_{50} > 2.64 mg/L	LOW TOXICITY
Inhalation, 4-hour body	Rat/Sprague-Dawley	LC_{50} > 0.5 mg/L	SLIGHT TOXICITY
Skin irritation	Rabbit/NZW	PIS = 0	Non-irritant
Eye irritation	Rabbit/NZW	MAS[a] = 13.7 unwashed MAS = 7.7 washed	Mildly irritating
Skin sensitization (maximization)	Guinea pig	Negative	
Acute Toxicity of End-Use Product—Scholar 50WP Fungicide			
Oral	Rat/HSD:SD	LD_{50} = approx. 5050 mg/kg bw	LOW TOXICITY
Oral	Rat/HSD:SD	LD_{50} > 5050 mg/kg bw	LOW TOXICITY
Dermal	Rabbit/NZW	LD_{50} > 2020 mg/kg bw	LOW TOXICITY
Inhalation, 4-hour whole body	Rat/HSD:SD	LC_{50} > 6.49 mg/L	LOW TOXICITY

Study Type	Species	Result	Comment
Skin irritation	Rabbit/NZW	MIS[b] = 0.33 at ¾ hours MAS = 0	Minimally irritating
Eye irritation	Rabbit /NZW	MIS: 6.67 at 1 hour MAS = 1.45	Minimally irritating
Skin sensitization (Maximisation)	Guinea pig / Pirbright White	Negative	

[a] MAS = maximum average score for 24, 48 and 72 hours
[b] MIS = maximum irritation score

Table 3 Toxicity Profile of Fludioxonil Technical Fungicide

Study Type	Species	Results[a] (mg/kg/day)
21-day dermal	Rat/Tif:RAIf	NOAEL: 200 mg/kg bw/d LOAEL: 1000 mg/kg bw/d; thymus histopathy in females, clinical chemistry, ↑ adrenal weights in males/females, no dermal effects
14-day dietary	Mouse/CD-1	Range-finding; blue stain all doses, clinical chemistry at 5000 ppm, nephropathy, hepatic hypertrophy in 7000 ppm males
90-day dietary	Mouse/CD-1	NOAEL: 445 mg/kg bw/d LOAEL: 1052 mg/kg bw/d; nephropathy, hepatic hypertrophy at 1052 mg/kg bw/d in males/females, (↑ liver weight, hepatic hypertrophy in 445 mg/kg bw/d females, non-adverse)
20-day dietary	Rat/Sprague-Dawley	Range-finding; Black feces at 5000 ppm and up, nephrosis at 5000–20 000 ppm, ↑ kidney/liver weights, black kidney foci at higher doses
90-day dietary	Rat/Sprague-Dawley	NOAEL: 64 mg/kg bw/d LOAEL: 428 mg/kg bw/d; ↓ bwg/food consumption, kidney pathology, liver changes, clinical chemistry (blue urine at 64 mg/kg bw/d and up, hepatic hypertrophy in 64 mg/kg bw/d males, non-adverse)
90-day dietary	Dog/Beagle	NOAEL: 5 mg/kg bw/d LOAEL: 50 mg/kg bw/d; diarrhea, bile duct hyperplasia, ↑ liver weight, anaemia at 375/250 mg/kg bw/d
52-week dietary	Dog/Beagle	NOAEL: 33.1 mg/kg bw/d LOAEL: 298 mg/kg bw/d; ↓ body weight/body-weight gain, enlarged liver, clinical chemistry (blue feces at 33.1 and 298 mg/kg bw/d)
2-year dietary (F-00018)	Rat/Sprague-Dawley	Chronic: NOAEL: 3.7 mg/kg bw/d LOAEL: 113 mg/kg bw/d; ↑ centrilobular lesions in females Carcinogenicity: No evidence

