Proposed Re-evaluation Decision PRVD2018-05

Folpet and Its Associated End-use Products

Consultation Document

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Proposed Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Folpet is a fungicide used on a number of food and ornamental crops and as a material preservative in vinyl plastics. Folpet is also used as a material preservative in paints and coatings, however, these uses are not included in this re-evaluation. The PMRA plans to publish a document in the future to provide a broader examination of material preservatives for paints and coatings.

This document presents the proposed regulatory decision for the re-evaluation of folpet, including proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing folpet registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public, including manufacturers and stakeholders, may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration any comments and information received.

Outcome of Science Evaluation

Folpet is a broad-spectrum, contact protectant fungicide used in several important crops and as a material preservative.

As a material preservative, folpet is registered for use in paints and coatings and in vinyl plastics. The material preservative use of folpet in paints and coatings will be re-evaluated at a later date. The primary uses of folpet-treated vinyl plastics are in the manufacture of window gaskets for homes and cars, vinyl flooring backing, outdoor upholstery (seats for boats), coatings applied to tents, exterior vinyl products, awnings and roof membranes. Use of folpet for treating vinyl plastics is proposed for cancellation due to risks of concern for workers manufacturing these vinyl plastics.

As an agricultural fungicide, folpet is a valuable pest management tool and contributes to integrated pest management programs on several important crops, including apples, grapes and strawberries, due to its multi-site mode of action and low risk for resistance development. The use of folpet on cranberries and cut flowers did not meet current standards for the protection of human health. Therefore these uses are proposed for cancellation. For the azalea stem soak use, there was insufficient data to conduct a health risk assessment. Hence, this use is also proposed for removal.

For remaining agricultural uses, health and environmental standards are met when used according to the revised label directions proposed in this document.

Folpet can enter soil and surface water when used as a fungicide. Folpet may pose risks of concern to certain aquatic organisms and small mammals; therefore, preventative measures to reduce risk to these organisms are proposed. To protect non-target organisms from spray drift, updated aquatic buffer zones are proposed.

Proposed Regulatory Decision for Folpet

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, some uses of folpet do not meet standards for human health protection and, are therefore, proposed for removal. These include use as a material preservative in vinyl plastics, use on cranberries and cut flowers, and as an azalea stem soak.

Remaining agricultural uses of folpet are considered acceptable for continued registration with the implementation of the mitigation measures summarized below. For details of proposed label changes, see Appendix XIII.

Human Health

To protect mixer/loader/applicators:

- Require that the wettable powder agricultural product be packaged in water soluble packages.
- Require additional protective equipment when mixing/loading and applying.
- Remove the stem soak use from commercial labels.
- Cancel the soluble powder product for the manufacture of treated plastics.

To protect workers entering treated sites:

- Revise or establish restricted entry intervals (REIs) for some crops.
- Require restrictions on number of applications allowed per season for some crops.
- Require label statements to clarify the acceptable greenhouse uses of folpet.
- Remove crop uses with agronomically unfeasible REIs (cranberry and cut flower (field and greenhouse)).

To protect bystanders from spray drift:

- Require a statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift.

To protect consumers from potential residues in, or on, food:

- A rotational plantback interval of 12 months for crops not registered for use with folpet.

Residue definition for enforcement:

- The residue of folpet in all commodities is currently expressed as folpet per se for enforcement and dietary risk assessment purposes. It is proposed that the residue definition be amended to include the phthalimide metabolite, expressed as folpet.

Environment

To protect aquatic habitats, the following measures are proposed:

- Advisory statements to inform users that folpet is toxic to non-target organisms including small mammals, aquatic invertebrates, fish, algae and frogs.
- Spray buffer zones to protect aquatic habitats from drift.
- Advisory statements to inform users of conditions that may result in run-off and leaching.
- A statement advising that transformation products could potentially reach groundwater, particularly in areas where soils are permeable and/or the depth to the water table is shallow.

Though not proposed as a requirement, certain additional information may allow for the refinement of occupational and residential exposure risk assessment. This could potentially reduce restrictions and mitigation measures proposed in this document, and may allow uses to be maintained which are proposed for removal. These data include, but are not limited to the following:

- Dermal absorption study (such as rat in vivo, triple pack of rat in vivo and rat/human in vitro studies);
- Exposure study for workers handling solid formulations in industrial settings;
- Dislodgeable foliar residue studies conducted under conditions relevant to the Canadian climate and use pattern;
- Postapplication worker exposure studies following application of folpet and performing activities that are relevant to Canadian climate and agricultural practices.

International Regulatory Context

Folpet is currently acceptable for use in other OECD member countries, including the United States.

Next Steps

Before finalizing a re-evaluation decision for folpet, the PMRA will consider any comments received during this consultation. A Re-evaluation Decision document will be published which will include a summary of comments received and the PMRA’s responses, as well as any revisions to this proposed re-evaluation decision.

Science Evaluation

1.0 Introduction

Folpet is a fungicide used as a material preservative in vinyl plastics, and as a broad spectrum, contact protectant to manage diseases on a number of food and ornamental crops. The use of folpet as a material preservative in paints and coatings in not included in this document and will be assessed in a separate document.

The primary antimicrobial uses of folpet in Canada are for window gaskets for homes and cars, roof membranes and exterior vinyl products. Interior uses as a material preservative are extremely limited.

Folpet is registered for control of specific crop diseases where a limited number of other multi-site fungicides are currently registered. It is a valuable pest management tool and contributes to integrated pest management programs on several important crops, including apples, grapes and strawberries due to its multi-site mode of action and low risk for resistance development. Folpet belongs to the Resistance Management Mode of Action (MoA) group M4, as classified by the Fungicide Resistance Action Committee (FRAC). It works by interfering with metabolic respiration in susceptible fungal pathogens.

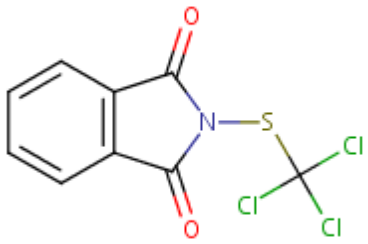
Appendix I lists all registered products containing folpet as of December 15th, 2017. Appendix II lists all uses for which folpet is registered. One domestic class ready-to-use dust product, co-formulated with carbaryl and malathion, is currently being phased-out as a result of the re-evaluation decision for carbaryl. As such, this product was not included in the re-evaluation of folpet.

2.0 The Technical Grade Active Ingredient

2.1 Identity

Common name	Folpet
Function	Fungicide, material preservative
Chemical Family	Phthalimide
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	*N*-(trichloromethylthio)phthalimide or *N*-(trichloromethanesulfenyl)phthalimide

2	**Chemical Abstracts Service (CAS)**	2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2*H*)-dione
	CAS Registry Number	133-07-3
	Molecular Formula	$C_9H_4Cl_3NO_2S$
	Structural Formula	



Registration Number	22040

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	0.021 mPa
Ultraviolet (UV) / visible spectrum	No absorbance at λ >350 nm
Solubility in water at 20-25°C	0.8 mg/L
n-Octanol/water partition coefficient	Log K_{ow} = 3.02; K_{ow} = 1047
Dissociation constant	Not applicable

3.0 Human Health Assessment

3.1 Toxicology Summary

Folpet is a chloroalkylthio fungicide sharing structural similarities to captan, another fungicide of the same chemical class.

A detailed review of the toxicological database was conducted. The database includes the standard complement of studies currently required for hazard assessment purposes, as well as mechanistic data. Published studies were also incorporated into the hazard assessment. Overall, study results were consistent and indicated a contact irritation mechanism targeting the mucosal membranes in test animals.

Folpet was readily absorbed by rats following single or repeat exposure to low oral doses of radiolabelled compound. Peak blood levels were achieved in less than one hour, suggesting rapid absorption. The data also indicate that absorption of folpet is rapid in mice, with decreased absorption at elevated dose levels. Metabolism occurred rapidly in both rats and mice via hydrolysis or reaction with thiols in the gastrointestinal tract to yield phthalimide and thiophosgene. Thiophosgene is a highly reactive metabolite common to folpet's structural analogue captan. Further metabolism of thiophosgene occurred rapidly through three pathways including hydrolysis to carbon dioxide, conjugation to form thiazolidines and conjugation to form disulphonic acids.

The absorption of thiosphosgene from the gastrointestinal tract is unlikely due to its highly reactive state; however, its degradates, namely thiazolidine and disulphonic metabolites, were identified in the duodenum of rats and mice shortly after administration of folpet. Levels of glutathione in the small intestine decreased in both species shortly after exposure, rebounding hours later to levels greater than that of control animals. This effect was more pronounced in mice than rats. This finding provides an explanation for the increased presence of thiazolidine metabolites observed in the duodenum of mice compared to rats. It is likely that following the depletion of glutathione stores in mice, an increased binding to other sulfhydryl groups (thiols) occurs, resulting in the disruption of local cellular membranes. The thiophosgene–based metabolites were excreted primarily in the urine, with air and feces as secondary routes of excretion. Unmetabolised folpet was detected in the urine of rats in one oral study but levels were not provided as it was not considered a major component.

The phthalimide-based metabolites of folpet reached most organs, with concentrations being highest in the gastrointestinal tract, the liver and the kidneys. Excretion of phthalimide-based metabolites was rapid and occurred primarily through the urine, with fecal elimination becoming more prominent with increasing dose.

Recently published toxicokinetic data investigated the fate of folpet in humans following oral and dermal dosing. The studies were conducted in volunteers, followed informed consent procedures and were approved by a university research ethics committee. The studies showed rapid absorption of the biomarker phthalimide, monophasic elimination of phthalimide from the plasma and urinary elimination half-lives of 27-30 hours for phthalimide and phthalic acid. Relatively small volumes of distribution suggested the absence of significant tissue storage.

Folpet was of low acute toxicity to rats and mice via the oral route and to rabbits via the dermal route. Slight to moderate acute toxicity was noted in rats exposed to folpet via inhalation. Folpet was mildly to severely irritating to the eyes of rabbits in several assays but was not a dermal irritant. Folpet was a skin sensitizer in guinea pigs in both the Beuhler and Maximization assays.

In repeat-dose oral studies in mice and rats, the gastrointestinal tract was the target organ. Toxicological effects at the site of contact consistent with mucosal irritation (hyperkeratosis/acanthosis, edema, ulceration) and regenerative responses (increased cell proliferation/hyperplasia, hypertrophy), were typically observed in test species following several weeks of exposure. The gastrointestinal irritation targeted primarily the stomach in rats and the proximal regions of the small intestine in mice. Dogs showed a different profile of toxicity at low

doses, with emesis and/or body weight effects and accompanying alterations in clinical chemistry parameters; at higher doses, additional targets of toxicity were the male reproductive organs, thyroid and lymphatic/hematopoetic systems.

Excessive irritation in the repeat-dose dermal toxicity study at low levels of exposure precluded an assessment of systemic toxicity. Acute studies indicated that inhalation was likely the most sensitive route of exposure for test animals exposed to folpet. This finding was confirmed with a repeat-dose inhalation toxicity study in rats. At the lowest dose tested, squamous metaplasia of the larynx occurred, progressing in severity and incidence at higher dose levels. Although the registrant put forth an argument that these lesions were adaptive, the PMRA considered these lesions adverse, given the incidence, severity (up to moderate in degree), involvement of multiple sites (ventral diverticulum and ventral seromucous gland) and accompanying laryngeal findings (keratinization, hyperplasia, fibrosis and inflammation). Lesions of the nasal mucosa, trachea and lungs were also evident at higher dose levels. Inhalation toxicity studies conducted with captan showed similar portal-of-entry responses. The physiological responses to folpet and captan were attributed primarily to the formation of the thiophosgene moiety. Increasing duration of inhalation exposure with captan led to increased severity of inhalation toxicity including lower effect levels. A similar pattern of increased toxicity with increased duration of exposure is anticipated for folpet. It bears noting that folpet is more potent than captan for irritation effects.

In dietary lifetime toxicity studies in mice, folpet was irritating to the proximal region of the gastrointestinal tract (stomach, duodenum) with irritation also observed in the esophagus; at higher dose levels, the jejunum and ileum were also targets of toxicity. Chronic administration to mice resulted in an increased incidence of hyperplasia, adenomas and adenocarcinomas of the small intestine (primarily in the duodenum), gastric ulceration, and stomach papillomas. At higher doses, jejunal adenomas/adenocarcinomas were also observed. In rats, chronic dietary exposure to folpet resulted in irritation of the esophagus (hyperkeratosis), as well as the non-glandular stomach (hyperkeratosis/acanthosis and ulceration/erosion) but did not produce an increase in the incidence of tumours of the gastrointestinal tract.

In view of the fact that gastrointestinal irritation observed following oral exposure is attributable to the reactive metabolite thiophosgene, mechanistic assays with folpet and captan were considered informative in considering the carcinogenicity data. The available evidence for captan and folpet suggests that, initially, the duodenal tissue is irritated, resulting in disorganization of the villi, inflammation of the lamina propria, migration of the immature enterocytes to the tip of the villi, and hyperplasia of the crypt cells as a compensatory response. The hyperplastic condition of the crypt cells results from the need to rapidly regenerate the damaged villi as indicated by a decrease in villi height, decreased cell maturity, increased mitotic figures in the crypt cells and increased crypt cell:villi ratios.

It was considered likely that the increased crypt stem cell hyperplasia results in an increased incidence of neoplastic lesions, mediated by diminished capacity for the cellular repair of DNA damage.

Chronic oral administration of folpet affected the duodenum of the small intestine in mice in a manner similar to captan, but captan did not affect the stomach until much higher dose levels, at

which point hyperplasia of the jejunum was also observed. The slight differences in target sites of gastrointestinal irritation between captan and folpet are attributed to differing rates of thiophosgene production under physiological conditions. Although a long-term assay investigating the ability of animals to recover following exposure to folpet was not available, a 96-week study investigating the effects of captan on the duodenum of mice following various treatment and recovery periods showed decreases in the incidences of duodenal hyperplasia to levels similar to those in control animals following cessation of treatment. However, tumours, observed as early as 24 weeks, did not regress with cessation of captan treatment.

Observations in long-term toxicology studies with folpet indicated that the dose at which non-neoplastic gastrointestinal effects are observed in rats and mice is similar. Although interspecies differences in kinetics and enzyme induction were observed, the difference in neoplastic responses between mice and rats exposed to folpet was not conclusively explained. The data suggest that the neoplasms in the murine gastrointestinal tract are secondary to pronounced irritation and ensuing compensatory response. Irritation thresholds of 9 mg/kg bw/day and 16 mg/kg bw/day for rats and mice, respectively, were established based on gastrointestinal tract effects following oral exposure. Pathology indicative of gastrointestinal irritation was not observed in the dog.

In vivo mutation assays with folpet including a chromosome aberration assay, dominant lethal assays and a mouse spot assay, were negative, indicating a low likelihood of clastogenic or mutagenic potential. Furthermore, two in vivo assays focused on the duodenal cells of the mouse, namely a novel nuclear aberration assay and a Comet assay, were negative. In vitro gene mutation assays presented mixed results, with positive results observed primarily in the absence of metabolic activation. Mixed results were also noted in the in vitro chromosomal aberration assays. Negative results were noted in unscheduled DNA synthesis assays but folpet was noted to interact with DNA in aqueous medium. It is likely that the attenuation or elimination of mutagenicity and clastogenicity in vivo is due to the presence of S-containing targets (such as glutathione) for the detoxification of the highly reactive thiophosgene. Folpet is unlikely to represent a genotoxic concern under normal metabolic conditions.

In dietary multigenerational reproductive toxicity assays in rats, maternal effects were consistent with other short-term dietary studies and included irritation of the gastrointestinal tract and decreases in body weight gains. Effects on the reproductive system were not observed. Offspring toxicity was limited to reduced weight gain and was observed only at maternally toxic doses. Although folpet displayed some anti-androgenicity in one published screening study in yeast cells, it was not shown to be endocrine-active in a battery of in vitro screening studies in mammalian cells or in in vivo studies conducted for the US Endocrine Disruptor Screening Program. Effects on the male reproductive system were observed only in the dog following repeated oral administration of folpet at doses approaching or exceeding the limit dose.

Two rat gavage developmental toxicity studies were available. In one study, developmental toxicity, including angulated ribs and decreased ossification, was observed in the absence of maternal toxicity. A small number of malformations were noted at a high dose in this study which also resulted in significant maternal toxicity.

The second study showed maternal toxicity at lower levels than those in the first study; however, decreased ossification of the fetuses occurred at comparable levels. No evidence of sensitivity or malformations was noted in the latter study.

Four gavage developmental toxicity studies were available in rabbits. The first study had small group sizes, but was conducted with the highest dose levels of all four studies. No evidence of sensitivity of the young animal or malformation was observed, but serious effects were noted at the high dose level including an increase in early resorptions and post-implantation loss. In the second study, hydrocephalus and cranial malformations were observed in rabbit fetuses at dose levels producing decreases in body weight gain in the dams. In the third study, lens malformations not previously seen in the conducting laboratory, in addition to increased late resorptions and post-implantation loss, were noted at a dose producing significant maternal toxicity. The fourth study involved pulse dosing pregnant females for 3-day intervals during different periods of gestation. Single incidences of hydrocephaly were seen in fetuses from dams exposed on gestation days 10-12 and 16-18. An increased number of fetuses with irregularly-shaped fontanelles was noted in the group of dams receiving folpet treatment on days 13-15 of gestation.

Developmental toxicity data for the structural analog captan also shows similar effects of fetal loss and malformations at maternally toxic doses (see PRVD 2016-13, Captan). As with captan, the registrant contends that the fetus is not exposed to folpet given the rapid and extensive breakdown of folpet in the gut (PMRA 2585638). The PMRA notes that there is some potential for absorption of folpet, albeit slight, however the developing fetus would be exposed primarily to phthalimide and other metabolites. Although there was no evidence of treatment-related malformations or resorptions in a rabbit developmental toxicity study with phthalimide, a sufficiently high dose may not have been used. Furthermore, no developmental toxicity data were available for the other metabolites. Consequently, the folpet studies are considered more relevant for risk assessment in that all metabolic degradates were considered.

In conclusion, the folpet data are suggestive of developmental toxicity at doses $\geq$ 30 mg/kg bw/day. The effects are not likely a species-specific response (that is, bacteriogenic action in the rabbit) as suggested by the registrant (PMRA 2585638) given the observed findings in multiple species with captan. The lack of consistent structural targets suggests that malformations may be secondary to maternal toxicity as opposed to a direct teratogenic effect. Studies on captan suggest a similar mode of action. Time-course data in mice receiving a high dose of folpet (~900 mg/kg bw/day) demonstrated duodenal effects after 7 days of dosing (crypt cell hyperplasia and villous hypertrophy). Although gastrointestinal disturbance is likely a common stressor in pregnant animals at high-dose levels, data to support this contention at lower dose levels are limited, other than for non-specific effects on body weight and food consumption. Regardless, the impact of maternal stress is not species-specific and, therefore, the animal findings are relevant to humans.

Toxicology data on the metabolites/degradates of folpet were limited to a developmental toxicity study in rabbits with phthalimide. Based on the lack of toxicity in this study, phthalimide would appear to be less toxic than folpet; this likely reflects the absence of the reactive group on the phthalimide moiety. Data were insufficient to characterize the extent of this difference. No data were available on any other metabolites of folpet.

The results of the toxicology studies conducted on laboratory animals with folpet and relevant degradates are summarized in Appendix III, Table 1. The toxicology reference values for use in the human health risk assessment are summarized in Appendix III, Table 2.

3.1.1 *Pest Control Products Act Hazard Characterization*

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 to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity data as it pertains to the toxicity to infants and children, the database contains more than the standard complement of required studies for folpet including two reproductive toxicity assays in rats, two developmental toxicity studies in rats and four developmental toxicity studies in rabbits.

No sensitivity of the young was noted in the reproduction studies and effects in offspring were limited to reductions in weight gain. Delays in fetal ossification were observed in the absence of maternal toxicity in one rat developmental toxicity assay and in the presence of maternal toxicity in another study. Rat fetuses in the former study also displayed angulated ribs at the lowest dose tested and a low incidence of malformations at the maternally toxic high dose level. Malformations and/or resorptions were present in the rabbit developmental toxicity assays, but only at a dose resulting in maternal toxicity (decreased body weight/ body weight gain and food consumption).

Overall, the database is adequate for characterizing effects on the young and there was minimal evidence that young animals were more sensitive than adult animals to folpet toxicity. The fetal effects observed in the rabbit developmental toxicity assays were considered serious endpoints, although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor has been reduced to 3-fold when using a rabbit developmental toxicity assay to establish the point of departure for women of child bearing age. In exposure scenarios for children, the risk was considered well characterized, and the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to folpet from potentially treated imported foods is also included in the assessment. Dietary exposure

assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults.

Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Sufficient information was available to adequately assess the dietary risk from exposure to folpet. Acute, chronic and cumulative dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America (NHANES/ WWEIA) 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). Further details on the consumption data are available in Science Policy Note SPN 2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on dietary risk estimates and the residue chemistry information used in the dietary assessment, see Appendices IV and V.

Residue Definition for Risk Assessment

The residue of folpet in all commodities is currently expressed as folpet *per se* for enforcement and dietary risk assessment purposes. The PMRA has determined that based on the lack of data to quantify the difference between the toxicity of folpet and phthalimide, the parent (folpet) toxicology reference values apply to the phthalimide (PI) metabolite.

In addition, folpet metabolism studies showed that residues in all animal commodities and in some plant-based raw agricultural commodities (RACs) can only be monitored using a complex residue definition, as parent folpet is not present in any animal tissue and is not the predominant metabolite (not a good marker) in all plant commodities. The stability of folpet residues is variable and matrix dependant: folpet degrades into PI in macerated samples due to endogenous enzyme activity. Furthermore, studies simulating hydrolytic conditions for pasteurisation, boiling/brewing/baking and sterilisation indicated that folpet is completely degraded during processing; PI is formed predominantly under conditions of pasteurisation while levels of phthalic acid increase under conditions simulating boiling/brewing/baking and sterilisation. Phthalic acid and phthalamic acid can naturally occur in the environment and, therefore, cannot be considered as specific to folpet. Thiophosgene, the common metabolite to both folpet and captan is also not included in the residue definition because it is a transitory, short-lived compound. PI is the only relevant metabolite to be taken into account.

Consequently, it is proposed that the residue definition for plant and animal commodities be amended to include the metabolite PI, expressed as folpet, for enforcement and acute and chronic dietary risk assessment.

For the cumulative risk assessment, only folpet (parent) and captan (parent), which can be metabolized to the highly irritating thiophosgene when ingested, are considered to contribute to the common endpoint of gastrointestinal irritation. The folpet metabolite PI and the captan metabolite THPI (tetrahydrophthalimide) are not considered to be contributors to the common endpoint for the cumulative dietary risk assessment.