Study Type	Species	Results[a] (mg/kg/day)
18-month dietary (F-00019, F-00071)	Mouse/CD-1 (CR)	Chronic: NOAEL: 360 mg/kg bw/d LOAEL: 590 mg/kg bw/d; nephropathy, kidney calcification (males/females), ↑ liver weight. ↓ food efficiency, liver necrosis, bile duct hyperplasia (males) Carcinogenicity: No evidence
Two-generation reproduction—dietary	Rat/Sprague-Dawley	**Parental systemic NOAEL:** 20 mg/kg bw/d **Parental systemic LOAEL:** 190 mg/kg bw/d; ↓ body weight **Reproductive NOAEL:** 190 mg/kg bw/d **Reproductive LOAEL:** > 190 mg/kg bw/d **Offspring systemic NOAEL:** 20 mg/kg bw/d **Offspring systemic LOAEL:** 190 mg/kg bw/d; ↓ pup body weight-weight
Teratology—Preliminary	Rat/Sprague-Dawley	**Maternal NOAEL:** not determined **Maternal LOAEL:** 100 mg/kg bw/d; ↓ body weight gain **Developmental NOAEL:** not determined **Developmental LOAEL:** 100 mg/kg bw/d; dilated ureter/renal pelvis
Teratology—Definitive	Rat/Sprague-Dawley	**Maternal NOAEL:** 100 mg/kg bw/d **Maternal LOAEL:** 1000 mg/kg bw/d; ↓ body weight gain/food consumption **Developmental NOAEL:** 100 mg/kg bw/d **Developmental LOAEL:** 1000 mg/kg bw/d; dilated renal pelvis
Teratology—Preliminary	Rabbit/NZW	**Maternal NOAEL:** 1200 mg/kg bw/d **Maternal LOAEL:** > 1200 mg/kg bw/d; body weight loss at early dose; non-adverse **Developmental NOAEL:** 1200 mg/kg bw/d **Developmental LOAEL:** > 1200 mg/kg bw/d
Teratology—Preliminary	Rabbit/NZW	**Maternal NOAEL:** 100 mg/kg bw/d **Maternal LOAEL:** 1000 mg/kg bw/d; ↓ body weight gain/food consumption, stomach lesions, death **Developmental NOAEL:** N/A **Developmental LOAEL:** N/A; study terminated
Teratology—Definitive	Rabbit/NZW	**Maternal NOAEL:** 100 mg/kg bw/d **Maternal LOAEL:** 300 mg/kg bw/d; ↓ body weight gain/food consumption/food efficiency **Developmental NOAEL:** 300 mg/kg bw/d **Developmental LOAEL:** > 300 mg/kg bw/d; no treatment-related changes
Ames *S. Typhinurium* Genotoxicity	TA98, 100, 1535, 1537	Negative
In vitro Mammalian Point Mutation	CH V79 (lung)	Negative
In vitro Chromosome Aberration	Chinese hamster ovary cells	**Positive** ↑ polyploidy +/- activation at all doses; ↑ mitotic index with activation/mitotic inhibition at higher doses

Study Type	Species	Results[a] (mg/kg/day)
Mouse micronucleus	Tif:MAGF mice bone marrow	Negative
Rat micronucleus in vivo	Tif:RAIf rat Hepatocytes	**Positive** in mitogenically stimulated hepatocytes only
Dominant lethal test	Tif:MAGF mice	Negative
In vitro unscheduled DNA synthesis	Tif:RAIf rat hepatocytes	Negative
In vivo/in vitro unscheduled DNA synthesis	Tif:RAIf rat Hepatocytes	Negative
In vitro mouse lymphoma[b]	—	**Positive**
Metabolism	Rat	**Absorption** Greater than 67% of the administered dose was eliminated in the bile and 10–30% was eliminated in the urine indicating that absorption was extensive. Maximum blood concentration was reached ½ hour after treatment. **Distribution** Tissue burdens minimal with the liver, kidneys, lungs and blood exhibiting the highest concentrations. As a maximum level of 1 ppm was found in the kidneys of high-dose animals 7 days post treatment, fludioxonil does not appear to have a potential to accumulate in the body. **Excretion** The majority of fludioxonil is eliminated within 24 hours (75–90%) and 97% was eliminated by the end of 7 days. Bile and urine elimination were consistent in proportions with bile elimination remaining the major route of elimination in all cases. **Metabolism** Orally administered fludioxonil does not appear to show significant sex-differences in rats. Three oxidative metabolites were identified with the major route of fludioxonil degradation being oxidation at position 2 of the pyrrole ring, with hydroxylation of the phenyl ring yielding the corresponding phenol as an alternate degradation pathway. All phase I metabolites excreted in the bile were glucuronic and to a lesser extent sulphuric acid conjugates. Conjugates excreted in the bile are deconjugated in the intestinal tract leading to reactive exocons that, in turn, give rise to numerous artifacts including non-extractable feces residues. A coloured metabolite was identified in the urine and feces, which accounted for 1–2% of the administered dose at steady state. The coloured metabolite was found to be a dimer formed by autoxidation following deconjugation.