3.2.1 Determination of Acute Reference Dose (ARfD)

Acute Reference Dose (ARfD) - Females 13-49 Years of Age

To estimate acute dietary risk, a developmental toxicity study in rabbits in which hydrocephaly and cranio-facial anomalies were observed in fetuses at a lowest adverse effect level (LOAEL) of 20 mg/kg bw/day was selected for risk assessment. A no observed adverse effect level (NOAEL) of 10 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold. Thus, the composite assessment factor is 300.

$$\text{ARfD} = \frac{10 \text{ mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw}$$

Acute Reference Dose (ARfD) - General Population, Excluding Females 13-49 Years of Age)

To estimate acute dietary risk, a developmental toxicity study in rabbits in which effects on body weight were observed in the 30 mg/kg bw/day dams in the first few days of dosing was selected for risk assessment. Although the study had an overall maternal LOAEL of 10 mg/kg bw/day, a NOAEL of 10 mg/kg bw was established for this specific acute endpoint. This endpoint was deemed to be applicable to all populations. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. Thus, the composite assessment factor is 100.

$$\text{ARfD} = \frac{10 \text{ mg/kg bw/day}}{100} = 0.1 \text{ mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of combined residues of folpet and PI that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure is not of concern.

The assessment was conducted by using Canadian Food Inspection Agency (CFIA) and Pesticide Data Program (PDP) food monitoring data for all the commodities except hops, citrus oil, crabapple, loganberry and pummelo. Field trial residue distribution data were used for hops. Maximum residue limits (MRLs) were used for citrus oil, crabapple, loganberry and pummelo; however, this had limited impact on the exposure estimates since these commodities are not consumed significantly in the population. Since no monitoring or field trial data were available for PI, PI residues were estimated on the basis of metabolite ratios derived from metabolism studies. The total residue was calculated by multiplying the folpet residue (from monitoring data, field trial or MRL) by the appropriate metabolite ratio. The residues for livestock and dairy commodities were estimated on the basis of the maximum theoretical dietary burden and transfer factors derived from metabolism studies. In addition, the following inputs were used: available percent crop treated (PCT) information in Canada and in the US; 100% crop treated for all commodities for which no PCT information was available; available information on the proportion of domestic production and import supply; DEEM default processing factors; and drinking water environmental estimated concentrations (EECs) of combined residues of folpet and PI obtained from water modelling [see Section 3.3].

The acute dietary (food + water) exposure estimate (at the 99.9th percentile) for females 13-49 years of age is 84% of the ARfD and is, therefore, not of concern. The main contributors to the risk are hops and drinking water (direct and indirect, from all sources), accounting for approximately 55% and 36% of the total exposure (46% and 30% of the ARfD), respectively. The high contribution of hops to the risk results from the use of field trial residue distribution data in absence of monitoring data. The high contribution of water results from the use of a single point estimate from water modelling.

The acute dietary (food + water) exposure estimates (at the 99.9th percentile) for population subgroups other than females 13-49 years of age range from 12% (children 6-12 years old) to 49% (males 20-49 years old) of the ARfD and are, therefore, not of concern. For the most exposed subgroup (males 20-49 years old), the main contributor to the risk is hops, accounting for 91% of the total exposure (~45% of the ARfD). As noted previously, the high contribution of hops to the risk results from the use of field trial residue distribution data in absence of monitoring data.

3.2.3 Determination of Acceptable Daily Intake (ADI)

Acceptable Daily Intake, Females 13-49 Years of Age

To estimate risk from repeat dietary exposure, a developmental toxicity study in rabbits in which hydrocephaly and cranio-facial anomalies were observed in fetuses at a LOAEL of 20 mg/kg bw/day was selected for risk assessment. A NOAEL of 10 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold. Thus, the composite assessment factor is 300.

$$\text{ADI} = \frac{\text{10 mg/kg bw/day}}{300} = 0.03 \text{ mg/kg bw/day}$$

Acceptable Daily Intake (General Population, excluding Females 13-49 Years of Age)

To estimate risk from repeat dietary exposure, the chronic/carcinogenicity assay in Sprague Dawley rats was selected. An increased incidence of irritation of the non-glandular stomach was observed at the LOAEL of 35 mg/kg bw/day. The NOAEL for this study was 9 mg/kg bw/day. The rabbit developmental toxicity study was selected as a co-critical study with a LOAEL of 10 mg/kg bw/day. Effects at this level on body weight gain and food consumption were relatively minor and did not warrant the application of an uncertainty factor for the lack of a NOAEL. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. Thus, the composite assessment factor is 100.

$$\text{ADI} = \frac{\text{9 mg/kg bw/day}}{100} = 0.09 \text{ mg/kg bw/day}$$

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. The estimated exposure was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The assessments were conducted using average residues from the same CFIA and PDP food monitoring data used in the acute assessment [see Section 3.2.2]; the supervised trial median residue for hops; MRL/Tolerance-level residues for citrus oil, crabapple, loganberry and pummelo; available PCT in Canada and US; 100% crop treated for commodities for which no PCT information was available; DEEM default processing factors; and the chronic drinking water EEC point estimate for combined residues of folpet and PI obtained from water modelling [see Section 3.3].

Residues for livestock and dairy commodities were estimated on the basis of the maximum theoretical dietary burden. Metabolite ratios were used to account for PI residues in plant commodities.

The chronic dietary (food + water) exposure estimate for females 13-49 years of age is approximately 2% of the ADI and is, therefore, not of concern. The chronic dietary (food + water) exposure estimates for population subgroups other than females 13-49 years of age range from <1% to 2% of the ADI and are, therefore, not of concern.

3.2.5 Cancer Assessment

Dietary administration of folpet resulted in gastrointestinal tumors in mice. No treatment-related tumors were seen in rats. The tumors in mice arose via a non-genotoxic mode of action involving gastrointestinal irritation. Cancer risk (threshold) was addressed through the selected toxicology reference values and chronic risk assessment.

3.2.6 Cancer Dietary Exposure and Risk Assessment

A separate quantitative cancer assessment was not required (See Section 3.2.5).

3.3 Exposure from Drinking Water

Residues of folpet (parent only) and combined residues of folpet and PI in potential drinking water sources were estimated from water modelling.

3.3.1 Concentrations in Drinking Water

The environmental EECs were calculated using PRZM/EXAMS and LEACHM models for surface water and groundwater, respectively. A refined (Level 2) peak concentration of 0.0538 ppm for combined residues of folpet and PI in surface water was used in the acute assessments. A Level 1 surface water reservoir yearly average EEC value of 0.0015 ppm for combined residues of folpet and PI was used in the chronic assessments. A Level 1 surface water yearly average EEC value of 0.0011 ppm for residues of folpet (parent only) was used in the folpet cumulative risk assessment (Section 3.6) [please refer to the Environmental Assessment section of this document for details on the EECs].

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC point estimates incorporated directly in the dietary (food and drinking water) assessments; there were no risks of concern. Please refer to Sections 3.2.2, 3.2.4, and 3.2.6 for details.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Dermal Risk Assessment, All Durations

In order to estimate short-, intermediate- and long- term risk from the dermal route of exposure, the developmental toxicity study in rabbits in which hydrocephaly and cranio-facial anomalies were observed in fetuses at a LOAEL of 20 mg/kg bw/day was selected for risk assessment. A NOAEL of 10 mg/kg bw/day was established. The developmental endpoints are considered relevant to the dermal risk assessment, in that a developmental toxicity assay in which animals were exposed via the dermal route was not available. For residential scenarios, a target MOE of 300 was derived which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold *Pest Control Products Act* factor (as outlined in the *Pest Control Products Act* Hazard Characterization section). For occupational exposure scenarios, the target MOE of 300 includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold factor for the seriousness of the endpoint.

Short-term Inhalation Risk Assessment

In order to estimate short-term risk from the inhalation route of exposure, a 28-day inhalation study with folpet in rats was selected. No NOAEC was established in this study; the lowest observed adverse effect concentration (LOAEC) of 5.2 μg/L (1.4 mg/kg bw/day) was based on laryngeal lesions and, in males, an increase in lung weight. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor was applied for the lack of a NOAEC. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold given that the inhalation point of departure is protective of the developmental toxicity concerns. The target margin of exposure is 300. The selection of this endpoint is supported by the results of the captan 21-day inhalation study (NOAEC of 5.3 μg/L) given that folpet is approximately 3-fold more toxic than captan (on the basis of gastrointestinal irritation in repeat-dose oral studies).

Intermediate- and Long- term Inhalation Risk Assessment

Since a 90-day inhalation toxicity study with folpet was not conducted, the 28-day inhalation study with folpet in rats was selected for intermediate and long-term inhalation risk assessment No NOAEC was established in this study; the LOAEC of 5.2 μg/L was based on laryngeal

lesions and, in males, an increase in lung weight. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied along with a 3-fold uncertainty factor for the lack of a NOAEC. The current information suggests that the inhalation toxicity of folpet is expected to increase with increased duration of exposure, as was seen with captan. Consequently, an additional uncertainty factor of 3-fold was applied for the intermediate-term assessment to account for potential durational effects, resulting in an overall target MOE of 1000.

Given the irritant nature of folpet, increased duration of exposure is expected to result in progressive toxicity to the respiratory tract. For this reason, this uncertainty factor was raised to 10-fold for the long-term assessment to account for potential durational effects, resulting in a target MOE of 3000.

Dermal Absorption

A dermal absorption value of 20% was chosen for the re-evaluation of folpet based on a weight-of-evidence approach using available dermal absorption studies (a human in vivo study, three rat in vivo studies, and a rat and human in vitro study), the physical/chemical properties of folpet, and observations from toxicology studies.

3.4.2 Non-Occupational Exposure and Risk Assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The following scenarios were assessed:

- Postapplication exposure for individuals who conduct activities on residential apple and crabapple trees that may have been previously treated by a commercial applicator;
- Individuals who contact plastic products containing folpet;
- Bystander exposure from drift

Residential Applicator Exposure and Risk Assessment

A residential applicator assessment was not required since the only domestic-class pesticide product containing folpet is being cancelled.[1]

Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation and/or incidental oral (non-dietary ingestion) routes as a result of handling a product that has been treated with a pesticide, or being in a residential environment that has been previously treated with a pesticide.

[1] There is one domestic class folpet product, which is coformulated with carbaryl. This product is being cancelled as a result of the carbaryl re-evaluation (RVD2016-02).

Residential Trees

The 2012 USEPA Residential Standard Operating Procedures (SOPs) were used to estimate exposure to people contacting apple and crabapple trees which may have been previously treated by a commercial applicator. The SOPs have standard default assumptions for postapplication exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms may be used in the absence of, or as a supplement to, chemical- and/or site-specific data and generally result in high-end estimates of exposure. The assumptions and algorithms relevant to the folpet re-evaluation are outlined under "Section 4: Gardens and Trees" of the SOPs.

The following scenarios were assessed for the postapplication exposure to folpet:

- Trees
  - Adult, youth, and children (6 <11 years old) dermal exposure resulting from activities on trees

The PMRA is primarily concerned with the potential for short-term dermal exposure (that is, 30 days or less) to these populations conducting post-application activities in treated areas. Based on the vapour pressure of folpet, inhalation exposure is not likely to be of concern.

Calculated MOEs for outdoor residential postapplication exposure exceed the target MOE and, therefore, risks are not of concern. See Appendix VI, Table 1 for more information.

Plastic Products

For plastic products that contain folpet, a qualitative postapplication risk assessment was conducted. Risks were determined to not be of concern, as contact with the treated plastic products (gaskets, vinyl flooring backing, outdoor upholstery, coatings applied to tents, awnings and roof membranes) is expected to be minimal and intermittent with very low amounts of folpet available at the material surface for transfer and exposure.

Bystander Exposure

Folpet residues were detected in the ambient air near Canadian agricultural areas in BC and Quebec during the spray season in 2004. Based on the current use pattern of folpet, potential bystander exposure was assumed to be of intermediate-term duration (that is, several months). The peak air concentration was used to estimate exposure, thus resulting in conservative (upper bound) exposure estimates. As noted in Appendix VI, Table 2, MOEs were greater than the target MOE for all subpopulations and are not of concern.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to folpet in occupational scenarios from workers handling the pesticide during the application process in agricultural and industrial settings, and potential for postapplication exposure from workers entering into areas previously treated with folpet.

Handler Exposure and Risk Assessment

Agricultural Uses

For commercial-class products used in agricultural areas, there are potential exposures to mixers, loaders and applicators (M/L/A). The following scenarios were assessed:

- Mixing/loading of wettable powders.
- Mixing/loading of water dispersable granules (WDG).
- Groundboom application to strawberries, cranberries, cucumbers, melons, pumpkins, squash, tomatoes, roses, asters, China asters, phlox, carnations, marigolds, zinnias, chrysanthemums, iris and snapdragons.
- Handheld application to strawberries, cranberries, roses, asters, China asters, phlox, carnations, marigolds, zinnias, chrysanthemums, iris, snapdragons, and poinsettias. Handheld application includes backpack, mechanically pressurized handgun, and manually pressurized handwand.
- Airblast application to apples, crabapples, grapes, and cranberries
- Stem soak of azaleas

Based on the number of applications and timing of application, workers applying folpet would generally have a short-term (<30 days) duration of exposure. Custom applicators may have intermediate-term (up to several months) exposure for those crops with multiple applications. For workers in greenhouses, there is potential for intermediate-term (up to several months) duration of exposure.

The PMRA estimated handler exposure based on different levels of personal protective equipment (PPE):

- Baseline PPE: Long pants, long-sleeved shirt and chemical-resistant gloves (unless specified otherwise). For groundboom application, this scenario does not include gloves, as the data quality was better for non-gloved scenarios than gloved scenarios.
- Mid-Level PPE: Cotton coveralls over long pants, long-sleeved shirt, and chemical-resistant gloves. Max-Level PPE: Chemical-resistant coveralls over long pants, long-sleeved shirt, and chemical-resistant gloves.
- Engineering Controls: Represents the use of appropriate engineering controls, such as closed cab tractor or closed loading systems. Engineering controls may not be possible for handheld application methods.
- Chemical Resistant Headgear. Chemical resistant headgear that covers the neck (for example, Sou'Wester hat, rain hat).Respirator: a respirator with a NIOSH- approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides

No appropriate chemical-specific handler exposure data were available for folpet at the initiation of the re-evaluation. Dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database Version 1.1 (PHED) and Agricultural Handlers Exposure Task Force (AHETF) studies. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-

specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment. The open cab airblast scenario from AHETF was used in the risk assessment. In most cases, PHED and AHETF did not contain appropriate data sets to estimate exposure to workers wearing cotton coveralls or a respirator. This was estimated by incorporating a 75% clothing protection factor for cotton coveralls, a 90% protection factor for chemical-resistant coveralls and a 90% protection factor for a respirator into the unit exposure values, where applicable. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min).

For commercial stem soak and planting of treated stems, adequate data to estimate exposure were not available. This use is proposed for removal unless adequate data are submitted and an updated risk assessment supports the registration of this use.

For agricultural uses, calculated MOEs for M/L/A exceeded target MOEs for mixing, loading, and application scenarios and are not of concern, provided engineering controls, and personal protective equipment are used as summarized on page 21 and in Appendix VII. Appendix VII Tables 1-3 summarize the calculated MOEs for mixers/loaders and applicators.

Industrial Uses (Material Preservative)

For commercial-class products used in vinyl plastic, there is potential exposures for workers who add folpet during the manufacturing process.

Exposure to folpet from its use in manufacturing is expected to be intermittent (a few minutes daily or once a week) over an intermediate to long-term duration (i.e. >30 days to several months), predominantly via the dermal route.

Exposure estimates were based on the American Chemical Manufacturer's Association (CMA), Antimicrobial Exposure Assessment Study. The study monitored 46 replicates for 6 active ingredients used in 4 different settings for 4 different application methods. Each replicate was representative of the time spent performing the antimicrobial-related task in one day; therefore the data was not normalized. Since application of biocides in industrial processes is similar regardless of the use site (for example, cooling towers, pulp and paper, etc.), it was considered appropriate to combine replicates based on the application method. Due to limitations in the exposure study (low and variable laboratory and field recoveries), the 90th percentiles generated from the input CMA data were used to estimate potential exposure to operators handling industrial products containing folpet.

The commercial products registered for this use are formulated as soluble powders. Therefore, the following scenarios were assessed:

-
- Mixing/transfer of solids, open pour
- Mixing/transfer of solids, place method (water soluble packages)

Since most individuals in the CMA study wore long sleeves, long pants, and cotton gloves, this data is considered to be representative of an individual wearing a single layer, and gloves. However, it should be noted that in each scenario, there was at least one replicate that did not wear gloves, and one replicate that wore short-sleeves.

For material preservative uses, calculated MOEs for mixing/transfer of solids did not reach the target MOE, and, therefore, risks are of concern. To mitigate this risk, it is proposed that the folpet soluble powder formulation commercial product be cancelled. Appendix VII, Table 4 summarizes the calculated MOEs for mixers/loaders.

Postapplication Worker Exposure and Risk Assessment

Industrial Uses (Material Preservative)
There is no available data to quantify potential postapplication exposure to workers contacting plastic preserved with folpet during the manufacture of products, or when using those manufactured products.

For workers contacting plastics preserved with folpet during manufacturing, exposure is expected to be low given the occupational hygiene standards in these workplaces which require safe work conditions to address chemical exposures. Also, many of these downstream processes are highly automated, which would also help to minimize exposure.

For workers contacting products manufactured from plastic preserved with folpet, exposure to folpet is expected to be low, as contact with treated plastic products is expected to be low and intermittent, gloves are likely to be worn, and very low amounts of folpet would be available at the material surface for transfer and exposure.

Agricultural Uses
The postapplication occupational risk assessment considers exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact. Based on the folpet use pattern, there is potential for short-to intermediate-term (<30 days to several months) postapplication exposure to folpet residues for workers. For greenhouse uses, there is potential for long-term (> 6 months) postapplication exposure.

Potential exposure to postapplication workers was estimated using updated activity-specific transfer coefficients (TCs), and chemical-specific dislodgeable foliar residue (DFR), if available. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, harvesting cut flowers) and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the ARTF were used. Postapplication exposure activities for agricultural crops include (but are not limited to): harvesting, pruning and scouting. For more information about estimating worker postapplication exposure, refer to the PMRA's Regulatory Proposal PRO2014-02, U*pdated Agricultural Transfer Coefficients for Assessing Occupational PostApplication Exposure to Pesticides*.

Chemical-specific DFR studies available in the literature and submitted to the PMRA were considered in the postapplication risk assessment. DFRs for apples and crabapples were calculated using an avocado DFR study. For this study, the linear equation of plotting the natural logarithm (ln) of DFRs versus dissipation time (postapplication interval) following the final application was not sufficiently predictive (r^2 was less than 0.85); therefore, actual residue data from the sampling days in the study was used. Estimated DFR values were adjusted proportionally for maximum Canadian application rates. The DFR for multiple application scenarios was modelled by summing residues from a single application. For other outdoor crops, as no acceptable chemical-specific DFR data were available, default values were used (peak DFR of 25% of the application rate with 10% dissipation per day). For further information on these default values, refer to the PMRA's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferrable Residues in Occupational and Residential Postapplication Exposure Assessments.* As there were no DFR studies available for greenhouse ornamentals, default values were used (peak DFR of 25% of the application rate with 2.3% dissipation per day).

As none of the available DFR studies measured phthalimide residues, these could not be included in the risk assessment for postapplication exposure and thus, this is an uncertainty in the postapplication risk assessment. Exposure to the thiophosgene metabolite was not considered to be relevant for dermal exposure, as it is not formed in appreciable quantity through this route of exposure.

For workers entering a treated site, REIs are calculated to determine the minimum length of time required before people can safely enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse in order for residues to decline to a level at which there are no risk concerns for postapplication worker activities (for example, in the case of folpet, performance of a specific activity that results in exposures above the target MOE of 300).

The PMRA is primarily concerned with the potential for dermal exposure for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of folpet, inhalation exposure is not likely to be of concern provided that the minimum 12-hour REI is followed.

The risks associated with occupational postapplication scenarios are not of concern for most crops when REIs are increased for some activities and the number of applications is reduced. REIs were considered to be agronomically feasible for all crops except cut flowers (field, greenhouse) and cranberries. However, information on the feasibility of these REIs is requested during the PRVD comment period. Appendix VIII, Table 1 summarizes the postapplication exposure and risk assessment.

To mitigate the risks on crops with agronomically unfeasible REIs, cut flowers (field, greenhouse) and cranberries are proposed for cancellation. The use pattern for most crops is proposed to be reduced, such as 3 applications for apples/crabapples, and 1 application for grapes, strawberries, field tomato, cucumber, melon, pumpkin, and squash. Refer to Appendix XIII for the proposed reduce use pattern and REIs.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Risk estimates were performed for those scenarios where the individual exposure routes met the target MOEs and were not of concern.

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

Aggregate exposure to folpet may be comprised of food, drinking water and residential exposure. The irritative properties, as observed by the gastrointestinal and respiratory lesions, are believed to be due to the dissociation and formation of thiophosgene as a site-specific reaction and are therefore not relevant to an aggregate exposure risk assessment.

For females 13-49 years of age, the most relevant endpoint for aggregate assessment is developmental toxicity. This endpoint is applicable to all routes and durations of exposure. The rabbit developmental toxicity study in which hydrocephaly and associated cranial effects were observed in fetuses at a LOAEL of 20 mg/kg bw/day was selected. A NOAEL of 10 mg/kg bw/day was established. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied and, as discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold. The resulting target MOE is 300. This MOE is considered to be protective of pregnant women and their unborn children.

For the general population (including children), the most relevant endpoint for aggregate assessment is decreased bodyweight in pups from the rat reproductive toxicity study. A NOAEL of 17 mg/kg bw/day was established with effects observed at the LOAEL of 70 mg/kg bw/day. This endpoint was deemed appropriate for aggregation as it was less influenced by site-specific irritation than other endpoints. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied and as discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The target MOE is 100.

3.5.2 Residential, Non-Occupational, and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological endpoints can be aggregated.

Scenarios where a quantitative risk assessment was conducted and which did not have risks of concern were aggregated to determine whether aggregation of exposures would result in risks of concern. An aggregate assessment was conducted for adults, youth, and children (6<11 years old) for short-term dermal exposure from residential trees and chronic food exposure. A

quantitative aggregate risk assessment was not conducted for bystanders, since the inhalation MOEs exceeded the target MOE by several orders of magnitude and the contribution of this route to the total aggregate exposure (food and drinking water) is expected to be very low. Calculated aggregate MOEs exceeded the target MOE, and therefore are not of concern (see Appendix IX, Table 1).

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity.

3.6.1 Toxicology Reference Values for Cumulative Risk Assessment

Folpet and captan have the potential to cause irritation to mucous membranes through the formation of thiophosgene. Although differences in potency exist between these two fungicides, a common mechanism of toxicity of irritation was established, thus warranting a cumulative risk assessment. All routes of exposure are targets for the irritation properties of these compounds; however, the dissociation and formation of thiophosgene is a site-specific reaction, producing variable site-specific effects, and for this reason, it was not considered appropriate to cumulate the route-specific risks.

Accordingly, the oral route of exposure is the focus for the cumulative risk assessment. With oral exposure, captan causes gastrointestinal irritation to mice (but not rats) and targets primarily the duodenum. Similarly, folpet primarily causes irritation to the duodenum of mice, although the proximal regions of the gastrointestinal tract are also affected. In contrast to captan, folpet causes irritation to the non-glandular stomach of rats at similar doses to those causing irritation to the gastrointestinal tract of mice. It was concluded that the most appropriate point of departure for establishing a cumulative risk assessment is that of gastrointestinal irritation in mice. The NOAEL values for gastrointestinal irritation established in chronic/carcinogenicity assays in mice for captan and folpet are 60 mg/kg bw/day and 16 mg/kg bw/day, respectively. Given the nature of the endpoint, and consistent with the approach used in the respective risk assessments for captan and folpet, the *Pest Control Products Act* factor was reduced to 1-fold. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The composite assessment factor for the cumulative risk assessment is 100-fold. Therefore, the cumulative reference values for captan and folpet are 0.6 and 0.16 mg/kg bw/day, respectively, and would be relevant for all populations.

3.6.2 Cumulative Exposure and Risk Assessment

A residential cumulative risk assessment, focussed on the predominant route of exposure (dermal), was not required. Although dermal irritation was noted following repeated dermal exposure to captan or folpet, the former resulted in irritation at very high dose levels in contrast to folpet. The low potential for cumulative toxicity coupled with the low likelihood of co-exposure did not necessitate a cumulative risk assessment for this scenario.

For the cumulative endpoint of gastrointestinal irritation following oral exposure, it was assumed that consumption of foods containing captan residues and folpet residues would co-occur. The duration of exposure was considered to be chronic, as the gastrointestinal irritation progresses over the course of time. Therefore, the chronic risk estimates from both chemicals were combined to assess cumulative risk. The cumulative risk was calculated using the aggregate risk index (ARI) methodology:

$ARI = 1 / (\%\ RfD_{captan} + \%\ RfD_{folpet})$
$\%\ RfD_{captan}$ and $\%\ RfD_{folpet}$ are the calculated risks from exposure to captan and folpet, respectively (see Appendix IV, Table 2). As a general rule, an ARI greater than or equal to 1 is not of concern. An ARI less than 1 would require mitigation. The ARIs for the dietary exposure (from food and drinking water) to both captan and folpet are all greater than 1 for all populations and are, therefore, not of concern.

3.7 Incident Reports

As of 20 June 2017, there have been 6 human incidents involving folpet submitted to the PMRA. All incidents occurred in Canada and involved a domestic product containing folpet co-formulated with malathion and carbaryl. As such, no conclusions can be made regarding the role of folpet in the incidents. Furthermore, this product is being cancelled due to the re-evaluation decision on carbaryl[2].

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

Environmental fate data for folpet are summarized in Appendix X, Table 1.

Folpet has low solubility in water (1.0 mg a.i./L) and is not expected to evaporate under dry field conditions (vapour pressure 2.1×10^{-5} Pa) but can volatilize and enter the atmosphere from moist soil or water surfaces (Henry's law constant $< 2.96 \times 10^{3}$ atm m^3/mole), but available information indicates that folpet will breakdown rapidly in the atmosphere (half-life of 6.2 hr). Phototransformation in soils and water is a minor route of transformation for folpet where hydrolysis (half-life = 2.6 hours at pH5, 1.1 hours at pH 7 and 67 seconds at pH9) is driving the process of transformation.

Folpet is not persistent in water because it breaks down rapidly via chemical and biological processes. Folpet transforms rapidly in aerated soils (half-life of 0.2 – 3.8 days) as well as in non-aerated soils (half-life of 7-14.6 days). Folpet also transforms rapidly in oxygenated water (half-life <1 hour). The major transformation products of folpet obtained from microbial degradation and chemical breakdown are phthalimide (PI), phthalamic acid (PAM) and phthalic acid (PA.I.). These transformation products are also non-persistent in soil and water.

[2] Re-evaluation Decision RVD2016-02, *Carbaryl.*

Although adsorption/desorption studies suggest folpet is mobile in soils (K_{oc} =7.4 – 304 mL/g), a soil column leaching study demonstrated that folpet is immobile, staying in the top 2 cm of soil. Also, the leaching potential of folpet assessed using the criteria of Cohen et al. (1984) and the groundwater ubiquity score (GUS) of Gustafson (1989) indicates that folpet is not expected to leach to groundwater. The transformation products phthalimide, phthalamic acid and phthalic acid are immobile to slightly mobile in soils based on K_{oc} values. Terrestrial field dissipation studies indicate that folpet and phthalimide dissipate quickly in loamy fine sand of Washington state (ecoregion equivalent to British Columbia), with estimated half-life values of less than 1.1 days. Folpet and phthalimide are not expected to carry over in soil to the next season. Accordingly, there is a low potential for this fungicide to persist and accumulate in soils.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level). Summaries of toxicity data for both terrestrial and aquatic non-target organisms to folpet are presented in Appendix X, Tables 2 and 3)

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

The risk assessment for folpet to terrestrial organisms was based upon an evaluation of toxicity data of folpet to bees, beneficial arthropods, three species of birds and two species of mammals. No data on toxicity to plants were available for review, but a vegetative vigour endpoint provided by the EFSA (2006) was used to characterize the risk to terrestrial plants. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with folpet.

Bees and other arthropods

The screening level risk assessment indicated that the levels of concern for terrestrial invertebrates such as bees, earthworms or beneficial insects were not exceeded at the maximum application rates. Limited data was available on chronic effects to bees such as hive/brood studies or other field studies. A honey bee brood study was not available. However, a higher tier study that assessed colony survival (including brood) was evaluated. Stoner and Wilson (1985) studied folpet and a combination of folpet and other compounds that were fed or exposed to honey bee field colonies to determine long-term toxic effects. Results indicate that folpet had no significant long term effect. Moreover, folpet is known to bear the same mechanism of action as the fungicide captan because they have very similar chemical structures (Bernard and Gordon, 2000). As such, a study on bee brood exposed to captan was considered (Everich et al. 2009). In this study, the effects of commercial applications of captan on honey bees was studied in California (5.0 kg a.i./ha during bloom). Hives were evaluated for hive health and brood development parameters for approximately 2 months after application. This study showed that the application of captan was not harmful to foraging honey bees or their brood. Based on lack of toxicity from acute laboratory exposures, evidence from available studies and considering the mode of action of folpet fungicide, chronic effects on pollinators such as bees are not expected. Results are summarized in Appendix X, Tables 4-6.

Birds and mammals

Standard exposure scenarios on vegetation and other food sources based on correlations in Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994) were used to determine the concentration of pesticide (EEC) on various food items (on a dry weight basis) in the diet of birds and small wild mammals, and are expressed as an estimated daily exposure (EDE). Exposure is dependent on the body weight of the organism and the amount and type of food consumed. In the screening level assessment a set of generic body weights was used for birds (20, 100, 1000 g) and small wild mammals (15, 35, 1000 g) to represent a range of bird and small wild mammal species. The screening level assessment uses relevant food categories for each size group consisting of 100% of a particular dietary item. These items include the most conservative residue values for plants, grains/seeds, insects, and fruits.

Birds can be exposed to folpet through the consumption of contaminated food (for example, seeds, insects, vegetation), as well as from drinking water and dermal contact. The current risk assessment considers only food sources. The avian and mammalian risk assessments are summarized in Appendix X, Tables 7 -17. The results show that there is apparent risk to both birds and mammals for most of the feeding guilds and size classes, as RQs generally exceed the LOC for both on and off field as well as maximum and minimum residue exposure scenarios.

While potential risks have been identified based on the determination of risk quotients, they are in large part driven by the following assumptions (i) the maximum application rates as well as the maximum number of applications per season will be used, (ii) adverse effects will occur at the exposure concentrations identified by toxicity tests, (iii) all six applications permitted per season are made successively without changing the class of fungicide, thus reducing the time interval between treatments, (iv) first treatments are done early during the growing season, and (v) farm activities, including noise, have no repelling effect on birds and mammals, especially during spray treatment

The parameters used to assess the risk of folpet to birds and mammals at the screening and refined risk assessment levels are presented in Appendix X, Table 7.

At the screening level for groundboom application (tomatoes and cucurbits), the rate, number of applications and application interval used in the risk assessment (6 × 4.0 kg a.i./ha, interval of 7 days between folpet applications) represents a conservative exposure scenario. A more likely application scenario involves alternating between folpet and other fungicides that have different modes of action for resistance management. An interval of 14 days between folpet applications was used in the refined risk assessment.

At the screening level for airblast applications (apple orchards), the rate, number of applications and application interval in apple orchards (6 × 2.4 kg a.i./ha, interval of 10 days between folpet applications) represents a conservative exposure scenario. For resistance management purposes, 6 applications of folpet per year is considered unlikely. A more likely interval of 20 days between folpet applications was used in the refined risk assessment.

In addition, although folpet labels allow early season spray on crops, there are several fungicides that are more effective than folpet for early season treatment. The best timing for maximum efficiency of folpet starts at flowering and continues until harvest, especially for fruit protection. This period would begin at full canopy development, which would be in June in Southern Canada. Nesting birds are less likely to be exposed to folpet as spraying begins later in the season, and row crops (such as tomato and cucurbits) and apple orchard are not considered good nesting sites as there are high levels of farm activities during spring and summer seasons, restricting nesting to off-field areas. Small mammals could be exposed to direct spray treatment in field. Due to sprayer movement, tractor motion and noise during spray activities, medium and large mammals are likely to be repelled during farm operations.

For the screening level risk assessment, a conservative foliar DT_{50} of 8.9 days was used. Fate studies (hydrolysis and biotransformation in water) suggest an increase in the rate of degradation of folpet on leaves can be considered due to alkaline dew on leaf surface. A faster degradation rate (3 days) that was proposed by the USEPA was used in the refined risk assessment for birds and mammals.

Available acute toxicity endpoint for birds and mammals are greater than the highest dose tested. As a result, when calculated RQs based on these values indicate exceedances of the LOCs, this is based on the conservative assumption that the relevant effects endpoints are equal to the highest concentration tested. Reported acute RQs are best interpreted as less than values. Bird and mammal acute risks from actual use of folpet in the field are not expected to be as high as the calculated RQs would suggest and acute risk to birds and mammals is not expected to be of concern.

The reproductive RQs also exceeded the level of concern for both birds and mammals at the screening level. The refined risk assessment for birds indicates that only small insectivores may be at risk from groundboom application (mean nomogram residues RQ = 1.4 - 3.0, Appendix X, Table 9) and airblast applications (mean nomogram residues RQ = <1.0 - 1.7, Appendix X, Table 12). Appendix X, Tables 10 and 13 show the percentage contamination (1/RQ × 100) of bird diet required to reach the LOC. A diet based on the high percentage of contaminated food (for example, insects) is considered unrealistic as flying contaminated insects can leave the treated fields and non-contaminated insects can colonize recently sprayed fields. In addition birds and mammals may feed outside of treated fields. These factors combined may contribute to significantly reducing bird and mammal exposure to contaminated food. For birds, there were no adverse reproductive effects in laboratory studies up to the highest test concentration, (NOEL = 78.3 mg a.i./kg bw/d). Because of this, the reproductive risk for birds is considered to be low.

The refined risk assessment for mammals was based on an environmentally relevant effect (LOEL of 70 mg a.i./kg bw/d) and levels of concern were marginally exceeded (mean nomogram residues RQ = <1.0 – 1.9, Appendix X, Tables 15 and 17). Given that the reproductive endpoint is based on an environmentally relevant effect, the exceedances of the LOC observed for mammals are of potential concern, even though the on-field RQ values for mean nomogram residues are not large in the refined risk assessment. As a result, a hazard label statement is proposed.

Non-target Terrestrial Plants

The risk to non-target plants was assessed using the EFSA (2006) endpoint of EC_{25} >6400 g a.i./ha and EECs of 9157,8 g a.i./ha for groundboom application and 4394.9 g a.i./ha for airblast. For both scenarios, the level of concern was not exceeded based on off-field spray drift and therefore buffer zones are not required to protect non-target terrestrial plants.

4.2.2 Risks to Aquatic Organisms

Available toxicity data on folpet consisted of 16 freshwater species (two invertebrates, nine fish, four algae and one vascular plant) and three estuarine/marine species (one mollusc, one fish and one alga). A summary of aquatic toxicity data for folpet is presented in Appendix X, Table 3. Chronic toxicity data were not available for estuarine/marine invertebrates or fish. For the assessment of risk, toxicity endpoints chosen from the most sensitive taxonomic groups were used as surrogates for the wide range of species that can be potentially exposed following treatment with folpet. For the screening level risk assessment, expected environmental concentrations were determined based on a direct overspray of an 80 cm deep body of water for fish and invertebrate assessments and a 15 cm depth was used to estimate risk to amphibians. Folpet is not expected to be persistent in aquatic systems near treated areas given that it has a half-life of less than 1 day, however, based on the high frequency and volume of use on some crops, repeated exposure of non-target aquatic organisms may result in chronic exposure.

At the screening level, risk quotients for freshwater invertebrates, fish and amphibians exceeded the acute and chronic LOCs by a wide margin for direct application and for spray drift from both groundboom application to cucurbits and tomatoes (Appendix X, Table 18) and airblast application to apples (Appendix X, Table 19).

Refined Aquatic Risk Assessment

The risk to aquatic organisms due to spray drift can be refined by taking into consideration the percent deposition from different application methods (ground boom (6% drift), aerial application (23% drift) and orchard airblast (59-74% drift) based on a spray quality of ASAE medium) into an adjacent water body 1 m downwind from the site of application. For the refined assessment, the water body consists of a 1 ha wetland with an average depth of 80 cm and a drainage area of 10 ha. A 15 cm deep seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level.

Appendix X, Tables 20 and 21 summarize the refined risk to aquatic organisms resulting from exposure to spray drift for ground boom and airblast applications of folpet. The LOC is exceeded for freshwater and marine/estuarine organisms, with RQ values as high as 148. Mitigation in the form of spray buffer zones will be required to mitigate these risks.

The risk to aquatic organisms due to runoff can be refined using EECs generated from water modeling. The PRZM/EXAMS models simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the refined assessment, the water body consists of a 1 ha wetland with an average depth of 80 cm and a drainage area of 10 ha. A 15 cm deep seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level. The EECs generated represent concentrations of pesticide resulting from runoff only; potential deposition from spray drift is not included. See Appendix XI for more details on aquatic ecoscenario runoff modelling.

Using modelled EEC values, the level of concern was exceeded for both the groundboom (RQ <130) and airblast (RQ <1.4) scenarios (Appendix X, Tables 22). The highest RQ (130) was for acute risk to groundboom application for amphibians. The next highest RQ was 24.7 for acute risk to rainbow trout from groundboom application. For amphibians, the folpet toxicity data for freshwater fish was used as a surrogate in the risk assessment (i.e. 1/10 LC_{50} of 1.5 µg a.i./L for rainbow trout, and chronic NOEC 8.81 µg a.i./L for fathead minnow). Because of the limited persistence of folpet in the aquatic environment, elevated risks are not expected for prolonged periods of time. Advisory statements to inform users of conditions that may favour run-off are required. In addition, the use of vegetated filter strips, which could reduce soil transport in runoff to water bodies, is also recommended.

4.3 Incident Reports

As of 17 January 2017, there was one environmental Canadian incident reports for folpet, involving crop damage. However application of herbicides in conjunction with folpet was reported. Thus, the association of folpet causing the crop damage cannot be established. Therefore, no additional mitigation for folpet is required.

5.0 Value

5.1 Value of Folpet

Folpet is a fungicide used to protect the plasticizer in vinyl plastics from degradation due to mildew. Folpet is incorporated into gaskets for homes and cars, outdoor upholstery (seats for boats), and coatings applied to exterior vinyl products such as tarps, tents, awnings and roof membranes. Interior uses are limited to gaskets for windows and refrigerators, and vinyl floor backing. Alternatives to folpet used as a material preservative in plastics are available, and include copper (present as cuprous oxide), 4,5-dichloro-2-n-octyl-3(2h)-isothiazolone, 2-n-octyl-4-isothiazolin-3-one, 10,10'-oxybis(phenoxarsine), 3-(trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride and zinc borate.

Folpet is registered for the management of apple scab in apples. Apple scab is an economically important disease to be managed in Canada, and has been identified as having widespread, yearly occurrence with medium to high pest pressure in all apple producing regions of Canada. This disease impacts the quality and grading of the crop, reducing its value if infection on fruit is found. Under heavy disease pressures, season-long management is required, and as such folpet plays an important role for its efficacy as well as for resistance management as a rotational and tank mix partner for other single site active ingredients. Because it is a broad spectrum fungicide, other diseases are also controlled when apple scab is managed.

Folpet is registered for the management of downy mildew on grapes. Downy mildew on grapes is widespread with yearly occurrences and high disease pressure in Ontario, Quebec and Nova Scotia. Folpet is very effective for the management of downy mildew, and is important as a rotational fungicide for this disease.

Folpet controls several economically important diseases such as Botrytis and common leaf spot in strawberries. Botrytis grey mould has been identified as having widespread, yearly occurrence with high pest pressure in all strawberry producing regions of Canada. Folpet provides good control of Botrytis grey mould, and as several fungicide applications are required to manage this disease. As a multi-site fungicide, folpet plays an integral role in resistance management.

Ornamental production is a high-value industry in Canada, and folpet is a valuable tool for the management of several foliar diseases. Ornamental horticulture represents the largest segment of horticultural production, representing over 40% of horticulture's $5.4 billion in annual farm gate receipts. Maintaining high quality plants with good visual appeal is desirable in this sector, and folpet is valuable both as a broad-spectrum fungicide and as a rotational tool for resistance management.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03, the assessment of folpet and its transformation products against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

Folpet and its transformation products (phthalimide, phthalamic acid and phthalic acid) do not meet Track 1 criteria, and do not form any transformation products which meet the Track 1 criteria. See Appendix XII, Table 1for comparison with Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the *Canada Gazette.* The list is used as described in the PMRA Notice of Intent NOI2005-01[3] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[4] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Folpet does not contain any contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

[3] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[4] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

List of Abbreviations

↑	increased
↓	decreased
♀	females
♂	males
µg	microgram(s)
µM	micromolar
A	applicator
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apps	applications
AR	androgen receptor
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-Entry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	area under the curve
BCF	bioconcentration factor
BRDU	bromodeoxyuridine
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CDK	cyclin dependent kinase
CEPA	*Canadian Environmental Protection Act*
CFIA	Canadian Food Inspection Agency
Cl	chloride
cm	centimetre(s)
CMA	Chemical Manufacturer's Association
Cmax	peak plasma concentration
CR	chemical resistant
d	day(s)
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
DFR	dislodgeable foliar residue
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 90% (the dose required to observe a 90% decline in concentration
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration
EbC_{50}	EC_{50} in terms of algal biomass
ECD	electron capture detection

EDE	estimated daily exposure
EEC	estimated environmental concentration
ER_{50}	effective rate for 50% of the population
ERα	estrogen receptor α
ERβ	estrogen receptor β
ErC_{50}	EC_{50} in terms of reduction of growth rate
F_0	parental generation
F_1	first filial generation
F_2	second generation
Fc	food consumption
FRAC	Fungicide Resistance Action Committee
g	gram(s)
GC	gas chromatography
GD	gestation day
GI	gastrointestinal
GLC	gas liquid chromatography
GSH	glutathione
GST	glutathione S-transferase
GUS	groundwater ubiquity score
ha	hectare(s)
HPLC	high performance liquid chromatography
hr	hour(s)
IC_{50}	concentration needed to inhibit a biological/biochemical function by half
IT	intermediate-term
K_d	soil-water partition coefficient
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	n-octanol/water partition coefficient at 25°C
L	litre(s)
LC_{50}	median lethal concentration
LD_{25}	lethal does 25%
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
ln	logarithm
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest adverse effect level
LOD	limit of detection
LOEC	low observed effect concentration
LOEL	lowest observable effect level
LR_{50}	lethal rate 50%
LT	long-term
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
M/L/A	mixer/loader/applicator
MoA	mode of action
MOE	margin of exposure

mPa	millipascal(s)
MRID	USEPA's master record identifier number
MRL	maximum residue limit
MSD	mass selective detection
N/A	not applicable
NCHS	National Center for Health Statistics
NHANES/WWEIA	National Health and Nutrition Examination Survey, What We Eat in America
NIOSH	National Institute for Occupation Safety and Health
nm	nanometre(s)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OECD	Organization for Economic Cooperation and Development
OM	organic matter content
Pa	Pascal
PA1	phthalic acid
PAM	phthalamic acid
PBI	plant back interval
PCNA	proliferating cell nuclear antigen
PCT	percent crop treated
PDP	Pesticide Data Program
PHED	Pesticide Handlers Exposure Database
pH	numeric scale used to specify the acidity or alkalinity of a solution
PI	phthalimide
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
PWC	Pesticide in Water Calculator
RAC	raw agricultural commodities
REI	restricted entry interval
rel	relative
Resp	respirator
RfD	reference dose
RQ	risk quotient
RTI	re-treatment interval
SOP	standard operating procedures
ST	short-term
$t_{½}$	half-life
T4	thyroxine
TC	transfer coefficient
TCM	trichloromethyl
TGAI	technical grade active ingredient
THPI	tetrahydrophthalimide
Tmax	time when maximum plasma concentration is reached

TMT	trichloromethyl
TSH	thyroid stimulating hormone
USEPA	United States Environmental Protection Agency
UV	ultra-violet
VSM	ventral seromucuous glands
wc	water consumption
WDG	water dispersible granule
WG	wettable granule
WP	wettable powder
WSP	water soluble package
wt	weight
w/w	weight per weight dilution

Appendix I Registered Folpet Products[5]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (%)
15605	Commercial	TROY CHEMICAL CORPORATION	Fungitrol II Powder	Soluble powder	Folpet = 95.9
15654	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	Folpan 50WP (Folpet) Fungicide	Wettable powder	Folpet = 50 a.e.[6]
27733	Commercial	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	Folpan 80 WDG	Water dispersible granules	Folpet = 80
32928	Commercial	TROY CHEMICAL CORPORATION	Fungitrol 11E	Soluble powder	Folpet = 95.9%
22040	Technical	ADAMA AGRICULTURAL SOLUTIONS CANADA LTD.	Folpan Folpet Technical	Solid	Folpet = 95.9

5 As of December 15, 2017, excluding discontinued products or products with a submission for discontinuation.

6 Acid equivalents

Appendix II Registered Uses of Folpet in Canada[1]

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (a.i. / ha)		Maximum Number of Application per year	Minimum Number of Days Between Applications
				Maximum Single	Maximum Cumulative		
Use Site Category 18: Materials							
Fungicidal additive for vinyl plastics (not to be used in food packaging materials or in areas where food is processed, handled or stored)	Mildew	Soluble powder	Operator exposure takes place in the production facility. Applicator exposure results from application by the homeowner	0.24 – 0.959% w/w based on the weight of plasticizer	Not applicable	Not applicable	Not applicable
Use Site Category 6: Greenhouse Non-Food Crops							
Poinsettias (Greenhouse)	Pythium root rot	Wettable powder	Ground - foliar	1.12 kg a.e./ 1000 L of water (1.12 kg a.e./ha calculated using 1000 L/ha spray volume)	2.24 kg a.e./ha per year	2	10
		Water dispersible granules		1.12 kg a.i./ 1000 L of water (1.12 kg a.i./ha calculated using 1000 L/ha spray volume)	2.24 kg a.i./ha per year		
Use Site Category 6: Greenhouse Non-Food Crops and Use Site Category 27: Ornamentals Outdoors							
Roses	Mildew	Wettable powder	Ground - foliar	1.0 kg / 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6*	7
Carnations	Blight (Alternaria leaf spot)	Wettable powder		1.0 kg / 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6*	14
		Water dispersible granules		1.0 kg / 1000 L of water (1.0 kg a.i./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.i./ ha per year		
Azaleas	Stem rot of cuttings	Wettable powder	Soak cuttings for 15 to 30 minutes before planting	1.5 kg a.e./ 1000 L of water	1.5 kg a.e./ 1000 L of water per year	1	Not applicable
		Water dispersible granules		1.52 kg a.i./ 1000 L of water	1.52 kg a.i./ 1000 L of water per year		