[a] Effects observed in males and females unless otherwise reported

[b] Cytotoxicity test only for in vitro unscheduled DNA synthesis study

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Fludioxonil

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	MOE
	No ArfD required.			
Chronic Dietary	NOAEL = 3.7 mg/kg bw/d	Two-year carcinogenicity studies in rats	Increased incidence of liver lesions (degeneration/atrophy/necrosis/ inflammation) in 37 mg/kg bw/d females.	100
	ADI = 0.037 mg/kg bw/day			
Short-term Dermal	NOAEL = 20 mg/kg bw/d	Two-generation reproduction study in rats	Decreased bodyweights and bodyweight gains in females.	100

Table 5 Integrated Food Residue Chemistry

NATURE OF THE RESIDUE IN PLANTS	Regulatory Note for Switch 62.5 WG Fungicide, REG2006-08
The proposed metabolic pathway was similar in peaches, tomatoes, grapes, green onions and wheat and is well understood. Fludioxonil is absorbed into the plant tissue where it is oxidated at the 2 or 5 position of the pyrrole ring and eventually conjugated with plant sugars. Results from metabolism studies carried out as seed treatments and foliar applications show that the major component of the TRRs is the parent compound fludioxonil. Metabolism studies on file also indicate that fludioxonil applied to the surface is not systemic and has little potential to translocate. Isolated foliar applications to peaches indicate that residues are localized to the site of application. Therefore, the results observed in the previously reviewed studies are representative of the fate of the compound on the surface of food and are adequate for the current petition.	
NATURE OF THE RESIDUE IN ANIMALS	PMRA # 1163391, 1163380, 116381
Fludioxonil animal metabolism studies (hen, goat) indicated that the majority of the administered dose was eliminated in the excreta and the remaining fludioxonil is extensively metabolized. A significant portion of the residues in tissues was not extractable. The target tissues for the residual radioactivity were the liver and kidney. The major metabolites of fludioxonil were mainly conjugates of the parent compound with glucose or sulfate at the pyrrole ring following hydroxylation. Although the metabolites were detected in amounts in excess of 10% of the total radioactivity, no firm identification could be made.	
RESIDUE TRIALS ON POME FRUIT (Apples, Pear)	PMRA #: 1036130; 1036131; 1036132
Proposed GAP: Use SCHOLAR 50WP Fungicide as a postharvest dip or drench on pome fruit (crop group 11) once at a rate of 0.25 kg a.i./ 200 000 kg fruit/season (227 g product/ 90 000kg fruit). Data summarized below are from trials conducted with the 50WP formulation.	

Commodity	Total Rate (kg a.i./ 200 000 kg fruit)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Median	Mean	SD
Postharvest Dip + wax										
Apple	0.5	0	Fludioxonil	10	0.35	1.1	0.93	0.66	0.7	0.2
Apple - Juice	0.5	0		1	0.1	0.1	0.1	0.1	0.1	—
Apple - Wet pomace	0.5	0		1	7.3	7.3	7.3	7.3	7.3	—
Pear	0.5	0		8	0.67	2.7	2.15	1.07	1.25	0.7
Postharvest Spray + wax										
Apple	0.5	0	Fludioxonil	4	0.57	1.7	1.5	0.9	1.1	0.5
Pear	0.5	0		4	1.3	2.5	1.96	1.5	1.7	0.6
Postharvest Dip + Postharvest Spray + wax										
Apple	1	0	Fludioxonil	4	1.8	2.4	2.3	2.2	2.1	0.3

RESIDUE TRIALS ON STONE FRUIT (Peach, plum, cherry) | PMRA #: 1036133; 1036134; 1036135, 1036136, 1036137

Proposed GAP: Use SCHOLAR 50WP Fungicide as a postharvest dip or drench once on apricot, nectarine, peach, plum (including chickasaw, damson and japanese plum), plumcot, prunes (fresh) at a rate of 0.25 kg a.i./ 200 000 kg fruit/season. Cherries (sweet, tart, as well as other cultivars and hybrid of cherries) should be treated with a postharvest drench once only at a rate of 0.25 kg a.i./25 000 kg fruit/season.

Data summarized below is from trials conducted with both the 50WP and 230SC formulations. Data also combines data from fruit treated with and without fruit wax. There was no significant difference in the magnitude of residues resulting from treatment with either formulation or between fruit treated with or without fruit wax.