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (a.i. / ha)		Maximum Number of Application per year	Minimum Number of Days Between Applications
				Maximum Single	Maximum Cumulative		
Marigolds, zinnias	Alternaria leaf spot	Wettable powder	Ground - foliar	1.0 kg a.e./ 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6**	3
		Water dispersible granules		1.0 kg a.i./ 1000 L of water (1.0 kg a.i./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.i./ ha per year	6	
Asters, China asters, phloxes	Powdery mildew	Wettable powder		1.0 kg a.e. / 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6*	7
Chrysanthemums	Powdery mildew, septoria leaf spot	Wettable powder		1.0 kg a.e./ 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6*	7
	Septoria leaf spot	Water dispersible granules		1.0 kg a.i. / 1000 L of water (1.0 kg a.i./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.i./ ha per year	6	
Iris	Didymellina leaf spot	Wettable powder		1.0 kg a.e. / 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	4.0 kg a.e./ ha per year	4**	7
		Water dispersible granules		1.0 kg a.i. / 1000 L of water (1.0 kg a.i./ ha calculated using 1000 L/ha spray volume)	4.0 kg a.i./ ha per year	4	
Snapdragon	Anthracnose, powdery mildew	Wettable powder		1.0 kg a.e./ 1000 L of water (1.0 kg a.e./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.e./ ha per year	6*	3

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (a.i. / ha)		Maximum Number of Application per year	Minimum Number of Days Between Applications
				Maximum Single	Maximum Cumulative		
	Anthracnose	Water dispersible granules		1.0 kg a.i. / 1000 L of water (1.0 kg a.i./ ha calculated using 1000 L/ha spray volume)	6.0 kg a.i./ ha per year	6	
Use Site Category 13: Terrestrial Feed Crops and Use Site Category 14: Terrestrial Food Crops							
Apples	Alternaria leaf spot, black rot, Brooks spot, fly-speck, scab, sooty blotch	Wettable powder	Ground - foliar	1.0 kg a.e./ 1000 L of water (2.0 kg a.e./ha calculated using registrant recommended spray volume of 2000 L/ha)	12.0 kg a.e./ha per year	6**	10††
		Water dispersible granules		3.0 kg a.i./ha	14.4 kg a.i./ha maximum allowable per year	6	10††
Use Site Category 14: Terrestrial Food Crops and Use Site Category 27: Ornamentals Outdoors							
Crabapples	Alternaria leaf spot, black rot, Brooks spot, fly-speck, scab, sooty blotch	Wettable powder	Ground - foliar	1.0 kg a.e./ 1000 L of water (2.0 kg a.e./ha calculated using registrant recommended spray volume of 2000 L/ha)	8.0 kg a.e./ha per year	4**	10††
		Water dispersible granules		3.0 kg a.i./ha	9.6 kg a.i./ha maximum allowable per year	4†	10††
Use Site Category 14: Terrestrial Food Crops							
Grapes	Dead arm	Wettable powder	Ground - foliar	1.0 kg a.e. / 1000 L of water (1.0 kg a.e./ ha calculated using a spray volume of 1000L/ha - extrapolated from information on other product)	6.0 kg a.e./ ha per year	6 Based on rotation of products, the application interval, and application to target one of the pathogens will prevent the onset of other diseases or simultaneously control other listed pathogens.	10††
		Water dispersible granules		1.0 kg a.i./ ha	6.0 kg a.i./ ha per year		
	Black rot	Wettable powder		1.0 kg / 1000 L of water (1.0 kg a.e./ ha calculated	6.0 kg a.e./ ha per year		

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (a.i. / ha)		Maximum Number of Application per year	Minimum Number of Days Between Applications
				Maximum Single	Maximum Cumulative		
				using a spray volume of 1000L/ha - extrapolated from information on other product)			
		Water dispersible granules		1.0 kg a.i./ ha	6.0 kg a.i./ ha per year		
	Downy mildew	Wettable powder		1.0 kg a.e./ 1000 L of water (1.0 kg a.e./ ha calculated using a spray volume of 1000L/ha - extrapolated from information on other product)	6.0 kg a.e./ ha per year		
		Water dispersible granules		1.0 kg a.i./ ha	6.0 kg a.i./ ha per year		
	Powdery mildew	Wettable powder		1.0 kg / 1000 L of water (1.0 kg a.e./ ha calculated using a spray volume of 1000L/ha - extrapolated from information on other product)	6.0 kg a.e./ ha per year		14
		Water dispersible granules		1.0 kg a.i./ ha	6.0 kg a.i./ ha per year		10††
Strawberries	Grey mould, fruit rot, leaf spot	Wettable powder	Ground -foliar	1.0 kg a.e./ 1000 L of water (2.0 kg a.e./ha calculated using registrant recommended spray volume of 2000 L/ha)	12 kg a.e. / ha per year	6**	7
		Water dispersible granules		2.0 kg a.i./ha	12 kg a.i. / ha per year	6	
Cranberries	Fruit rot	Wettable powder	Ground -foliar	5 kg a.e./ ha	10 kg a.e./ha per year	2	10
		Water dispersible granules		2.6 kg a.i./ ha	5.2 kg a.i./ha per year		
Cucumbers, melons, pumpkins, squash	Anthracnose, downy mildew, powdery mildew	Wettable powder	Ground -foliar	2.0 kg a.e./1000 L of water (4.0 kg a.e./ha calculated	24 kg a.e./ha per year	6**	7

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (a.i. / ha)		Maximum Number of Application per year	Minimum Number of Days Between Applications
				Maximum Single	Maximum Cumulative		
				using 2000 L/ha spray volume)			
	Anthracnose, downy mildew	Water dispersible granules		4.0 kg a.i./ha	24 kg a.i./ha per year	6	
Tomatoes	Anthracnose	Wettable powder	Ground -foliar	2.0 kg a.e./1000 L of water (4.0 kg a.e./ha calculated using 2000 L/ha spray volume)	24 kg a.e./ha per year	6**	7
		Water dispersible granules		4.0 kg a.i./ha	24 kg a.i./ha per year	6	

[1]as of December 15, 2017

*Although not stated on the label, the number of applications was extrapolated from information on other ornamentals.

**Although not stated on the label, the number of applications was extrapolated from information on other products.

† Although not stated on the label, four applications were supported by the registrant

†† Although not stated on the label, the number of applications was extrapolated from registrant-provided information.

Appendix III Toxicological Information For Health Risk Assessment

Table 1 Toxicity Profile of Technical Folpet

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/ Animal/ PMRA Number	Study Results
Toxicokinetic/Metabolism Studies	
Rats – ^{14}C ring-labelled folpet by gavage – 14.6-16.4 mg/kg bw single dose (PMRA 1347685); 10 and 500 mg/kg bw single dose and 10 mg/kg bw/day 14-day repeated dose (PMRA 1347684)	**Distribution:** Radiolabel detected in all tissues shortly after acute or repeated dosing (2 hours). Highest concentrations detected in GI tract, kidneys and liver. Five days post-dosing with low or high levels of folpet, low levels of radiolabel only detected in GI tract. **Excretion:** With a single low dose, approximately 92% of the radiolabel was excreted via urine over 5 days with most excreted within 6 hours of dosing. Levels of urinary excretion were similar with a repeated low dose but occurred primarily during the first 24 hours. With a single high dose, 57% (♂) or 61% (♀) of the radiolabel was excreted via urine over 5 days with most excreted 6-24 hours post-dosing. The remainder was excreted via feces; no radioactivity was detected in air in a pilot study. **Metabolism:** Unconjugated phthalamic acid in the 0-24 hour urine accounted for 80-85% of the radiolabelled dose at 10 mg/kg bw (single or repeated-dose) and 45% of the single radiolabelled dose at 500 mg/kg bw. Low levels (<2% of administered dose) of unchanged folpet, phthalimide, phthalic anhydride and phthalamic acid were present in the feces following a single or repeated low dose. With a single high dose, level of unchanged folpet ↑ accounting for 15-20% of the administered dose at 0-24 hours and 24-48 hours. No significant sex differences were noted in the toxicokinetic or metabolism profile.
Rats – ^{14}C phthalimide-labelled folpet by gavage - 75 mg/kg bw single dose and 7-day repeated dose (PMRA 1347681)	**Absorption:** Peak blood levels occurred at 30 minutes and 45 minutes following repeat and acute dosing, respectively. **Distribution:** Radiolabel detected in all tissues shortly after acute or repeated dosing (30 min). **Excretion:** Following repeated dosing, 64% and 17% of administered radiolabel was excreted at 24 hours in urine and feces, respectively. Seven days later, excreted levels were 68-71% in the urine and 26% in the feces.
Rats and Mice– 0, 50 or 5000 ppm folpet in diet for 21 days (0, 3, 300 mg/kg bw/day for rats, 0, 70, 700 mg/kg bw/day for mice) followed by an acute gavage dose of ^{14}C TMT-labelled folpet (10-20% of dietary dose)(PMRA 1347682)	**Absorption:** Readily absorbed in both species. **Distribution:** At 2 hours post-dosing, highest levels of radioactivity in the stomach contents of both low and high dose rats and in the cecum content of low and high dose mice. In rats, higher levels of radioactivity were noted in stomach walls compared to other areas of GI tract at the low dose but more evenly distributed in walls of stomach, duodenum, jejunum and ileum at the high dose. In mice, levels of radioactivity were evenly distributed in the walls of stomach, duodenum, jejunum and ileum at the low dose but higher in the walls of jejunum, ileum and cecum at the high dose. Radiolabel in the stomach, jejunum and ileum decreased at 4 and 6 hours post-dosing in rats but increased in the cecum. A greater proportion of covalently bound radiolabel was identified in the gastrointestinal tissues of mice when compared to rats. Gastrointestinal transit time was less in mice than rats (2 hours in mice, 4-6 hours in rats). **Excretion:** Rapid excretion in both species. Similar pattern between low and high dose rats: 44-53% urine, 33-41% expired air, 11-14% feces, 2% carcass. Similar pattern between low and high dose mice: 46-53% urine, 24-28% expired air, 13-17% feces, 1% carcass.

Study Type/ Animal/ PMRA Number	Study Results
Metabolism: Primarily disulfonic acid with thiazolidine and the glutathione conjugate of thiophosgene were identified in the duodenum of rats at 2, 4 and 6 hours following dosing. Similar results were observed in mice. In the urine, thiazolidine-2-thione-4-carboxylic acid (TTCA) and disulfonic acid metabolites predominated with the former increased in the high-dose mice and the latter increased in the high-dose rats, suggesting an increased reliance on GSH for the removal of thiophosgene in mice. The report indicates that there was also some evidence of the presence of unmetabolised folpet in the urine of rats but levels were not provided as it was not considered a major component. **Additional Findings:** 1. Slight depletion of hepatic and gastrointestinal GSH occurred in both species following acute and repeated exposure. Following depletion, a rebound effect was observed with small intestine GSH levels ↑ above control levels 6 hours following treatment with the effect more pronounced in the mice compared to rats. 2. A ↓ in malondialdehyde (as a marker for lipid peroxidation) was observed in the stomach, duodenum and jejunum (and also the ileum at high doses) of both rats and mice. Effects were slightly more pronounced in the rats. These results are consistent with an↑ in peroxide scavenging ability due to↑ GSH and GST activity. 3. Glutathione selenium-dependant peroxidase activity was ↓ slightly in the stomach of rats, but not mice. 4. GST activity was ↑ in both species at the highest dose. In both species, GST was ↑ in the stomach through to the ileum, with the largest ↑ occurring in the duodenum and jejunum. The↑ in duodenal GST activity was greater in rats than mice. 5. At high doses (but not low doses), liver GSH was depleted in mice, but not rats. GSH was ↑ at the high dose in the duodenum, jejunum and ileum of both rats and mice with the ↑ being more pronounced in the proximal regions of the small intestine of both species. A sub experiment with a single gavage dose indicated GSH depletion in the GI tract of mice treated with a low dose and in rats at a 10-fold higher dose. 6. At doses which induced GSH depletion, ↓ cytochrome P450 and aniline hydroxylase activity were observed in the livers of mice, but not rats. However, the assay was deemed to be insensitive and results may have often been below the level of accurate measurement. 7. 6. The pH of gastric and small intestinal lumen contents declined with high doses, with mouse duodenal and jejunal pH being slightly more affected (↓) than that of the rats (only the pH of rat jejunum was affected). There was no effect on pH in either species following low dose exposure. 8. At 1, 3 and 6 hours after the last dose, there were no differences in thymidine incorporation in rats or mice in the stomach, duodenum, jejunum and ileum.
Metabolic Pathway: Hydrolysis of folpet, which is expected to occur primarily in the GI tract, yields phthalimide and the highly reactive thiophosgene. Further metabolism of phthalimide results primarily in phthalamic acid. Other minor phthalimide metabolites include phthalic acid, 3-OH phthalimide and 5-OH phthalimide. Metabolism of the thiophosgene metabolite is not believed to be quantifiable due to the rapidity of breakdown. Thiophosgene either hydrolyzes to form carbon dioxide or is conjugated by thiols to form thiazolidine-2-thione-4-carboxylic acid as well as disulfonic acids.
Rats – single dose of 10 mg/kg bw of Folpan 80WG via intratracheal instillation or intraperitoneal injection (PMRA 2564600) **Absorption:** Plasma Tmax comparable (around 0.25 hours) for degradation products phthalimide and phthalamic acid with both routes indicating rapid degradation. Comparable elimination $t_{½}$ between routes for phthalimide (2.2 – 2.6 hours) and phthalamic acid (4.6 – 5.0 hours). Cmax for intratracheal route was higher than intraperitoneal route (4.6 and 3.2 fold higher for phthalimide and phthalamic acid respectively). AUC for intratracheal route was higher than intraperitoneal route (3.2 and 2.0 fold higher for phthalimide and phthalamic acid respectively).
In vitro ^{14}C-labelled folpet in human blood (PMRA 1347656) The t½ of folpet in human blood was 4.9 seconds; virtually all degraded to phthalimide.

Study Type/ Animal/ PMRA Number	Study Results
Toxicokinetics –humans received oral dose of 1 mg/kg bw (PMRA 2564599, 2408565) Plasma levels of phthalimide ↑ progressively with peak levels observed at 6 hours post-dosing; monophasic elimination from plasma with elimination $t_{½}$ of 31.5 hours. Phthalimide had a relatively small volume of distribution (4.3 L). Peak levels of phthalimide and phthalic acid were seen in urine between 3-12 hours post-dosing with elimination $t_{½}$ of 27.3 and 27.6 hours, respectively. Cumulative excretion of phthalic acid and phthalimide in urine over 96 hrs was 25% and 0.02% respectively, of ingested dose.	
Toxicokinetics – humans exposed to 10 mg/kg bw folpet on the skin for 24 hours (PMRA 2408554, 2408565) Plasma levels of phthalimide ↑ progressively with peak levels observed at 10 hours post-dosing; monophasic elimination from plasma with elimination $t_{½}$ of 29.7 hours for phthalimide . Phthalimide had a relatively small volume of distribution (6 L). Peak levels of phthalic acid and phthalimide were seen in urine at 12 hours post-dosing with elimination $t_{½}$ of 29.6 and 28.8 hours respectively. Cumulative excretion of phthalic acid and phthalimide in urine over 96 hours was 1.8% and 0.002% of dermally-applied dose, respectively.	
Acute Toxicity Studies	
Acute Oral Toxicity Sprague-Dawley Rats PMRA 1347614	LD_{50} > 5000 mg/kg bw Effects noted at very high doses included: diarrhea, pale feces, ↓motor activity, ↓fc, dyspnea, eye and nasal discharge, weakness. **Low Toxicity.**
Acute Oral Toxicity Sherman Rats PMRA 2565011	LD_{50} (♂/♀ adult, ♀weanling) >5000 mg/kg bw **Low Toxicity.**
Acute Oral Toxicity Sprague Dawley Rats PMRA 1347613	LD_{50} (♂/♀) > 2000 mg/kg bw No treatment-related effects noted. **Low Toxicity.**
Acute Oral Toxicity CF1 Mice PMRA 1347611	LD_{50}> 2000 mg/kg bw Effects noted included lethargy, ↓reflex activity, tremors, ↓respiratory rates, staggering motion, convulsions. Necropsy findings observed in the GI tract. **Low Toxicity.**
Acute Dermal Toxicity NZW Rabbits PMRA 1199643	LD_{50}> 2000 mg/kg bw Effects noted included mild diffuse keratosis and dermatitis. **Low Toxicity.**
Acute Dermal Toxicity Sprague Dawley Rats PMRA 1347616	LD_{50} > 2000 mg/kg bw No signs of systemic toxicity or irritation. **Low toxicity.**
Acute Inhalation Toxicity (whole-body) Rats PMRA 1347619	LC_{50}: ♂:0.34 mg/L, ♀:1.00 mg/L Clinical signs during exposure included salivation, labored breathing, gasping. Clinical signs post-dosing included eye, nasal and anogenital discharge, corneal opacity, abnormal respiration, ↓motor activity, reduced feces, diarrhea, unkempt appearance, ↓bw. Histopathological lesions in lung, trachea and liver. **Moderately Toxic.**
Acute Inhalation Toxicity Rats PMRA 2063223	LC_{50}: ♂:0.39 mg/L, ♀:0.43 mg/L **Moderately toxic.**
Acute Inhalation Toxicity (whole-body) Sprague Dawley Rats PMRA 1246321	LC_{50}:♂:1.38 mg/L, ♀:1.30 mg/L Clinical signs during exposure included gasping, lacrimation, nasal discharge, dyspnea, salivation. These signs were also seen post-dosing in addition to abnormal respiration, piloerection, ↓motor activity, ↓bw. Necropsy findings observed in the GI tract, trachea, nasal passages and lungs. **Slightly toxic.**

Study Type/ Animal/ PMRA Number	Study Results
Acute Inhalation Toxicity (nose-only) Sprague Dawley Rats PMRA 1347618	LC_{50} (♂/♀) =1.89 mg/L (micronized form) Clinical signs during exposure included abnormal respiration and gasping. Clinical signs post-dosing included the above plus vocalization, underactivity, altered posture, partially closed eyes, nasal staining, piloerection, ↓bw. Necropsy findings observed in trachea and lungs. **Slightly toxic.**
Eye Irritation NZW Rabbits PMRA 1199644, 1246322, 1347621	**Mildly to Severely Irritating** (3 studies).
Dermal Irritation NZW Rabbits PMRA 1347624, 1246324, 1347623, 1671841	**Non-Irritating** (4 studies).
Dermal Sensitization Guinea Pigs PMRA 1199645, 1347625	**Skin Sensitizer** (Buehler and Maximization methods).
Dermal Sensitization Guinea Pigs PMRA 1347626	**Skin Sensitizer** (Maximization method)(micronized form).
Short-Term Toxicity Studies	
4-week Toxicity (diet) B6C3F1 Mice PMRA 1347636	≥ 874/1021 mg/kg bw/day: ↓fc, ↓bw, ↓bwg. 1921 mg/kg bw/day:↓rel. spleen wt (♀). **Study considered supplemental** (range-finding study).
21-Day Toxicity (diet) Sprague Dawley Rats PMRA 1347634	≥ 250 mg/kg bw/day: ↓fc (♀). 600 mg/kg bw/day: ↓bw; piloerection, scruffy underweight appearance, ↓fc (♂). **Study considered supplemental** (range-finding study).
90-Day Toxicity (diet) F334 Rats PMRA 1347630	LOAEL = 100 mg/kg bw/day ≥ 100 mg/kg bw/day: ↓ALP, ↓ALT, irritation of proximal GI tract, hyperkeratosis of non-glandular gastric mucosa; ↓LDH, ↓AST (♂); ↓BUN, slight acanthosis of stomach (♀). ≥ 200 mg/kg bw/day: ↑BUN, ↑Cl, ↓bw, ↓fc, ↓total serum proteins (♂); ↓albumin (♀). 400 mg/kg bw/day: ↓bw, ↓fc, ↓AST, ↓total protein (♀).
90-Day Toxicity (diet) Sprague Dawley Rats PMRA 1347628, 1347629	610/720 mg/kg bw/day: ↓bwg, ↓serum protein, ↓rel. brain wt., ↓rel. kidney wt., irritation of the stomach (including: acanthosis, hyperkeratosis, submucosal edema, pleocellular inflammatory infiltrate, focal erosion/ulceration). Stomach effects were reversible following two-week recovery period. **Study considered supplemental** (lack of dietary analysis, low animal numbers, limited endpoints, histopathological analysis limited to two highest dose groups).
4-Week Toxicity (capsule) Beagle Dogs PMRA 1347635	≥ 20 mg/kg bw/day: emesis during first 18 days of dosing, ↓bwg, ↓fc. ≥ 60 mg/kg bw/day: weight loss. ≥ 180 mg/kg bw/day: slight ↓BUN (♂). 540 mg/kg bw/day: slight ↓cholesterol, total protein, albumin, albumin/globulin ratio and calcium; slight ↑Cl and gamma-glutamyl transpeptidase, ↓ALP (♂). **Study considered supplemental** (range-finding, low animal numbers).
90-Day Toxicity (capsule) Beagle Dogs PMRA 1347631	LOAEL = 790 mg/kg bw/day ≥ 790 mg/kg bw/day: vomiting, diarrhea, ↓fc, ↓brain wt., ↓liver wt., ↓kidney wt., ↓spleen wt., atrophy/depletion/fibrosis of the lymphatic and hematopoetic system, thyroid degeneration, muscular dystrophy; ↓testicular wt., gonadal degeneration

Study Type/ Animal/ PMRA Number	Study Results
	with prostatic atrophy and fibrosis (♂). ≥ 1800 mg/kg bw/day: poor condition, abdominal distention, excessive salivation, ↓bwg; ↓testicular size (♂). 4000 mg/kg bw/day: death (all ♂, 1♀). There were no treatment-related effects on neurology or ophthalmoscopy.
52-Week Toxicity (capsule) Beagle Dogs PMRA 1347632	NOAEL = 10 mg/kg bw/day ≥ 60 mg/kg bw/day: ↓bw, ↓bwg, ↓fc; ↓cholesterol, ↓total protein, ↓albumin, ↓globulin (♂). 120 mg/kg bw/day: ↓cholesterol, ↓total protein, ↓albumin, ↓globulin (♀).
52-Week Toxicity (capsule) Beagle Dogs PMRA 1193259	LOAEL = 325 mg/kg bw/day ≥ 325 mg/kg bw/day: vomiting (≥ week1), diarrhea (≥ week2-3), excess salivation (≥ week2-3), mild (typically transient) deterioration of physical condition, ↑rel.adrenal wt.; ↓urea (♂); ↓bwg (♀). ≥ 650 mg/kg bw/day: deterioration of physical condition, ↓bw (weeks 7-53), ↓rel. liver wt.; ↓bwg, ↓cholesterol, ↓glucose (♂); ↓calcium (♀). 1300 mg/kg bw/day: ↓fc, ↓bw; degeneration of the germinal epithelium (2/5), no spermatozoa in epididymal ducts (2/5), moderate glandular atrophy of the prostate, ↓abs. testes wt. (♂); ↑Cl, ↑abs. liver wt., ↑abs. thyroid wt. (♀).
28-Day Dermal Toxicity Sprague Dawley Rats PMRA 1347637	≥1 mg/kg bw/day: dermal redness, dose-related ↑ irritation, acanthosis; swelling, dry/flaky skin, scabs, escharotic exudate, hyperkeratosis , ↓bw, ↓bwg (♂). ≥ 10 mg/kg bw/day: skin ulcer (♂); swelling, dry/flaky skin, escharotic exudate, hyperkeratosis (♀). 30 mg/kg bw/day: sloughing: scabs, skin ulcer, ↑segmented neutrophils, ↓lymphocytes, ↑potassium, ↑BUN, ↑creatinine, ↑BUN/creatinine (♀). Note: bw effects likely associated with irritation. Due to excessive irritation, the high dose was reduced from 30 to 20 mg/kg bw/day in ♂ on day 6; dosing was discontinued for these ♂ on day 13 and ♂ allowed to recover. A second ♂ group (also at 30 mg/kg bw/day) was terminated on day 15 due to severe irritation. **Study considered supplemental** (low animal numbers**).**
28-Day Inhalation Toxicity Sprague Dawley rats PMRA 2590411 (non-guideline)	LOAEC = 5.2 µg/L ≥ 5.2 µg/L: laryngeal mucosa lesions consisting of squamous/squamoid metaplasia of the epithelium in the ventral seromucous glands (VSM) and ventral diverticulum, VSM hyperplasia of the stratified squamous epithelium, VSM keratinization and mucosal fibrosis, ↑ incidence and/or severity of inflammatory cells; piloerection, ↑lung wt. (♂); ↓fecal volume, transient ↓bwg (♀). ≥ 26 µg/L: slight ↑incidence/severity of laryngeal lesions; ↓fecal volume, transient ↓bwg, single incidence each of metaplasia of the nasal mucosa (respiratory), degeneration/atrophy of the nasal mucosa (olfactory) and inflammatory cells of the trachea (♂); piloerection, ↓bwg, slight ↓fc, ↓thymus wt. (♀). 97 µg/L: ↓bw, peribronchiolar inflammation as well as atrophy, degeneration, metaplasia, ulcer, and hypertrophy/hyperplasia of the nasal mucosa, inflammatory debris in the nasal lumen and metaplasia and inflammation of the trachea; one mortality due to pulmonary edema, ↓bwg, transient ↓fc (♂); ↓fc, ↑lung wt. (♀).
Neurotoxicity Studies	
13-Week Neurotoxicity (diet) Sprague Dawley Rats PMRA 1347662	≥ 181/201 mg/kg bw/day: ↓bwg. ≥ 363/397 mg/kg bw/day: ↓bw, ↓fc (♂). 701/790 mg/kg bw/day: ↓bw, ↓fc (♀). No treatment-related effects on reflex responses or neurohistopathology. **Study considered supplemental** (non-guideline).
Chronic Toxicity/Oncogenicity Studies	
98-104 Week Carcinogenicity (diet)	NOAEL = 16 mg/kg bw/day ≥ 47/51 mg/kg bw/day: duodenal villous hyperplasia (1♂), jejunal hyperplasia

<table>
<tr><th>Study Type/ Animal/ PMRA Number</th><th>Study Results</th></tr>
<tr><td>CD-1 Mice
PMRA 1347643</td><td>(1♂); benign stomach papilloma (1 ♀).
≥151/154 mg/kg bw/day: benign stomach papillomas (1♂, 3♀); slight ↓bwg, slight ↓food efficiency, ↓liver wt., ↓spleen wt., duodenal hyperplasia (2♂), jejunal/ileal hyperplasia (1♂) (♂); duodenal villous hyperplasia (3♀), duodenal adenoma (1♀), duodenal masses, thickening of stomach wall, keratoacanthosis of the nonglandular stomach (♀).
No duodenal adenomas or stomach papillomas in controls.</td></tr>
<tr><td>104-Week Carcinogenicity (diet)
B6C3F1 mice
PMRA 1347645</td><td>LOAEL = 150 mg/kg bw/day
≥ 150 mg/kg bw/day: ↑ulceration of the non-glandular gastric mucosa and thickening of the gastric and duodenal walls, hyperkeratosis of esophagus and stomach, papillomas of the nonglandular stomach, duodenal hyperplasia, duodenal adenomas, duodenal adenocarcinoma.
≥ 525-750 mg/kg bw/day: ↓fc (1st few weeks), ↓bwg, ↓longevity; marked acanthosis and hyperkeratosis of the nonglandular gastric mucosa (♂); thickening of jejunal wall (♀).
1050-1500 mg/kg bw/day: erythema, dry flaking skin, reddish fur discolouration, weeping skin, jejunal adenocarcinoma (1); thickening of jejunal wall (♂).
Note: Dose reduced in mid- and high-dose group at week 22.

Evidence of carcinogenicity.
<table>
<tr><th>Dose (mg/kg bw/day)</th><th></th><th>0</th><th>150</th><th>525</th><th>1050</th></tr>
<tr><td>No. of animals</td><td>♂</td><td>52</td><td>52</td><td>52</td><td>52</td></tr>
<tr><td></td><td>♀</td><td>51</td><td>52</td><td>52</td><td>52</td></tr>
<tr><td colspan="6">Stomach</td></tr>
<tr><td>Papilloma</td><td>♂</td><td>0</td><td>2</td><td>3</td><td>2</td></tr>
<tr><td></td><td>♀</td><td>2</td><td>1</td><td>5</td><td>7</td></tr>
<tr><td>Squamous cell</td><td>♂</td><td>0</td><td>0</td><td>3</td><td>1</td></tr>
<tr><td>carcinoma</td><td>♀</td><td>2</td><td>2</td><td>5</td><td>7</td></tr>
<tr><td colspan="6">Duodenum</td></tr>
<tr><td>Atypical</td><td>♂</td><td>0</td><td>8*</td><td>35*</td><td>37*</td></tr>
<tr><td>hyperplasia</td><td>♀</td><td>0</td><td>1</td><td>17*</td><td>23*</td></tr>
<tr><td>Adenoma</td><td>♂</td><td>0</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td></td><td>♀</td><td>0</td><td>0</td><td>2</td><td>0</td></tr>
<tr><td>Carcinoma</td><td>♂</td><td>0</td><td>1</td><td>6</td><td>3</td></tr>
<tr><td></td><td>♀</td><td>0</td><td>0</td><td>4</td><td>5</td></tr>
<tr><td colspan="6">*p<0.05</td></tr>
</table></td></tr>
<tr><td>112-Week Carcinogenicity (diet)
CD-1 Mice
PMRA 1347651</td><td>LOAEL = 95 mg/kg bw/day
≥95 mg/kg bw/day: abdominal distention, duodenal hyperplasia, duodenal adenocarcinoma.
≥500 mg/kg bw/day: ↓grooming, ↓bw, ↓bwg, splenic extramedullary hematopoiesis, duodenal adenoma, jejunal hyperplasia, ileal hyperplasia; stomach papillomas (♂).
1300 mg/kg bw/day: alopecia around eyes, possible macrocytic anemia (↑mean cell hemoglobin, ↑mean cell volume, ↓red blood cells; ↓hemoglobin, ↓hematocrit, ↓mean cell hemoglobin concentration (♂)), ileal hyperplasia; jejunal adenoma/adenocarcinoma (♂).</td></tr>
</table>

<table>
<tr><th>Study Type/
Animal/ PMRA
Number</th><th>Study Results</th></tr>
<tr><td></td><td>Evidence of carcinogenicity.

<table>
<tr><th>Dose (mg/kg bw/day)</th><th>0</th><th>95</th><th>500</th><th>1300</th></tr>
<tr><td colspan="5">Stomach</td></tr>
<tr><td>Papillomas ♂</td><td>1%</td><td>1.3%</td><td>6.3%</td><td>7.7%</td></tr>
<tr><td colspan="5">Duodenum</td></tr>
<tr><td>Adenomas ♂</td><td>1/87</td><td>1/61</td><td>2/67</td><td>10/71*</td></tr>
<tr><td>♀</td><td>0/88</td><td>0/63</td><td>5/67</td><td>29/73*</td></tr>
<tr><td>Adeno- ♂</td><td>0/87</td><td>1/61</td><td>7/67*</td><td>34/71*</td></tr>
<tr><td>carcinomas ♀</td><td>0/88</td><td>0/63</td><td>5/67*</td><td>29/73*</td></tr>
<tr><td colspan="5">Jejunum</td></tr>
<tr><td>Adenomas ♂</td><td>0/94</td><td>0/62</td><td>1/62</td><td>1/62</td></tr>
<tr><td>♀</td><td>0/97</td><td>0/61</td><td>0/66</td><td>2/68</td></tr>
<tr><td>Adeno- ♂</td><td>0/94</td><td>1/62</td><td>0/62</td><td>7/62*</td></tr>
<tr><td>carcinomas ♀</td><td>0/97</td><td>0/61</td><td>0/66</td><td>3/68</td></tr>
<tr><td colspan="5">*p<0.05</td></tr>
</table>
</td></tr>
<tr><td>104-Week Chronic/
Carcinogenicity (diet)
Sprague Dawley Rats
PMRA 1347653</td><td>NOAEL = 9/11 mg/kg bw/day
≥ 35/45 mg/kg bw/day: hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach.
145/180 mg/kg bw/day: submucosal edema/inflammation of the stomach, ovarian medullary tubule hyperplasia.
No evidence of carcinogenicity.</td></tr>
<tr><td>104-Week Chronic
Toxicity (diet)
F344 Rats
PMRA 1347640</td><td>NOAEL = 12/15 mg/kg bw/day
≥ 81/100 mg/kg bw/day: ↑incidence and severity of hyperkeratosis of the esophagus and nonglandular epithelium of the stomach.
291/351 mg/kg bw/day: ↓bwg, ↓fc, ↓wc, ↓cholesterol, esophageal keratosis.
Considered supplemental when considered for carcinogenicity assessment. (low animal numbers).</td></tr>
<tr><td>104-Week Chronic/
Carcinogenicity (diet)
F344 Rats
PMRA 1347642</td><td>NOAEL = 25 mg/kg bw/day
≥50 mg/kg bw/day: hyperkeratosis of the gastric non-glandular mucosa
100 mg/kg bw/day: ulceration of the nonglandular stomach, hyperkeratosis of the esophagus; basophilic foci of the liver (♂).
No evidence of carcinogenicity.</td></tr>
<tr><td colspan="2">Developmental/Reproductive Toxicity Studies</td></tr>
<tr><td>2-Generation
Reproductive Toxicity
(diet)
Sprague Dawley Rats
PMRA 1347660</td><td>Parental:
NOAEL = 14/17 mg/kg bw/day
56/70 mg/kg bw/day: ↓bw/bwg in (F1 premating, gestation, ♂/♀).
250/300 mg/kg bw/day: ↓fc; ↓bw (F1 lactation) (♀).

Reproductive:
NOAEL = 250/300 mg/kg bw/day
No effects observed.

Offspring:
NOAEL = 17 mg/kg bw/day
70 mg/kg bw/day: ↓bw (F1and F2 pups).
No evidence of reproductive toxicity.
GI tract was not examined.</td></tr>
</table>

Study Type/ Animal/ PMRA Number	Study Results
2-Generation Reproductive Toxicity (diet) Sprague Dawley Rats PMRA 1347661	**Parental:** NOAEL = 14/18 mg/kg bw/day ≥ 83/110 mg/kg bw/day: hyperkeratosis of the non-glandular gastric mucosa (F0, F1), esophageal hyperkeratosis (F1). 282/376 mg/kg bw/day:↓bw (premating F0, F1); basophilic renal tubules F0)(♂); ↓bw (gestation F0, F1; lactation F1)(♀). **Reproductive:** NOAEL = 282/376 mg/kg bw/day No effects noted. **Offspring:** NOAEL = 18 mg/kg bw/day ≥ 110 mg/kg bw/day: ↓bw (F1at LD25). 411 mg/kg bw/day: ↓bw (F2 at LD25). **No evidence of reproductive toxicity.** Small intestine was not examined.
Developmental Toxicity (gavage) Sprague Dawley Rats PMRA 1347665	**Maternal:** NOAEL = 150 mg/kg bw/day ≥ 550 mg/kg bw/day: ↓bw, ↓gravid uterine wt. 2000 mg/kg bw/day: soft feces, staining of fur, perianal staining, ↓fc, death (1). **Developmental:** LOAEL = 150 mg/kg bw/day ≥ 150 mg/kg bw/day: angulated ribs, ↓ossification of interparietal bone. ≥ 550 mg/kg bw/day: ↓fetal bw, slight ↓crown-rump length, reduced ossification (cranial, pubic, sternebrae, metacarpals, metatarsals). 2000 mg/kg bw/day: 2 malformations (1 w/ multiple, 1 w/ unilateral microphthalmia), hepatic discoloration.
Developmental Toxicity (gavage) Sprague Dawley Rats (Pilot study) PMRA 1347663, 1217902	**Maternal:** ≥ 20 mg/kg bw/day: alopecia. ≥ 80 mg/kg bw/day: rales, ↓bwg. ≥ 320 mg/kg bw/day: salivation, chromorhinorrhea, gasping, ↓body temp, ↓fc 640 mg/kg bw/day: soft liquid feces, thinness, "tiptoe" walk, vocalization, ↓motor activity, dyspnea, distention of GI tract. **Developmental:** ≥ 320 mg/kg bw/day: ↓ fetal bw. **Study considered supplemental** (pilot study).
Developmental Toxicity (gavage) Sprague-Dawley Rats PMRA 1347664, 1217877	**Maternal:** NOAEL = 10 mg/kg bw/day ≥ 10 mg/kg bw/day: ↓corrected bwg. ≥ 60 mg/kg bw/day: ↓bwg, rales (infrequent, 3 dams). 360 mg/kg bw/day: rales, excessive salivation, chromorhinorrhea, ↓fc, ↓corrected bw, death (1). **Developmental:** NOAEL = 60 mg/kg bw/day 360 mg/kg bw/day: delayed ossification.
Developmental Toxicity (gavage) NZW Rabbits PMRA 1347668	**Maternal:** NOAEL = 40 mg/kg bw/day 160 mg/kg bw/day: ↓bw, ↓fc. **Developmental:**

Study Type/ Animal/ PMRA Number	Study Results
	NOAEL = 40 mg/kg bw/day 160 mg/kg bw/day: ↓gravid uterine wt. secondary to ↓fetal wt., ↑ small fetuses, ↑early resorptions, ↑post-implantation loss, delayed ossification, ↑presence of 13th ribs. **No evidence of teratogenicity.**
Developmental Toxicity (gavage) NZW Rabbits PMRA 1347666, 1199648	**Maternal:** NOAEL = 10 mg/kg bw/day ≥ 20 mg/kg bw/day:↓corrected bw, ↓bwg, ↓fc. 60 mg/kg bw/day: death (1). **Developmental:** NOAEL = 10 mg/kg bw/day ≥ 20 mg/kg bw/day: domed head, irregular shaped fontanelle of the skull, severe dilation of the lateral ventricles of the brain, hydrocephalus. **Evidence of teratogenicity.**
Developmental Toxicity (gavage) NZW Rabbits PMRA 2359930	**Maternal:** LOAEL = 10 mg/kg bw/day ≥ 10 mg/kg bw/day: few/pale feces, ↓bwg, ↓fc, ↓wc. ≥ 30 mg/kg bw/day: thin build, bw loss during first 9 days, ↓gravid uterine wt. 60 mg/kg bw/day: bw loss during first 14 days, ↓bw, ↑late resorptions, ↑post-implantation loss. **Developmental:** NOAEL = 10 mg/kg bw/day ≥ 30 mg/kg bw/day: ↓fetal wt, ↑incidence of variations (atelectasia of the lung, supernumerary ribs, 20 thoracolumbar vertebrae), ossification delay of epiphyses, metacarpals and phalanges). 60 mg/kg bw/day: ↑late resorptions, ↑post-implantation loss, ossification delay of pubis and astragalus, ↑overall incidence of malformations, ↑incidence of small/misshapen/oval lenses (8 fetuses/2 litters).
Developmental Toxicity (gavage) NZW Rabbits PMRA 1347667	**Maternal:** (all treated): ↑soft or liquid feces, ↓bwg during treatment Days 7-9, 10-12: 1 abortion in each group. **Developmental:** GD 10-12: hydrocephaly (1). GD 13-15: irregularly shaped fontanelle (13 fetuses/3 litters versus 5 fetuses/2 litters in controls - both exceed historical control mean). GD 16-18: hydrocephaly (1). **Study considered supplemental** (non-guideline; 60 mg/kg bw/day by "pulse dosing" schedule for 3-day periods during different periods of gestation (days 7-9, 10-12, 13-15, 16-18)(Control group treated GD7-18)). Fetal (litter) incidence (%) of irregularly-shaped fontanelle: control: 4.5(11), GD 7-9:0,GD 10-12:1.3(6.7), GD 13-15:12(20), GD 16-18:0.
Genotoxicity Studies	
Somatic cell mutation: Mouse spot test T-strain ♂ paired with C57B1/6 ♀ mice PMRA 1347674	**Negative** up to 5000 ppm. Low fertility in this study and the pilot study. ≥ 100 ppm: ↓pup survival. ≥ 1500 ppm: ↓pup birth wt. 5000 ppm: maternal effects (mortality, ↓bw, ↓fc) ↓pup bw.
Chromosomal aberration – bone marrow Sprague Dawley Rats	**Negative** up to 2000 mg/kg bw. ≥ 500 mg/kg bw: diarrhea.

Study Type/ Animal/ PMRA Number	Study Results
PMRA 1199649	
Nuclear aberration in duodenal crypt cells CD-1 Mice PMRA 2533060	**Negative** up to 2000 mg/kg bw/day.
Dominant lethal ICR/SIM Mice PMRA 2566127	**Negative** up to 5000 ppm.
Dominant lethal Osborne-Mendel Rats PMRA 1347676	Negative up to 200 mg/kg bw/day. Did not adversely affect spermatogenesis or fertility. Dose levels may not have been sufficient.
DNA damage – Comet assay in duodenal cells (gavage) CD-1 mice PMRA 1347658	**Negative** up to 2000 mg/kg bw.
Gene mutation S.typhimurium TA100 PMRA 1347669	**Positive** with and without activation.
Gene mutation S.typhimurium TA98, TA100, TA1535, TA1537 PMRA 1347670	**Positive** with and without activation in all strains with technical folpet containing 2200 ppm or <50 ppm perchloromethyl mercaptan.
Gene mutation S.typhimurium TA100, TA1535, TA1537, TA1538 E. Coli WP2 PMRA 2566127	**Positive** in TA100, TA1535 and WP2 with and without activation. **Negative** in TA1537 and TA1538 with and without activation.
Gene mutation S. typhimurium TA100, TA98, TA1535, TA 1536, TA1537, TA1538 B. subtilis TKJ6321, TKJ5211 PMRA 1238474	**Positive** in TA100, TKJ5211 and TKJ6321 without activation. **Positive** in TKJ6321 with activation. **Equivocal** in TKJ5211 with activation. **Negative** in remaining strains.
Gene mutation S.typhimurium TA1535, TA1536, TA1537, TA1538 E.Coli WP2hcr+, WP2hcr- B.subtilis H17rec+, M45rec- PMRA 2563266	**Positive** in S. typhimurium TA1535 only. **Positive** in E. coli WP2hcr+ and hcr-. **Weakly positive** in B. subtilis M45rec-.
Gene mutation S.typhimurium TA1535, TA98, TA100, JK1, JK3, JK947	**Positive** in TA 100 and TA1535 without activation. **Negative** in TA98 without activation. **Positive** in JK3 and JK947 (lactam test) without activation. **Negative** in JK1 (lactam test) without activation.