Commodity	Total Rate (see above)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Median	Mean	SD
Postharvest Dip										
Peach	0.25	0	Fludioxonil	8	1.8	5	4.8	2.5	3.1	1.3
	0.5	0		2	3	3.8	3.4	3.4	3.4	—
Plum	0.25	0		8	0.27	0.46	0.37	0.36	0.36	0.06
Cherry	0.25	0		10	0.62	1.2	1.2	0.95	0.94	0.2
		5		4	1	1.2	1.2	1.1	1.1	0.1
		10		4	0.85	1.3	1.1	0.9	0.99	0.2
	0.5	0		2	1.5	1.8	1.7	1.7	1.7	—
		5		4	1.4	1.7	1.6	1.5	1.5	0.1
		10		4	1.1	1.7	1.7	1.4	1.4	0.3
	1	0		8	1.8	4.1	2.9	2.8	2.8	0.9

Commodity	Total Rate (see above)	PHI (days)	Analyte	Residue Levels (ppm)						
				n	Min.	Max.	HAFT	Median	Mean	SD
Postharvest spray										
Peach	0.25	0	Fludioxonil	14	0.77	3.9	3.8	1.5	1.7	0.9
	0.375	0		2	1.3	1.9	1.6	1.6	1.6	0.4
	0.5	0		8	1.3	4.5	2.5	2.75	3.2	1.5
Plum	0.25	0		12	0.13	0.71	0.57	0.31	0.34	0.2
		5		4	0.11	0.52	0.48	0.28	0.3	0.2
		15		4	0.12	0.92	0.865	0.54	0.53	0.4
		25		4	0.14	0.77	0.66	0.36	0.41	0.3
	0.5	0		4	0.02	1.3	1.3	0.85	0.76	0.6
		5		4	0.31	1.9	1.8	0.96	1.03	0.8
		15		4	0.12	1.7	1.5	0.78	0.85	0.7
		25		4	0.24	1.5	1.3	0.74	0.81	0.6

PROCESSED FOOD AND FEED PMRA# 1036130

Apples were treated via postharvest dip at a rate of 0.5 kg a.i./200 000 kg fruit. After being allowed to dry, apples were processed into juice and wet pomace to simulate commercial processing.

Commodity	Total Rate (kg a.i./ 200 000 kg fruit)	PHI (days)	Analyte	n	Residue level (ppm)	Processing Factor
Apples Treated via Postharvest Dip						
Pre processing	0.5	0	Fludioxonil	1	1.1	—
Juice				1	0.1	0.1
Wet pomace				1	7.3	6.6

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

Fludioxonil: PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT		FLUDIOXONIL	
METABOLIC PROFILE IN DIVERSE CROPS		Similar in wheat, green onions, peaches, grapes and tomatoes	
Fludioxonil: ANIMAL STUDIES			
ANIMALS		**Poultry**	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT		Fludioxonil	
RESIDUE DEFINITION FOR RISK ASSESSMENT		To be determined with use expansions on feed items.	
METABOLIC PROFILE IN ANIMALS		Similar in rat, ruminant and hen	
FAT SOLUBLE RESIDUE		no	no
Fludioxonil: DIETARY RISK from food and water			
Chronic Non-Cancer Dietary Risk **ADI =0.037 mg/kg bw** **EEC = 35.3 µg/L**	POPULATION	**ESTIMATED RISK (% of ADI)**	
		Food (MRL)	**Food + EEC**
	All infants < 1 year old	28.7	35.3
	Children 1 to 2 years	**37.0**	**40.0**
	Children 3 to 5 years	26.6	29.3
	Children 6 to 12 years	14.8	16.8
	Youth 13 to 19 years	8.0	9.5
	Adults 20 to 49 years	7.3	9.2
	Adults 50+ years	10.4	12.3
	Total population	**11.1**	**13.1**

Appendix II Supplemental Maximum Residue Limit Information International Situation and Trade Implications

The proposed pome fruit and stone fruit Canadian MRLs are the same as those in the United States www.access.gpo.gov/nara/cfr/waisidx_04/40cfr180_04.html:

Table 1 Differences Between Canadian MRLs and Other Jurisdictions

Commodity	Canada (ppm)	United States (ppm)	Codex* (ppm)
Pome Fruit	5	5	Not reviewed by Codex
Stone Fruit			5 (interim MRL)

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary.

Appendix III Crop Groups: Numbers and Definitions

Crop Group Number	Name of the Crop Group	Commodity
Crop Group 11	Pome fruit	Apple, crapbapple, loquat, mayhaw, pear, oriental pear, quince.
Crop Group 12	Stone fruit	Apricot, sweet cherry, tart cherry, nectarine, peach, plum, Chickasaw plum, Damson plum, Japanese plum, plumcot, prune (fresh)

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A. LIST OF STUDIES/INFORMATION SUBMITTED BY APPLICANT

1.0 Chemistry Assessment

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