Study Type/ Animal/ PMRA Number	Study Results
PMRA 2563261	
Gene mutation S.typhimurium TA102, TA104 PMRA 2563260	**Positive** in TA104 with and without activation; mutagenic activity ↓with activation. **Negative** in TA102 with and without activation.
Gene mutation E.coli PQ37 PMRA 1238478	**Positive** without activation. **Negative** with activation.
Gene mutation S.typhimurium TA1535, E.coli WP2 hcr PMRA 2563263	**Positive** in TA1535 and WP2 hcr without activation. The addition of activation mix, activation mix minus co-factors, cysteine or rat blood eliminated or greatly reduced the mutagenic activity.
Mitotic recombination S. cerevisiae D3 PMRA 2566127	**Positive** with and without activation.
Gene mutation S.typhimurium TA98, TAMix Clastogenicity – micronucleus assay CHO-K_1 cells PMRA 2563262	**Positive** in both strains in gene mutation assay (lowest effective concentration was 6.25 μM without activation and 25 μM with activation. Positive with activation (≥30 μM), negative without activation in micronucleus assay.
Gene mutation Chinese Hamster v79, HGPRT locus PMRA 1347672	**Negative** with and without activation.
Gene mutation CHO cells. HGPRT locus PMRA 2563264	**Positive** without activation.
Gene mutation Mouse Lymphoma cells, TK +/- PMRA 2533060	**Positive** with and without activation.
Chromosomal Aberration CHO cells PMRA 1238480	Cytotoxic at 2.5 μg/mL without activation and 26 μg/mL with activation. **Positive** with activation. **Weakly Positive** without activation.
Chromosomal Aberration Human Lymphocytes PMRA 1238479	**Positive** without activation. **Negative** with activation.
Unscheduled DNA synthesis Human lymphocytes PMRA 2563265	**Negative.**
Unscheduled DNA synthesis Human fibroblasts PMRA 2566127	**Negative** with and without activation.
Interaction with DNA	The addition of calf thymus DNA significantly affected the hydrolysis of folpet in

Study Type/ Animal/ PMRA Number	Study Results
Calf thymus DNA PMRA 2563267	aqueous medium. The results from competitive binding with intercalator ethidium bromide, ctDNA melting and viscosity measurements and circular dichroism studies indicated folpet and its reactive intermediate can intercalate with DNA and phthalic acid can partially intercalate with DNA; both can result in structural changes of the DNA. Phthalimide did not show binding to DNA.
Special Studies (non-guideline)	
Acute Hepatotoxicity (gavage) Sprague Dawley ♂ Rats PMRA 2063221	No treatment-related effect on benzphetamine N-demethylase activity, cytochrome P450 levels or AST activity at 500 or 1000 mg/kg bw.
21-Day Toxicity (diet) CD-1 Mice PMRA 1347648	750 mg/kg bw/day: Glandular hyperplasia of crypt cells, hypertrophy of villous epithelium of the duodenum and jejunum, 2X ↑ duodenal cyclin-dependent kinases (CDK), 2X ↑ duodenal proliferating cell nuclear antigen (PCNA).
28-Day Toxicity (diet) CD-1 Mice PMRA 1347649	Folpet 692 mg/kg bw/day (5000 ppm): glandular hyperplasia of duodenal crypts (1st 2.5 cm), ↑PCNA staining, 2X ↑ CDK. Perchloromethyl Mercaptan 2 mg/kg bw/day (11 ppm): no effects on CDK or ↑PCNA. No effects on mortality or clinical signs. Proliferative stimulation in duodenum following folpet administration is believed to occur 3-4 weeks following initiation of treatment to high doses of folpet. Note: 5000 ppm technical grade folpet includes ~11 ppm perchlormethyl mercaptan.
Mechanistic 28-Day Toxicity (diet) CD1 Mice Focus on Gastrointestinal tract PMRA 1347644	≥69/82 mg/kg bw/day: thickened duodenal wall, villi fusion (♂); ↓bw, ↑crypt cells/crypt, ↑duodenal crypt cells, slight crypt cell hyperplasia (2/5) (♀). 686/826 mg/kg bw/day:↓fc, duodenal crypt hyperplasia (slight-moderate), ↑BRDU uptake in duodenum, ↓villus height, ↓villi:crypt height ratio, enlarged crypts;↓bw, inflammatory cells in lamina propria, red spots in the stomach (1/5), red duodenum (1/5), minimal focal glandular dilatation of the stomach (1/5), ↑crypt cells/crypt (♂); thickened duodenal wall (3/5), villi fusion, jejunal hyperplasia (♀). No effects on the jejunum or ileum in treated ♂. No effects in the ileum or stomach in treated ♀.
28-Day Toxicity (diet) CD-1 Mice Specialized study of the duodenum. PMRA 1347650	To investigate the effects of folpet on the duodenum. 1) Folpet (717 mg/kg bw/day): slight ↑ glandular hyperplasia of duodenal crypts, slight ↑hypertrophy of the duodenal villous epithelium, ↑protein in duodenal mucosal epithelium (0-2.5 cm> 2.5-6.0cm)*, ↑duodenal non-protein thiols (0-2.5 cm> 2.5-6.0cm)*, ↑CDK (0- 2.5 cm> 2.5-6.0cm), ↑duodenal PCNA. 2) Folpet (679 mg/kg bw/day+ perchlormethyl mercaptan (1.5 mg/kg bw/day): slight ↑glandular hyperplasia of duodenal crypts, slight ↑hypertrophy of the duodenal villous epithelium, ↑protein in duodenal mucosal epithelium (0- 2.5 cm> 2.5-6.0cm), ↑duodenal non-protein thiols, ↑CDK (1st 2.5 cm only), ↑duodenal PCNA. 3) Perchlormethyl mercaptan (1.6 mg/kg bw/day): No effects noted. 4) Hydrogen peroxide (527 mg/kg bw/day): ↓bwg, ↓food efficiency, slight ↑glandular hyperplasia of duodenal crypts, slight ↑hypertrophy of the duodenal villous epithelium , ↑duodenal non-protein thiols, ↑CDK (1st 2.5 cm only) *(0- 2.5 cm> 2.5-6.0cm) indicates that the effect was more prominent in the 1st 2.5 cm of the duodenum when compared to the following 3.5cm There does not appear to be any interactive effects between folpet and

Study Type/ Animal/ PMRA Number	Study Results
	perchlormethyl mercaptan. Duodenal effects were reversible for all endpoints.
28-Day Toxicity (diet) CD-1 Mice Specialized study of the duodenum PMRA 2565014	894/1024 mg/kg bw/day: ↓bwg (day 1-29 ♂, day 1-4 ♀), slight ↓fc, distension of cecum by day 7, crypt cell hyperplasia and villous hypertrophy of duodenum by day 7, hyperplasia of the limiting ridge of the stomach by day 14 (♀) or 28 (♂), hyperplasia and hyperkeratosis of the non-glandular region of the stomach by day 14. Treated animals allowed to recover for 17 days continued to show effects on the duodenum and stomach but at a lower incidence than treated animals with no recovery.
In Vitro Cytotoxicity Human bronchial epithelial cells (16HBE14o-) PMRA 2564601	Dose-related cytoxicity with folpet in DMSO, Folpan 80WG in DMSO and Folpan 80WG particles (IC50 of 3.32, 3.25 and 2.68 μg/cm^2, respectively). Cytotoxicity was time-dependant between 1-4 hours exposure but plateaued between 4 and 48 hours exposure. Due to lack of difference with the form tested, subsequent studies were conducted with Folpan 80WG particles and showed reactive oxygen species generation and lipid peroxidation (≥1.85 μg/cm^2) and apoptosis (≥2.37 μg/cm^2).
Anti-androgen screen hAR in S. cerevisiae PMRA 2564598	Similar potency to vinclozolin in antagonizing the binding of the androgen dihydrotestosterone to cells transfected with human androgen receptor.
Androgen and Estrogen Receptor Transcriptional Activation hERα, hERβ or hAR in CHO-K1 cells PMRA 2564604	Negative for agonist or antagonist activity for human ERα, ERβ and AR.
Androgen Receptor Binding Assay SD Rat prostate cytosol PMRA 2565008	Negative.
Aromatase Assay Human recombinant aromatase PMRA 2565008	Equivocal for aromatase inhibition.
Estrogen Receptor Binding Assay SD Rat uterine cytosol PMRA 2565008	Negative.
Estrogen Receptor Transcriptional Activation Assay hERα-HeLa cells PMRA 2565008	Negative. Note: ↓sensitivity of assay to very weak agonists.
Steroidogenesis Assay H295R cells PMRA 2565008	Negative for induction or inhibition of testosterone synthesis. Negative for induction of estradiol synthesis. Inhibition of estradiol synthesis at high concentration could not be confirmed.
Hershberger Assay (gavage) Sprague Dawley Rats PMRA 2565008	Negative for androgenicity and anti-androgenicity. Gastrointestinal dilatation common in treated groups. Some animals sacrificed at 800 mg/kg bw/day due to moribundity, loss of bw, abnormal breathing and/or soft feces.

Study Type/ Animal/ PMRA Number	Study Results
Uterotrophic Assay (gavage) Sprague Dawley Rats PMRA 2565008	Negative up to 1000 mg/kg bw/day; no effects on bw, bwg or uterine wt.
♀Pubertal Assay (gavage) Sprague Dawley Rats PMRA 2565008	No effects on age at vagina opening, age at first estrus, mean cycle length, percent cycling, percent regularly cycling, organ weights, TSH or on histopathology of the uterus, thyroid or kidneys up to 800 mg/kg bw/day. The number of antral follicles ↑ at 800 mg/kg bw/day but other types of ovarian follicles were unaffected. ≥ 400 mg/kg bw/day: bw loss, abnormal breathing and GI dilation in several animals prior to early sacrifice, ↓serum T4, ↑Cl, ↓ALT, ↓ALP.
♂ Pubertal Assay (gavage) Sprague Dawley Rats PMRA 2565008	No effects on age at preputial separation, TSH or on histopathology of the testes, epididymides, thyroid or kidneys up to 800 mg/kg bw/day. ≥ 200 mg/kg bw/day: ↓bw, ↓bwg, ↓liver wt, ↓serum T4, ↑Cl. ≥ 400 mg/kg bw/day: abnormal breathing/rales, distended abdomen, piloerection, hunched posture, nasal discharge prior to early sacrifice, ↓epididymides wt, ↓levator ani-bulbocavernosus wt, ↓absolute pituitary wt. 800 mg/kg bw/day: ↑kidney wt, ↓ALT, ↓ALP, ↓ protein, ↓albumin. Note: Serum chemistry and histopathology not conducted for 400 mg/kg bw/day group.
Reporter Gene Assay COS-7 simian kidney cells PMRA 2564605	No evidence of pregnane X receptor agonistic activity in cells transfected with human or mouse pregnane X receptor.
Metabolite Studies	
Developmental Toxicity (gavage) NZW Rabbits PMRA 2359927 Phthalimide	**Maternal:** NOAEL = 30 mg/kg bw/day No effects. Developmental: NOAEL = 30 mg/kg bw/day No effects.

Table 2 Toxicology Reference Values for Use in Health Risk Assessment for Folpet

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Rabbit developmental	NOAEL = 10 mg/kg bw/day ↓ bodyweight	100
	ARfD = 0.1 mg/kg bw		
Acute dietary females 13-49 years of age	Rabbit developmental	NOAEL = 10 mg/kg bw/day Malformations	300
	ARfD = 0.03 mg/kg bw		
Repeated dietary general population	Rat chronic Rabbit developmental	NOAEL = 9 mg/kg bw/day Gastrointestinal irritation LOAEL = 10 mg/kg bw/day ↓bodyweight gain, ↓food consumption, clinical signs	100
	ADI = 0.09 mg/kg bw/day		
Repeated dietary females 13-49 years of age	Rabbit developmental	NOAEL = 10 mg/kg bw/day Malformations	300

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
	ADI = 0.03 mg/kg bw/day		
Dermal[2]- all durations	Rabbit developmental	NOAEL = 10 mg/kg bw/day Malformations	300
Short-term inhalation	28-day rat inhalation	LOAEC = 5.2 µg/L (1.4 mg/kg bw/day) Laryngeal lesions and ↑ lung weight	300
Intermediate-term inhalation	28-day rat inhalation	LOAEC = 5.2 µg/L (1.4 mg/kg bw/day) Laryngeal lesions and ↑ lung weight	1000
Long-term inhalation	28-day rat inhalation	LOAEC = 5.2 µg/L (1.4 mg/kg bw/day) Laryngeal lesions and ↑ lung weight	3000
Aggregate general population (all routes)	Rat reproduction	NOAEL = 17 mg/kg bw/day ↓pup weight	100
Aggregate females 13-49 years of age (all routes)	Rabbit developmental	NOAEL = 10 mg/kg bw/day Malformations	300

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 20% was used in a route-to-route extrapolation.

Appendix IV Dietary Exposure and Risk Estimates

Table 1 Dietary Exposure and Risk Estimates for Folpet

Population Subgroup	Refined					
	Acute Dietary[1] (99.9th Percentile)				Chronic Dietary[2]	
	Food Only		Food + Water		Food + Water	
	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw/day)	%ADI
General Population	--	--	--	--	--	--
All Infants (<1 year old)	0.009443	9	0.020178	20	0.000885	1
Children 1-2 years old	0.020451	20	0.023601	24	0.002023	2
Children 3-5 years old	0.017318	17	0.018676	19	0.001286	1
Children 6-12 yrs old	0.010091	10	0.012307	12	0.000634	< 1
Males 13-19 yrs old	0.033515	34	0.033944	34	0.000531	< 1
Males 20-49 yrs old	0.047806	48	0.048586	49	0.001403	2
Adults 50+ years old	0.026360	26	0.027181	27	0.000674	< 1
Females 13-49 years old	0.023267	78	0.025109	84	0.000558	2

[1] Acute Reference Dose (ARfD) of 0.03 mg/kg bw applies to females 13-49 years of age. ARfD of 0.1 mg/kg bw applies to all other population subgroups.

[2] Acceptable Daily Intake (ADI) of 0.03 mg/kg bw/day applies to females 13-49 years old. ADI of 0.09 mg/kg bw/day applies to all other population subgroups.

Note:
The residue definition for acute and chronic risk assessment is the sum of folpet (parent) plus the metabolite phthalimide (PI) expressed as folpet, for residues in foods and drinking water.

Table 2 Cumulative Dietary Risk from Exposure to Captan and Folpet

Population Subgroup	Risk from Exposure to Captan		Risk from Exposure to Folpet		Cumulative Risk from Exposure to Captan and Folpet (ARI)
	Food + Water		Food + Water		Food + Water
	Exposure[1] (mg/kg bw/day)	%RfD_{captan}[2]	Exposure[1] (mg/kg bw/day)	%RfD_{folpet}[3]	ARI = 1 / (% RfD_{captan} + % RfD_{folpet})[4]
General Population	0.001545	0.3	0.000555	0.3	**167**
All Infants (<1 yr old)	0.002287	0.4	0.000385	0.2	**167**
Children 1-2 yrs old	0.007074	1.2	0.001079	0.7	**53**
Children 3-5 yrs old	0.004604	0.8	0.000629	0.4	**83**
Children 6-12 yrs old	0.002601	0.4	0.000340	0.2	**167**
Youth 13-19 yrs old	0.001333	0.2	0.000268	0.2	**250**
Adults 20-49 yrs old	0.001051	0.2	0.000732	0.5	**143**
Adults 50-99 yrs old	0.001012	0.2	0.000422	0.3	**200**
Females 13-49 yrs old	0.001048	0.2	0.000338	0.2	**250**

[1] The residue definition for the cumulative risk assessment is folpet (parent only) and captan (parent only) for residues in foods and drinking water. The metabolite PI (for folpet) and THPI (for captan) are not considered contributors to the cumulative risk. The chronic exposure estimates for captan are included in PRVD2016-13 - *Proposed Re-evaluation Decision for Captan*.

[2] Cumulative Reference Dose for Captan (RfD_{captan}) of 0.6 mg/kg bw/day applies to all populations.

[3] Cumulative Reference Dose for Folpet (RfD_{folpet}) of 0.16 mg/kg bw/day applies to all populations.

[4] The ARIs were calculated using the rounded %RfDs.

Appendix V Food Residue Chemistry Summary

Folpet is a non-specific thiol reactant fungicide currently registered for use in Canada for the control of a number of fungal diseases on apples, celery, crabapples, cranberries, cucumbers, grapes, melons, pumpkins, squash, strawberries and tomatoes.

For all registered uses, the nature of the residue in animal and plant commodities is adequately understood based on metabolism studies in lactating goats, wheat, grapes, avocados, potatoes and tomatoes. The avocado, grape and wheat studies were previously reviewed by the PMRA and deemed acceptable. The tomato and potato studies were reviewed by JMPR 1998 and JMPR 1999, respectively. The goat studies were reviewed by JMPR 1998.

The goat metabolism studies show that folpet is mostly excreted in feces and urine and expired as CO_2. Quantifiable residues were detected in liver, kidney and milk at levels up to 0.34 ppm, 0.26 ppm and 0.38 ppm, respectively. Folpet was found to be rapidly metabolized by cleavage of the trichloromethyl (TCM) moiety, yielding phthalimide (which hydrolyses into phthalamic acid and phthalic acid) and the highly reactive, short-lived thiophosgene intermediate. Thiophosgene ultimately incorporates the ^{14}C-TCM carbon into a wide range of natural products. No folpet as parent compound was detected in goat tissues or milk. No poultry feed items are associated with the registered uses of folpet. Therefore, a poultry metabolism study was not required. The major metabolic pathway of folpet in plants is quite similar to that found in animals. The relative predominance between parent folpet, phthalimide, phthalamic acid and phthalic acid appears to be crop dependant. Phthalamic acid and phthalic acid form conjugates in plants.

The residue definition (RD) in all plant and animal commodities is currently expressed as folpet perse for both enforcement and dietary risk assessment. As a result of the present re-evaluation, the PMRA has determined that based on the lack of data to quantify the difference between the toxicity of folpet and phthalimide, the parent (folpet) toxicology endpoints apply to the phthalimide (PI) metabolite. This is in line with other ccontemporary reviews [for example, European Food Safety Authority (EFSA) 2014, JMPR 2007] which do not rule out unequivocally toxic effects of PI. In addition, metabolism studies summarised above show that residues in all animal commodities and in some raw agricultural commodities (RACs) can only be monitored using a complex residue definition, as parent folpet is not present in any animal tissue and is not the predominant metabolite (not a good marker) in all plant commodities. The stability of folpet residues is variable and matrix dependant: folpet degrades into PI in macerated samples due to endogenous enzyme activity. Furthermore, studies simulating hydrolytic conditions for pasteurisation, boiling/brewing/baking and sterilisation indicated that folpet is completely degraded during processing; PI is formed predominantly under conditions of pasteurisation while levels of phthalic acid increase under conditions simulating boiling/brewing/baking and sterilisation. Phthalic acid and phthalamic acid are of no particular concern. Phthalic acid and phthalamic acid can naturally occur in the environment and, therefore, cannot be considered as specific to folpet. As mentioned above, thiophosgene is short-lived and, therefore, not quantifiable. Thus, PI is the only relevant metabolite to be taken into account. Therefore, it is proposed that the metabolite PI be included in the residue definition for plant and animal commodities for enforcement and risk assessment purposes.

There are currently no confined crop rotation data on file. The registrant has submitted waiver requests for confined crop rotation and field crop rotation trials stating that such studies have been submitted in previous petitions. However, no such data were found in PMRA files. As folpet is currently registered for use on crops which are typically rotated with other crops, the lack of this data is considered a deficiency in the residue chemistry database for folpet. Until an acceptable study is submitted, a minimum plant back interval (PBI) of 12 months (default PBI) must be observed for crops on which folpet is not registered.

Maximum Residue Limits (MRLs) have been established (on the basis of residue analysis for folpet only) on apples, celery, crabapples, cranberries, cucumbers, grapes, melons, pumpkins, squash, strawberries and tomatoes and on imported avocados, blackberries, blueberries, boysenberries, cherries, citrus fruits, currants, dewberries, garlic, gooseberries, huckleberries, leeks, lettuce, loganberries, onions and raspberries, and published in Health Canada's List of MRLs Regulated under the *Pest Control Products Act* on the Maximum Residue Limits for Pesticides webpage. Due to the proposed amendment of the residue definition, the PMRA recommends that new MRLs be established through a Category B submission.

Adequate analytical methods have been developed for the determination of folpet and its metabolite PI in plant commodities. Quantitation was performed by high performance liquid chromatography (HPLC) coupled with UV detection with a limit of detection of 0.05 ppm for both folpet and PI or by gas liquid chromatography (GLC) coupled with electron capture detection (ECD) with a limit of detection of 0.5 ppm for folpet only or by gas chromatography (GC) with mass selective detection (MSD) with a limit of quantitation in the range from 0.01 to 0.05 ppm for PI. Analytical methods for animal commodities are not required for current uses.

With regard to MRLs enforcement, a GC-ECD single analyte method which measures both folpet and PI in plant commodities is listed in the USEPA's residue analytical methods (RAM) repertory. CFIA's Pesticide Multiresidue Analytical Methods Manual indicates that folpet (parent only) is one of the compounds that can be analysed by the CFIA's multiresidue method used for the analysis of pesticides in fruits and vegetables. In addition, the USFDA PESTDATA database (PAM Volume I, Appendix I) indicates that folpet (parent only) is completely recovered through Sections 302 (E1-E3 + DG1-DG19). A multiresidue method evaluation for the metabolite PI in plant commodities is outstanding. An enforcement method for animal commodities is not required for current uses.

Appendix VI Non-Occupational Risk Assessment

Table 1 Residential Postapplication Dermal Exposure and Risk Assessment for Trees

Form	Sub-pop	App Rate[a] (kg a.i./ha)	Number of Apps	DFR (µg/cm^2) [b]	TC[c] (cm^2/hr)	Exposure[d] (mg/kg bw/day)	Dermal MOE[e] (Target = 300)
Residential Trees (Apple, Crabapple - commercial applicator)							
Liquid (Commercial Class WP Product)[f]	Adults	2.0 (WP)	1	5.80	1700	0.0213	471
	Youth (11<16 yrs)	2.0 (WP)			1400	0.0123	814
	Child (6<11 yrs)	2.0 (WP)			930	0.0145	688

Shaded cells indicate where the MOE is less than the target MOE. MOE = margin of exposure
Form = formulation; Sub-pop = sub-population or life stage; Apps = applications; MOE = margin of exposure; WP = wettable powder
[a] Application rate from commercial products.
[b] DFR = dislodgeable foliar residue. The default value of 25% of the application was used for all crops and formulations.
[c] TC = transfer coefficient. TCs from the USEPA Residential SOP (2012b).
[d] Exposure = DFR (µg/cm^2) × DA (20%) × TC × duration/Body Weight. Durations were 2.2, and 1 hr for gardens and trees, respectively for adults and youth. For children, durations were 1.1, and 0.5 hr for gardens and trees, respectively. Body weights were 80, 57, and 32 kg for adults, youth, and children (6<11 years), respectively.
[e] Oral NOAEL of 10 mg/kg bw/day from a rabbit development study and target MOE of 300.
[f] Residential exposure following commercial application of the water dispersible granule product was not included in this assessment as its label currently prohibits application in residential areas.

Table 2 Bystander Inhalation Exposure and Risk Assessment

Sub-population	Air Concentration[a] (ng/m^3)	Inhalation Exposure[b] µg/kg bw/day	MOE[c] Target = 1000
Adult (80 kg)	4.88	5.9×10^{-5}	24,000,000
Youth (11<16 years) (57 kg)		9.2×10^{-5}	15,000,000
Toddler (6<12 months) (9 kg)		2.9×10^{-4}	4,900,000

MOE = margin of exposure
[a] Maximum value from literature study (Bailey and Belzer, 2007).
[b] Inhalation exposure = air concentration × inhalation rate × exposure time × conversion factor (µg/1 × 10^6 pg)/ body weight. Inhalation rate was 0.64 m^3/hr for adults, 0.63 m^3/hr for youth, and 0.23 m^3/hr for toddlers. Exposure times were 2.3, 1.7 and 1.5 hr/day for toddlers, youth, and adults, respectively
[c] Based on a rat inhalation study with a NOAEL of 1.4 mg/kg bw/day and target of 1000 for intermediate-term inhalation exposure.

Appendix VII Commercial Mixer/Loader/Applicator Risk Assessment

Table 1 Occupational Short-to Intermediate-Term Mixer/Loader/Applicator Exposure and Risk Assessment for Groundboom Application

Form	Crop	A	App Rate	ATPD[a]	MOE					Combined MOE[bf] Target = 300	
					Dermal[b] Target = 300	Inhal (ST)[c] Target = 300		Inhal (IT)[de] Target = 1000			
						No Resp	Resp[g]	No Resp	Resp[g]	No Resp	Resp[g]
Open M/L, Open Cab- both wearing single layer, CR gloves (except for application)											
WDG	Strawberry	Farmer	2.0 kg a.i./ha	8 ha	1271	N/A	35354	N/A		N/A	1264
		Custom		26 ha	391		10878	N/A	10878		389
	Cucumber, Squash	Farmer	4.0 kg a.i./ha	4 ha	1271		35354	N/A			1264
	Pumpkin	Farmer		5 ha	1017		28283				1011
	Melon	Farmer		7 ha	726		20202				722
	Tomato	Farmer		9 ha	565		15713				562
	Flowers	Both	1.0 kg a.i./ha	26 ha	782		21756	N/A	21756		778
Open M/L wearing CR coveralls over single layer, CR gloves; Open Cab, wearing single layer, no gloves											
WDG	Field Veggies	Custom	4.0 kg a.i./ha	26 ha	348	N/A	5439	N/A	5439	N/A	345
	Cranberry	Both	2.6 kg a.i./ha	26 ha	535		8368	N/A			530
Closed M/L (WSP), Open Cab- both wearing single layer, CR gloves (except for application)											
WP	Strawberry	Farmer	2.0 kg a.i./ha	8 ha	4580	6140	N/A	N/A	N/A	4147	N/A
		Custom		26 ha	1409	1889		1889		1276	
	Cranberry	Both	5 kg a.i./ha	26 ha	451	756		N/A		416	
	Cucumber, Squash	Farmer	4.0 kg a.i./ha	4 ha	4580	6140				4147	
	Pumpkin	Farmer		5 ha	3664	4912				3317	
	Melon	Farmer		7 ha	2617	3509				2369	
	Tomato	Farmer		9 ha	2035	2729				1843	
	Field Veggies	Custom		26 ha	705	945		945[i]		638	
	Flowers	Both	1.0 kg a.i./ha	26 ha	2818	3779		3779		2552	
Closed M/L (WSP), Closed cab wearing single layer, CR gloves (except for application)											
WP	Field Veggies	Custom	4.0 kg a.i./ha	26 ha	1178	4487	N/A	4487	N/A	1136	N/A

Form = formulation; WP = wettable powder; WDG = water dispersible granule; A = applicator; ATPD = area treated per day; App Rate= application rate; Inhal = inhalation; M/L = mixer/loader; ST = short-term; IT = intermediate-term; No resp = without respirator; Resp = with respirator**;** CR = chemical-resistant; PPE = personal protective equipment; Single layer = long sleeved shirt, long pants; N/A = not applicable; field veggies = cucumber, squash, pumpkin, melon, tomato; MOE = margin of exposure

[a] ATPD values are refined where possible.

[b] Oral NOAEL of 10 mg/kg bw/day from a rabbit development study and a target MOE of 300. Since an oral NOAEL was selected, a dermal absorption value of 20% was used in a route-to-route extrapolation.
[c] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study and a short-term target MOE of300.
[d] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study and an intermediate-term target MOE of 1000. Intermediate-term inhalation exposure was assessed for crops where custom application is possible (strawberry, field vegetables)
[e] Where more than 3 applications are possible according to current label directions, intermediate-term inhalation exposure was considered for custom applicators.
[f] Combined MOE = NOAEL/ (dermal exposure + inhalation exposure), as both the dermal and inhalation exposure could contribute to the developmental endpoint identified in the oral developmental toxicity study.
[g] Respirators were required for WDG as they are currently on the label. Respirators were not included with closed cabs, as the protection factor is already accounted for in the closed scenario and would be a double counting of protection. Respirators were also not included with closed mixing/loading. For scenarios where engineering controls were only applied to either mixing/loading or application, the 'resp' column was used as a respirator was assumed for the activity that did not have an engineering control.
[h] NR = not required. MOE was met at a lower level of mitigation. Additional mitigation was investigated as the intermediate-term inhalation MOEs did not reach the target MOE at a lower level of mitigation.
[i] This MOE is considered to be in range of the target MOE. In addition, custom application is unlikely to be intermediate-term duration given the proposed limit on the number of applications as a result of the postapplication risk assessment.

Table 2 Occupational Short- Term Mixer/Loader/Applicator Exposure and Risk Assessment for Airblast Application

Formulation	Crop	App Rate	ATPD[a]	MOE			Combined MOE[bd] Target = 300	
				Dermal[b] Target = 300	Inhal (ST)[c] Target = 300			
					No Resp	Resp[e]	No Resp	Resp[e]
Open M/L wearing CR coveralls, CR gloves; Open Cab wearing CR coveralls over single layer, CR hat (application only), CR gloves								
WDG	Apples, crabapples	3.0 kg a.i./ha	20 ha	362	N/A	1848	N/A	352
		2.4 kg a.i./ha (typical)		452		2310		440
	Grapes	1.0 kg a.i./ha		1085		5545		1056
	Cranberries	2.6 kg a.i./ha		417		2133		406
Open M/L wearing CR coveralls over single layer, CR gloves; Closed Cab, wearing single layer, CR gloves								
WDG	Apples, crabapples	3.0 kg a.i./ha	20 ha	559	N/A	2737	N/A	543
		2.4 kg a.i./ha (typical)		698		3421		679
	Grapes	1.0 kg a.i./ha		1676		8211		1630
	Cranberries	2.6 kg a.i./ha		645		3158		627
Open M/L wearing cotton coveralls over single layer, CR gloves; Closed Cab, wearing single layer, CR gloves								
WP	Grapes	1.0 kg a.i./ha	20 ha	484	N/A	903	N/A	451
Closed M/L (WSP) wearing single layer, CR gloves; Open Cab wearing single layer, CR hat (application only), CR gloves								
WDG/WP	Grapes	1.0 kg a.i./ha	20 ha	458	N/A	5147	N/A	453
Closed M/L (WSP) wearing single layer, CR gloves; Open Cab wearing cotton coveralls over single layer, CR hat (application only), CR gloves								
WDG	Cranberries	2.6 kg a.i./ha	20 ha	428	N/A	1980	N/A	416
	Apples, crabapples	3.0 kg a.i./ha		371		1716		360

Formulation	Crop	App Rate	ATPD[a]	MOE			Combined MOE[bd] Target = 300	
				Dermal[b] Target = 300	Inhal (ST)[c] Target = 300			
					No Resp	Resp[e]	No Resp	Resp[e]
WP		2.0 kg a.i./ha		557		2574		540
ECs (Baseline): Closed M/L (WSP), Closed Cab wearing single layer, CR gloves								
WP	Cranberries	5.0 kg a.i./ha	20 ha	631	1474	N/A	596	N/A

WP = wettable powder; WG = wettable granule; ATPD = area treated per day; App rate = application rate; Inhal = inhalation; M/L = mixer/loader; A = applicator; ST = short-term; No resp = without respirator; Resp = with respirator; CR = chemical-resistant; PPE = personal protective equipment; Single layer = long sleeved shirt, long pants; Headgear = chemical resistant hat that covers the neck; N/A = not applicable; MOE = margin of exposure

[a] Default ATPD value.

[b] Oral NOAEL of 10 mg/kg bw/day from a rabbit development study and a target MOE of 300. Since an oral NOAEL was selected, a dermal absorption value of 20% was used in a route-to-route extrapolation.

[c] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study and a short-term target MOE of 300.

[d] Combined MOE = NOAEL/ (dermal exposure + inhalation exposure), as both the dermal and inhalation exposure could contribute to the developmental endpoint identified in the oral developmental toxicity study.

[e] Respirators were assumed for WDG as they are currently on the label. Respirators were not included with closed cabs as the protection factor is already accounted for in the closed scenario and would be a double counting of protection. Respirators were also not included with closed mixing/loading. For scenarios where engineering controls were only applied to either mixing/loading or application, the 'resp' column was used as a respirator was assumed for the activity that did not have an engineering control.

Table 3 Occupational Short- to Intermediate-Term Mixer/Loader/Applicator Exposure and Risk Assessment for Handheld Application

Form	Crop	App Eqip	App Rate (Kg a.i./1000 L)	ATPD[a]	MOE					Combined MOE[be] Target = 300	
					Dermal[b] Target = 300	Inhal (ST)[c] Target = 300		Inhal (IT)[d] Target = 1000			
						No Resp	Resp[f]	No Resp	Resp[f]	No Resp	Resp[f]
Open M/L, wearing single layer, CR gloves											
WDG	Strawberry	Man PHW	1.0	150 L	24086	N/A	161546	N/A		N/A	23594
		Backpack			4754		118293				4727
	Cranberry	Man PHW	2.6		7411		62133				7289
		Backpack			1463		45497				1456
	Poinsettia	Man PHW	1.125		17128		143597	N/A	143597		16847
		Backpack			3380		105150		105150		3365
	Other Flowers	Man PHW	1.0		19269		161546		161546		18952
		Backpack			3803		118293		118293		3786
WP	Strawberry	Man PHW	1.0		1080	525	N/A	N/A		839	N/A
		Backpack			3569	6312				3307	
	Cranberry	Backpack	5.0		714	1262				661	

Form	Crop	App Eqip	App Rate (Kg a.i./1000 L)	ATPD[a]	MOE					Combined MOE[be] Target = 300	
					Dermal[b] Target = 300	Inhal (ST)[c] Target = 300		Inhal (IT)[d] Target = 1000			
						No Resp	Resp[f]	No Resp	Resp[f]	No Resp	Resp[f]
	Poinsettia	Man PHW	1.125		960	466		466	4664	745	933
		Backpack			3173	5610		5610	N/A	2940	N/A
	Other Flowers	Man PHW	1.0		1080	525		525	5247	839	1050
		Backpack			3569	6312		6312	N/A	3307	N/A
Open M/L, wearing cotton coveralls over single layer, CR gloves											
WDG	Strawberry	Mech PHG	1.0	3800 L	413	N/A	1939	N/A		N/A	401
	Poinsettia		1.125		294		1723	N/A	1723		287
	Other Flowers		1.0		331		1939		1939		323
Open M/L, wearing CR coveralls over single layer, CR gloves											
WP	Strawberry	Mech PHG	1.0	3800 L	486	142	1422	N/A		329	464
	Cranberry		5.0		75	28	284			55	72
	Poinsettia		1.125		346	126	1264	126	1264	250	333
	Other Flowers		1.0		389	142	1422	142	1422	281	374
Closed M/L (WSP) wearing cotton coveralls over single layer, CR gloves											
WP	Strawberry	Mech PHG	1.0	3800 L	429	195	1952	N/A		328	416
	Poinsettia		1.125		305	174	1735	174	1735	245	298
	Other Flowers		1.0		343	195	1952	195	1952	275	335
Closed M/L (WSP) wearing CR coveralls over single layer, CR gloves											
WP	Cranberry	Mech PHG	5.0	3800 L	115	39	390	N/A		82	111
WDG			2.6		222	N/A	751			N/A	213

Shaded cells indicate MOEs that are less than the target MOE. MOEs below the target MOE, but considered to be in the range of the target MOE were not shaded.

Form = formulation; WP = wettable powder; WDG = water dispersible granule; App Equip = application equipment; ATPD = area treated per day; App Rate= application rate; Inhal = inhalation; M/L = mixer/loader; ST = short-term; IT = intermediate-term; No resp = without respirator; Resp = with respirator**;** Man PHW = manually-pressurized handwand; Mech PHG = mechanically pressurized handgun; CR = chemical-resistant; PPE = personal protective equipment; Single layer = long sleeved shirt, long pants; N/A = not applicable; MOE = margin of exposure

[a] Default ATPD values were used.

[b] Oral NOAEL of 10 mg/kg bw/day from a rabbit development study and a target MOE of 300. Since an oral NOAEL was selected, a dermal absorption value of 20% was used in a route-to-route extrapolation.

[c] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study and a short-term target MOE of 300.

[d] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study and an intermediate-term target MOE of 1000. Intermediate-term inhalation exposure was assessed for crops that could be grown in greenhouses (flowers, greenhouse vegetables)

[e] Combined MOE = NOAEL/ (dermal exposure + inhalation exposure), as both the dermal and inhalation exposure could contribute to the developmental endpoint identified in the oral developmental toxicity study.

[f] Respirators were assumed for WDG formulations as they are already on the label. Respirators were not included with closed mixing/loading. For scenarios where engineering controls were only applied to mixing/loading, the 'resp' column was used as a respirator was assumed for application which did not have an engineering control.

Table 4 Occupational Intermediate- to Long-Term Industrial Exposure and Risk Assessment for Use of Folpet in Manufacturing

Application Method	Absorbed Dermal Exposure (µg/kg bw/day) [a]	Inhalation Exposure (µg/kg bw/day) [a]		Dermal MOE (Target = 300) [b]	Inhalation MOE (IT Target = 1000) (LT Target = 3000) [c]		Combined MOE (Target = 300) [d]	
		No Resp	Resp		No Resp	Resp	No Resp	Resp
Solid, open pour	221.48	8.93	0.89	45	157	1570	43	45
Solid, place (closed)	61.56	2.15	0.22	162	651	6360	157	162

IT = intermediate-term; LT = long-term; N/A = not applicable; MOE = margin of exposure
Shaded cells indicate where the MOE is less than the target MOE(s)
[a] Calculated using the daily exposure values normalized for body weight from the CMA study. Dermal exposure also includes the dermal absorption of 20%.
[b] Oral NOAEL of 10 mg/kg bw/day from a rabbit development study and a target MOE of 300. Since an oral NOAEL was selected, a dermal absorption value of 20% was used in a route-to-route extrapolation.
[c] Inhalation NOAEL of 1.4 mg/kg bw/day from a rat inhalation study. The intermediate-term target MOE is 1000, while the long-term target MOE is 3000.
[d] Combined MOE = NOAEL/ (dermal exposure + inhalation exposure), as both the dermal and inhalation exposure could contribute to the developmental endpoint identified in the oral developmental toxicity study.

Appendix VIII Commercial Postapplication Risk Assessment

Table 1 Occupational PostApplication Risk Assessment for Agricultural Crops

Crop	Rates [a] (kg a.i./ha)	Number of Apps[b]	RTI (days)	Activity	TC[c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
Greenhouse Ornamentals								
Poinsettia	1.13	2	10	Potted flower: all activities	230	5.05	**431**	0.5
Carnations	1.0	6	14	Cut flower: hand harvesting, hand pruning, disbudding	4000	7.72	**16**	126
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**282**	3
		5	14	Potted flower: all activities	230	7.23	**301**	0.5
Marigolds, zinnias, snapdragons	1.0	6	3	Cut flower: hand harvesting, hand pruning, disbudding	4000	12.7	**10**	147
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**171**	25
		3	3	Potted flower: all activities	230	7.01	**310**	0.5
Roses, asters, china asters, phloxes, chrysanthemums	1.0	6	7	Cut flower: hand harvesting, hand pruning, disbudding	4000	10.4	**12**	139
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**210**	16
		3	7	Potted flower: all activities	230	6.43	**338**	0.5
Irises	1.0	4	7	Cut flower: hand harvesting, hand pruning, disbudding	4000	7.96	**16**	127
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**273**	5
		3	7	Potted flower: all activities	230	6.43	**338**	0.5
All cut flowers		1	N/A	Cut flower: hand harvesting, hand pruning, disbudding	4000	2.5	**50**	78
				Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**870**	0.5
Fruit and Berry Crops								
Apples, crabapples	3.0 (WDG)	6	10	Thinning fruit	3000	1.83	**91**	>35
				Hand harvesting	1400		**195**	6
				Hand pruning, scouting, training	580		**470**	0.5
				Transplanting	230		**1186**	0.5

Crop	Rates [a] (kg a.i./ha)	Number of Apps [b]	RTI (days)	Activity	TC [c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
				Hand weeding, propping, orchard maintenance	100		**2727**	0.5
				Moving irrigation pipes by hand	1750	REI not required. Only applicable for ornamental crabapple use.		
				Mechanical weeding, mechanical harvesting, irrigation (non-hand set), frost control, spreading bins	No TC	REI not required[g]		
		3	10	Thinning fruit	3000	1.39	**120**	21
				Hand harvesting	1400		**257**	3
				Hand pruning, scouting, training	580		**620**	0.5
				Transplanting	230		**1564**	0.5
				Hand weeding, propping, orchard maintenance	100		**3597**	0.5
		2	10	Thinning fruit	3000	1.10	**152**	6
				Hand harvesting	1400		**325**	0.5
				Hand pruning, scouting, training	580		**785**	0.5
				Transplanting	230		**1979**	0.5
				Hand weeding, propping, orchard maintenance	100		**4553**	0.5
		1	N/A	Thinning fruit	3000	0.85	**197**	3
				Hand harvesting	1400		**423**	0.5
				Hand pruning, scouting, training	580		**1020**	0.5
				Transplanting	230		**2572**	0.5
				Hand weeding, propping, orchard maintenance	100		**5915**	0.5
Apples, crabapples	2.0 (WP)	6	10	Thinning fruit	3000	1.22	**136**	35
				Hand harvesting	1400		**292**	0.5
				Hand pruning, scouting, training	580		**705**	0.5
				Transplanting	230		**1779**	0.5
				Hand weeding, propping, orchard maintenance	100		**4091**	0.5
				Mechanical weeding, mechanical harvesting, irrigation (non-hand set), frost control, spreading bins	No TC	REI not required[g]		
		3	10	Thinning fruit	3000	0.93	**180**	3
				Hand harvesting	1400		**385**	0.5
				Hand pruning, scouting, training	580		**930**	0.5
				Transplanting	230		**2346**	0.5
				Hand weeding, propping, orchard maintenance	100		**5396**	0.5
		2	10	Thinning fruit	3000	0.73	**228**	3
				Hand harvesting	1400		**488**	0.5
				Hand pruning, scouting, training	580		**1177**	0.5
				Transplanting	230		**2969**	0.5
				Hand weeding, propping, orchard maintenance	100		**6829**	0.5
Apples, crabapples	2.4 [g] (WDG-typical)	6	10	Thinning fruit	3000	1.47	**114**	>35
				Hand harvesting	1400		**244**	3
				Hand pruning, scouting, training	580		**588**	0.5

Crop	Rates [a] (kg a.i./ha)	Number of Apps [b]	RTI (days)	Activity	TC [c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
				Transplanting	230		**1482**	0.5
				Hand weeding, propping, orchard maintenance	100		**3409**	0.5
				Mechanical weeding, mechanical harvesting, irrigation (non-hand set), frost control, spreading bins	No TC	REI not required [g]		
		3	10	Thinning fruit	3000	1.11	**150**	6
				Hand harvesting	1400		**321**	0.5
				Hand pruning, scouting, training	580		**775**	0.5
				Transplanting	230		**1955**	0.5
				Hand weeding, propping, orchard maintenance	100		**4497**	0.5
		2	10	Thinning fruit	3000	0.88	**190**	3
				Hand harvesting	1400		**407**	0.5
				Hand pruning, scouting, training	580		**981**	0.5
				Transplanting	230		**2474**	0.5
				Hand weeding, propping, orchard maintenance	100		**5691**	0.5
Grapes	1.0	4	10	Table/raisin grapes only: girdling, turning	19300	3.78	**7**	36
				Hand harvesting, tying/training, leaf pulling	8500		**16**	29
				Scouting, hand weeding, hand pruning, propagating, bird control, trellis repair	640		**207**	4
				Transplanting	230		**575**	0.5
				Moving irrigation pipes by hand (hand-set)	1750	REI not required as handline irrigation does not occur in grapes		
				Mechanical harvesting, mechanical weeding, burn down, ditching, mechanical pruning, irrigation (non-hand-set)	No TC	REI not required [g]		
		1	N/A	Table/raisin grapes only: girdling, turning	19300	2.50	**10**	32
				Hand harvesting, tying/training, leaf pulling	8500		**24**	25
				Scouting, hand weeding, hand pruning, propagating, bird control, trellis repair	640		**313**	0.5
				Transplanting	230		**870**	0.5
				Moving irrigation pipes by hand	1750		**114**	10
Strawberries	2.0	6	7	Hand harvesting	1100	9.47	**48**	18
				Transplanting	230	REI not required as activity occurs before pesticide application		
				Scouting	210	9.47	**251**	2
				Hand weeding, canopy management	70		**754**	0.5
				Mechanical weeding, irrigation (non-hand-set)	No TC	REI not required [g]		
		1	N/A	Hand harvesting	1100	5.00	**91**	12
				Scouting	210		**476**	0.5
				Hand weeding, canopy management	70		**1429**	0.5

Crop	Rates [a] (kg a.i./ha)	Number of Apps [b]	RTI (days)	Activity	TC [c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
Cranberries	5.0 (WP)	2	10	Hand harvesting (raking), scouting	1100	16.9	**27**	23
				Transplanting	230	REI not required as activity occurs before pesticide application		
				Hand pruning (shears), hand weeding	70	16.9	**424**	0.5
				Mechanical harvesting (flooding), mechanical weeding, ditching, frost control, sanding, irrigation (non-hand-set)	No TC	REI not required [g]		
	2.6 (WDG)			Hand harvesting (raking), scouting	1100	8.77	**52**	17
				Hand pruning (shears), hand weeding	70		**815**	0.5
				Mechanical harvesting (flooding), mechanical weeding, ditching, frost control, sanding, irrigation (non-hand-set)	No TC	REI not required [g]		
	5.0 (WP)	1	N/A	Hand harvesting (raking), scouting	1100	12.5	**36**	21
				Hand pruning (shears), hand weeding	70		**571**	0.5
	2.6 (WDG)			Hand harvesting (raking), scouting	1100	5.00	**91**	12
				Hand pruning (shears), hand weeding	70		**1429**	0.5
Field Vegetable Crops								
Cucumbers, pumpkin, melons, squash	4.0	6	7	Hand harvesting, mechanically-assisted harvesting, training, turning (pumpkin, melon only)	550	18.9	**48**	18
				Transplanting	230	REI not required as activity occurs before pesticide application		
				Scouting, hand weeding, thinning fruit, hand pruning (melons only)	90	18.9	**293**	1
				Moving irrigation pipes by hand (hand-set)	1750		**15**	29
				Mechanical weeding, irrigation (non-hand set), fertilizing	No TC	REI not required [g]		
		1	N/A	Hand harvesting, mechanically-assisted harvesting, training, turning (pumpkin, melon only)	550	10.0	**91**	12
				Scouting, hand weeding, thinning fruit, hand pruning (melons only)	90		**556**	0.5
				Moving irrigation pipes by hand	1750		**29**	23
Cucumbers, pumpkin, melons, squash	3.0 (WP-typical)	6	7	Hand harvesting, mechanically-assisted harvesting, training, turning (pumpkin, melon only)	550	14.2	**64**	15
				Scouting, hand weeding, thinning fruit, hand pruning (melons only)	90		**391**	0.5
				Moving irrigation pipes by hand	1750		**20**	26
				Mechanical weeding, irrigation (non-hand set), fertilizing	No TC	REI not required [g]		
		1	N/A	Hand harvesting, mechanically-assisted harvesting, training, turning (pumpkin, melon only)	550	7.50	**121**	9
				Scouting, hand weeding, thinning fruit, hand pruning (melons only)	90		**741**	0.5

Crop	Rates [a] (kg a.i./ha)	Number of Apps [b]	RTI (days)	Activity	TC [c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
				Moving irrigation pipes by hand	1750		**38**	20
Tomatoes	4.0	6	7	Hand harvest, tying/training	1100	18.94	**24**	24
				Transplanting	230	REI not required as activity occurs before pesticide application		
				Scouting	210	18.94	**126**	9
				Hand weeding, hand pruning	70		**377**	0.5
				Irrigation (non-hand-set	No TC	REI not required[g]		
		1	N/A	Hand harvest, tying/training	1100	10.00	**45**	18
				Scouting	210		**238**	3
				Hand weeding, hand pruning	70		**714**	0.5
Outdoor Ornamentals								
Carnation	1.0	6	14	Cut flower: hand harvesting, hand pruning, disbudding	4000	3.24	**39**	20
				Moving irrigation pipers by hand (hand-set)	1750		**88**	12
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**671**	0.5
				Non-hand-set irrigation	No TC	REI not required[g]		
Marigold, Zinnias, Snapdragons		6	3	Cut flower: hand harvesting, hand pruning, disbudding	4000	7.84	**16**	28
				Moving irrigation pipers by hand (hand-set)	1750		**36**	21
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**277**	1
				Non-hand-set irrigation	No TC	REI not required[g]		
		5	3	Potted flower: all activities	230	7.33	**297**	0.5
				Moving irrigation pipers by hand (hand-set)	1750		**39**	20
Roses, asters, china asters, phloxes, chrysanthemums		6	7	Cut flower: hand harvesting, hand pruning, disbudding	4000	4.73	**26**	24
				Moving irrigation pipers by hand (hand-set)	1750		**60**	16
				Potted flower: all activities Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**459**	0.5
				Non-hand-set irrigation	No TC	REI not required[g]		
Irises		4	7	Cut flower: hand harvesting, hand pruning, disbudding	4000	4.54	**28**	23
				Moving irrigation pipers by hand (hand-set)	1750		**63**	15
				Potted flower: all activities Cut flower: container moving,	230		**479**	0.5

Crop	Rates [a] (kg a.i./ha)	Number of Apps[b]	RTI (days)	Activity	TC[c] (cm^2/hr)	Day 0 DFR [d]	Day 0 MOE [e] (Target = 300)	REI [f] (days)
				pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting				
				Non-hand-set irrigation	No TC	REI not required[g]		
All cut flowers		1	N/A	Cut flower: hand harvesting, hand pruning, disbudding	4000	2.50	**50**	18
				Moving irrigation pipers by hand (hand-set)	1750		**114**	10
				Cut flower: container moving, pinching, hand pruning (low height), hand weeding, plant support/staking, scouting, transplanting	230		**870**	0.5
Crabapples	3.0 (WDG)	6	10	All activities, except for moving irrigation pipes by hand	230	1.83	**1186**	0.5
				Moving irrigation pipes by hand	1750		**156**	21
		3	10	All activities, except for moving irrigation pipes by hand	230	1.39	**1564**	0.5
				Moving irrigation pipes by hand	1750		**206**	3
	2.0 (WP)	6	10	All activities, except for moving irrigation pipes by hand	230	1.22	**1779**	0.5
				Moving irrigation pipes by hand	1750		**234**	3
		3	10	All activities, except for moving irrigation pipes by hand	230	0.93	**2346**	0.5
				Moving irrigation pipes by hand	1750		**308**	0.5

Shaded cells indicate those calculated MOEs that are below the target MOE of 300 on the day after the last application.

NA = Not Applicable; RTI = Re-treatment Interval; DFR = Dislodgeable Foliar Residue; REI = Restricted Entry Interval; MOE = margin of exposure

[a] Maximum listed label rates expressed in kilograms a.i./hectare for both wettable powder (WP) and water dispersible granule (WDG), unless otherwise specified.

[b] Maximum number of applications per season. When calculated REIs were not agronomically feasible at the maximum number of applications per season, postapplication exposure was calculated with a reduced number of applications per season.

[c] Transfer coefficients (TC).

[d] Day 0 DFR = Dislodgeable Foliar Residues on Day 0 after application. Dislodgeable foliar residue values for non-tree crops were calculated using the peak DFR of 25% of the application rate for day 0 and 10% dissipation per day except for greenhouse crops. For greenhouse ornamental crops, the default dissipation rate of 2.3% per day was assumed. For apples and crabapples, actual DFR data from the avocado DFR study was used; therefore, the REI days were limited by the days that were sampled in the DFR study.

[e] Dermal MOE on Day 0 = NOAEL/ ($DFR_{Day\ 0}$ × Transfer Coefficient × 8 hr × 20% dermal absorption / 80 kg). MOE on day 0 after application; based on the NOAEL of 10 mg/kg bw/day from the oral rabbit developmental toxicity study, target MOE for all durations of 300.

[f] Day at which the dermal exposure results in an MOE ≥ Target MOE (300). For apples and crabapples, the REI day was limited by the available sampling days in the DFR study.

[g] Dermal exposure is expected to be minimal for this activity due to limited contact with treated foliage, so an REI is not required.

Appendix IX Aggregate Risk Assessment

Table 1 Residential Aggregate Exposure and Risk Assessment

Sub-population	Form	Scenario[a]	Residential Exposure[b] (mg/kg bw/day)	Dietary Exposure[c] (mg/kg bw/day)	Total Exposure[d] (mg/kg bw/day)	Aggregate MOE[e] Target = 300 (100 for children)
Trees (apple, crabapple, ornamental) following commercial application						
Adults (80 kg)	WP	Post-App activities	0.0238	0.00090	0.0247	405
Youth (57 kg)			0.0138	0.00039	0.0141	707
Children (32 kg)			0.0163	0.00072	0.0170	1000

Form = formulation, WP = wettable powder; Post-app = postapplication; MOE = margin of exposure

[a] Postapplication following commercial application of the commercial wettable powder product to residential trees

[b] Total exposure from postapplication activities.

[c] Chronic dietary background exposure.

[d] Total exposure from dermal and dietary exposure

[e] MOE = NOAEL/Total Exposure. Based on the short-term aggregate endpoints. For youth and adults: an oral NOAEL of 20 mg/kg bw/day and target MOE of 300. For children, an oral NOAEL of 17 mg/kg bw/day and target MOE of 100 was used.

Appendix X Environmental Fate, Toxicity and Risk Assessment of Folpet

Table 1 Fate and Behaviour of Folpet in the Environment

Study type	Test material	Study Conditions	Value or Endpoint	Interpretation[1,2, 3, 4 ,5, 6]	Transformation products*	Reference
Abiotic transformation						
Hydrolysis	Folpet	pH 4, 5, 7 and 9	DT_{50} at pH 4 = 0.27 d DT_{50} at pH 5 = 0.11 – 0.14 d^2 DT_{50} at pH 7 = 0.03 - 0.06 d^2 DT_{50} at pH 9 = 0.0008 – 0.001 d^2	An important route of transformation in the environment	Phthalimide (44% AR at pH 7) Phthalic acid (46.2% AR at pH 7)	1347712 1752901 1837706
	Phthalimide	pH 4, 7 and 9. 25^{0}C	DT_{50} at pH 4 = 0.23 d DT_{50} at pH 7 = 0.31 d DT_{50} at pH 9 = 0.08 – 0.11 d		Not determined	1347713
Phototransformation - soil	Folpet	pH 5.3, 2.9% OM	Not determined	Not a major route of transformation in the environment	Phthalimide (36% AR at end)	1752901
Phototransformation - water		pH 3	Not determined		Not determined	1130266
Biotransformation						
Soil- aerobic	Folpet	Clay loam, 20ºC, pH 7.5 Silt loam, 20ºC, pH 6.2 Loamy sand, 20ºC, pH 4.8 Silt loam, 10ºC, pH6.2	DT_{50} = 0.2 – 3.8 d (SFO) DT_{50} (80^{th} percentile of 5 soils) = 2.8 d	Non-persistent. A major route of transformation in the environment	Phthalimide (64.9% AR at day 5) Phthalic acid (16.6% AR at day 1) Phthalamic acid (16.6% AR at day 1)	1347719 1347718 1347721 1752901 1837706
	Phthalic acid	Clay loam, 20ºC, pH 7.5 Silt loam, 20ºC, pH 6.2 Loamy sand, 20ºC, pH 4.8 Silt loam, 10ºC, pH6.2	DT_{50} = 0.6 – 4.1 d		Not determined	1347719
	Phthalamic acid	Clay loam, 20ºC, pH 7.5 Silt loam, 20ºC, pH 6.2 Loamy sand, 20ºC, pH 4.8 Silt loam, 10ºC, pH6.2	DT_{50} = 0.4 – 0.8 d		Not determined	1347719
	Phthalimide	Clay loam, 20ºC, pH 7.5 Silt loam, 20ºC, pH 6.2 Loamy sand, 20ºC, pH 4.8 Silt loam, 10ºC, pH6.2	DT_{50} = 0.5 – 17.2 d	Non-persistent to slightly persistent	Not determined	1347719 1347721
Soil – anaerobic	Folpet	Sandy loam, pH 5.4, 2.0% OM	DT_{50} = 7.0 – 14.6 d (SFO)	Non-persistent. A major route of transformation in the environment	Phthalimide (36%AR at end) Phthalic acid (13.6% AR at end)	1130267 1837706

Water/sediment - aerobic	Folpet	Not reported	DT_{50} < 0.02 d DT_{90} < 0.06 d	Non-Persistent. A major route of transformation in the environment in combination with hydrolysis	Phthalimide (26% AR at end) Phthalamic acid (13.3%AR at end) Phthalic acid (37.5% AR at end) Benzamide (10.2% AR at end) 2-cyanobenzoic acid (39.7% at end)	1752899
	Phthalimide		DT_{50} = 0.5 – 0.6 d		Not reported	
	Phthalamic acid		DT_{50} = 3.6 – 6.0 d		Not reported	
	Phtalic acid		DT_{50} = 1.4 – 6.5 d		Not reported	
	Benzamide		DT_{50} = 1.6 d		Not reported	
	2-cyanobenzoic acid		DT_{50} = 0.3 – 0.7 d		Not reported	
Water/sediment- anaerobic	Folpet		No data			
Mobility						
Adsorption/ desorption	Folpet	Loamy sand, pH 5.1, 3% OM Sandy loam, pH 5.3, 2.9% OM Loam, pH 6.9, 1.3% OM Silt loam, pH 8, 1.4% OM	K_{oc} =7.4 – 304 mL/g	Moderate mobility to very high mobility	Not determined	1347726 1752901
	Phthalimide	Not reported	K_{oc} = 72 – 385 mL/g	Slight mobility	Not reported	1752899
	Phthalamic acid	Not reported	K_{oc} = 10 mL/g	Immobile	Not reported	
	Phtalic acid	Not reported loam	K_{oc} =73 mL/g	Slight mobility	Not reported	
Soil column leaching	Folpet	Sandy loam, pH 5.3, 2.9% OM	No detection< 0-15 cm soil segment	Not expected to leach	Not reported	1347728 1752901
Cohen criteria	Folpet	Solubility in water = 1.2 mg/L K_d = 0.13-0.22 K_{oc} = 7.4 – 304 Henry's law const. = 2.96×10^{-3} $atm.m^3/mol$ pKa = not applicable Hydrolysis DT_{50}= 0.06 d Soil phototransformation DT_{50} = 17 - 68 d Soil biotransformation DT_{50} = 0.2 – 3.8 d	3/8 citeria met	Low potential for leaching	-	1837706
GUS score	Folpet	Soil DT_{50} = 0.2 – 3.8 d K_{oc} = 7.4 - 304	-1.9 – 1.8	Not a leacher	-	1837706
Volatility	Folpet	Hydrolysis, pH 7 = DT_{50} = 0.03 - 0.06 d^2 Vapour pressure = 2.1×10^{-5} Pa	No data	Not expected to be volatile due to high hydrolysis rate and low vapour pressure	Not reported	1752899 1752901
Field Studies						
Field dissipation	Folpet	Loamy fine sand, pH 8.1, 0.5% OM	DT_{50} = 1.1	Non persistent	Phthalimide	1347707
	Phthalimide		DT_{50} = 2.8		Not determined	
Bioconcentration						
28-D BCF on Bluegill sunfish (lepomis macrochirus)	Folpet	Esposure period = 0, 0.17, 1, 3, 7, 14, 21 and 28 d	BCF < LOD in most fish parts	No bioconcentration	Phthalic acid (> 10% AR)	1347766 1752901

[1] Soil persistence classification according to Goring et al. 1975
[2] Water persistence classification according to McEwen and Stephenson, 1979
[3] Soil mobility potential classification according to McCall et al. 1981
[4] Ground Ubiquity Score (GUS) according to Gustafson (1989)
[5] Leaching Potential Criteria according to Cohen et al. 1984
[6] Volatility classification according to the USEPA, 1975.

Table 2 Toxicity of Folpet to Non-Target Terrestrial Organisms

Organism (Species)	Exposure	Test substance	Endpoint value	Comments	Reference (PMRA Number)
Invertebrates					
Earthworm	Acute	Folpan 80 WDG	14 d LC_{50}> 1000 mg product /kg	ND	1347868
	Acute	TGAI	14 d LC_{50}> 1000 mg a.i./kg	ND	1752899
	Acute	Folpan 80 WDG	14 d LC_{50}> 828 mg EP/kg		
	Reproduction	TGAI	Reproductivity NOEC = 5.18 mg a.i./kg soil		
Honey bee	Acute oral	TGAI	LD_{50} >236 µg a.i./bee LD_{50} >236 µg a.i./bee	Practically non-toxic	1347732 1752901 1752899 1347732
	Acute contact	TGAI	LD_{50} 12.1 µg a.i./bee LD_{50} > 200 µg a.i./bee		
	Chronic adult oral and brood	TGAI	NOEC = 1000 mg a.i./kg	ND	Stoner and Wilson, 1985
	Larvae	Captan TGAI	NOEC = 5000 g a.i./ha	ND	Everich *et al.* 2009
Predators and parasites *Typhlodromus pyri* (predatory mite) foliar dwelling	Acute oral	Folpan 80 WDG	LR_{50} > 5250 g a.i./ha	ND	1752899
	Acute oral	Folpan 80 WDG	**LR/ER_{50} > 5250 g a.i./ha**	ND	1752899
Birds					
Bobwhite quail	Acute oral	TGAI (92.5% a.i.)	LD_{50} > 2150 mg a.i./kg bw	Practically non-toxic	1752901 1752899 1226673
	5-d dietary	TGAI (92.5% a.i.)	5-d LC_{50} > 5000 mg a.i./kg diet > 1127 mg a.i./kg bw/d		
	Reproduction	TGAI	NOEC = 1000 mg a.i./kg diet (highest concentration tested) 78.3 mg a.i./kg bw/d	ND	
Mallard duck	Acute oral	TGAI (92.4% a.i.)	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	
	5-d dietary	TGAI (92.5% a.i.)	5-d LC_{50} > 5000 mg a.i./kg diet > 746 mg a.i./kg bw/d		
	Reproduction	TGAI	NOEC = 1000 mg a.i./kg diet (highest concentration tested) 90.0 mg a.i./kg bw/d	ND	
Japanese Quail	Acute oral	TGAI (92.4% a.i.)	LD_{50} > 2440 mg a.i./kg bw	Practically non-toxic	

Green finch	Acute oral	TGAI (92.4% a.i.)	LD_{50} > 1340 mg a.i./kg bw	Practically non-toxic	
Mammals					
Mice	Acute oral	TGAI	LD_{50} > 2440 mg a.i./kg bw/d	Low toxicity	1837706
	Acute dietary	TGAI	4-weeks NOEL = 180 mg a.i./kg bw/d 4-weeks LOEL = 874 mg a.i./kgbw/d	ND	1837706
Rats	Reproduction	TGAI	2- gen. NOEL: 14 mg a.i./kg bw/d 2- gen. LOEL: 70 mg a.i./kg bw/d	ND	1837706
Vascular plants					
Monocots: (wheat, barley, oat and rye)	Vegetative vigour	Folpan 80 WDG	EC_{25} > 6.4 kg a.i./ha	ND	1752899
Seedling emergence		NA	NA	Not needed at this time	NA

ND = Not determined; NA = Not available

Table 3 Toxicity Effects of Folpet and Transformation Products to Aquatic Organisms

Organism (Species)	Substance	Exposure	Test substance	Endpoint value	Degree of toxicity[1]	Reference (PMRA Number)
Freshwater species						
Invertebrate: *Daphnia magna*	Folpet	Acute	TGAI (90.3%)	48-hour EC_{50} = 20 µg a.i./L	Very highly toxic	1752901
			Formulation 88%	48-hour EC_{50} >1500 µg EUP/L	Moderately toxic	1752901
			Formulation 87.5%	24-hr EC_{50} = 85 µg EUP/L	Very highly toxic	1752901
			Folpan 80 WDG	48-hour EC_{50} = 680 µg a.i./L	Highly toxic	1752899
		Chronic	TGAI	NOEC = 1880 µg a.i./L highest concentration tested	-	1752901
	Phthalimide	Acute		48-hr EC_{50} = 39 000 µg a.i./L	Practically non-toxic	1752899
	Phthalic acid			48-hr $EC_{50} \geq$ 100 000 µg a.i./L		
	Phthalamic acid			48-hr $EC_{50} \geq$ 100 000 µg a.i./L		
	Benzamide			48-hr $EC_{50} \geq$ 102 000 µg a.i./L		
	2-cyanobenzoic acid			48-hr $EC_{50} \geq$ 100 000 µg a.i./L		
Invertebrate: *Gammarus fasciatus*		Acute	TGAI	96-hour EC_{50} >2500 µg a.i. /L	Moderately toxic	1752901
Cold fish: Rainbow trout *Onchorynchus mykiss*	Folpet	Acute	Flow-through TGAI (90.3%)	96-hour LC_{50} = 15 µg a.i./L	Very highly toxic	134774 1752901
			Flow-through Folpan 80 WDG (80.3%)	96-hour LC_{50} = 83 µg a.i./L NOEC = 24.1 µg a.i./L	Very highly toxic	1347838

			Formulation 88%	96-hour LC_{50} = 52.1 µg a.i./L	Very highly toxic	1752901
			75WP	96-hour LC_{50} = 170 µg a.i./L	Highly toxic	1752901
			50 WP	96-hour LC_{50} = 185 µg a.i./L	Highly toxic	1752901
			Fungitrol 11-50 (44% a.i.)	96-hour LC_{50} = 71 µg a.i./L	Very highly toxic	1752901
			Static – TGAI (90.3%)	96-hour LC_{50} = 218 µg a.i./L	Highly toxic	134774 1752899
			Folpan 500 SC	96-hour LC_{50} = 133 µg a.i./L	Highly toxic	1752899
	Phthalic acid Phthalamic acid Benzamide 2-cyanobenzoic acid		TGAI	96-hr LC_{50} > 100 000 µg a.i./L	Practically non-toxic	1752899
	Folpet	Chronic	Folpan 500 SC	28-day LC_{50} = 110 µg a.i./L	-	1752899
				28-day LC_{50} = 212 µg EUP/L (or 110 µg a.i./L) NOEC = 37.5 µg EUP/L (or 19.5 µg a.i./L	-	1347843
Cold fish:Brown trout, *Salmo trutta lacustris*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 29 µg a.i./L	Very highly toxic	1752901
				96-hour LC_{50} = 66 µg a.i./L		
			TGAI	96-hour LC_{50} = 98 µg a.i./L	Very highly toxic	1752899
Cold fish:Coho salmon, *Onchorynchus kisutch*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 106 µg a.i./L	Highly toxic	1752901
Cold fish:Lake trout *Salmo trutta sp.*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 24 µg a.i./L	Very highly toxic	1752901
				96-hour LC_{50} = 87 µg a.i./L	Very highly toxic	1752901
Warm fish:, Bluegill sunfish, *Lepomis macrochirus*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 47 µg a.i./L	Very highly toxic	1752901
			Formulation 88%	96-hour LC_{50} = 72 µg a.i./L	Very highly toxic	1752901
			50 WP	96-hour LC_{50} = 675 µg a.i./L	Highly toxic	1752901
			Fungitrol 11-50 (44% a.i.)	96-hour LC_{50} = 117 µg a.i./L	Highly toxic	1752901
	Phthalimide	Acute	TGAI	96-hour LC_{50} = 38 000 µg a.i./L	Practically non-toxic	1752899
Channel catfish, *Ictalurus punctatus*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 108 µg a.i./L	Highly toxic	1752901
Smallmouth bass *Micropterus dolomieu*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 91 µg a.i./L	Very highly toxic	1752901
Yellow perch *Perca flavescens*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 177 µg a.i./L	Highly toxic	1752901
Fathead minnow *Pimephales promelas*	Folpet	Early Life Stage	TGAI (93.2% a.i.)	LOEC = 17.7 µg a.i./L NOEC = 8.81 µg a.i./L[1]	-	1347765
Green algae, *Scenedesmus subspicatus*	Folpet	Acute	Folpan 80 WDG (80.6% a.i.)	ErC_{50} = 130 700 µg a.i./L EbC_{50} = 19 400 µg a.i./L NOEC = 8300 µg a.i./L	-	1347861
			TGAI	72-hr EC_{50} = 100 µg a.i./L	-	1752901

			TGAI	72-hr ErC_{50} and EbC_{50} >10 000 µg a.i./L	-	1752899
			TGAI (96%)	72-hr EbC_{50} = 6300 µg a.i./L NOEC = 700 µg a.i./L	-	1347777
Green algae, *Selenastrum capricornutum*	Folpet	Acute	Folpan 80 WDG (80.6% a.i.)	96-hr EC_{50} = 1400 µg a.i./L 96-hr ErC_{50} > 3000 µg a.i./L NOEC = 400 µg a.i./L	-	1347832
	Phthalic acid Phthalamic acid Benzamide 2-cyanobenzoic acid		TGAI	96-hr EbC50 > 100 000 µg a.i./L	-	1752899
Algae, *Navicula pelliculosa*	Folpet	Acute	Folpan 80 WDG (80.6% a.i.)	96-hr EC_{50} = 40.3 µg a.i./L 96-hr ErC_{50} > 46.0 µg a.i./L NOEC = 24.1 µg a.i./L	-	1347833
Algae, *Anabaena flos aquae*	Folpet	Acute	Folpan 80 WDG (80.6% a.i.)	96-hr EC_{50} = 900 µg a.i./L 96-hr ErC_{50} = 2200 µg a.i./L NOEC = 300 µg a.i./L	-	1347834
Vascular plant: *Lemna gibba*	Folpet	Dissolved	Folpan 80 WDG (80.6% a.i.)	7-day ErC_{50} and Eb C_{50} >2900 µg a.i./L NOEC = 1400 µg a.i./L	-	1347836 1347782
Marine species						
Shell deposition, Eastern oyster, *Crassostrea virginica*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50} = 120 µg a.i./L	-	1347744
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour LC_{50} = 65µg a.i./L NOEC = 38.1µ g a.i./L	Very highly toxic	1347763
Algae: diatom *Skeletonema costatum*	Folpet	Acute	Folpan 80 WDG (80.6% a.i.)	96-hour EC_{50} = 180 µg a.i./L NOEC = 30 µg a.i./L 96-hour ErC_{50} = 300µg a.i./L NOEC = 70 µg a.i./L	-	1347835

[2] USEPA classification, where applicable

Screening Level Risk Assessment to Terrestrial Invertebrates

Table 4 Screening Level risk Assessment for Honey Bees from Direct Applications of Folpet

Measurement Endpoint	Exposure Route	Single Application rate (kg a.i./ha)	Exposure Estimate [a]	Acute Effect Endpoint In µg a.i./bee (PMRA reference)	RQ	LOC (0.4) exceeded?
Foliar Applications (DT_{50} = 8.9 days)						
Individual Survival (adults)	Contact	5 (cranberries)+	12 μg a.i./bee	LD_{50} = 12.1 (1752901)	0.99	YES
				LD_{50} >200 (1752899, 1347732)	<0.06	NO
Individual Survival (adults)	Diet		145 μg a.i./bee	LD_{50} >236 (1752899, 1347732)	<0.61	YES
Individual Survival (adults)	Contact	4 (cucurbits and tomatoes)	9.6 μg a.i./bee	LD_{50} = 12.1 (1752901)	0.79	YES
				LD_{50} >200 (1752899, 1347732)	<0.05	NO
Individual Survival (adults)	Diet		116 μg a.i./bee	LD_{50} >236 (1752899, 1347732)	<0.58	YES
Individual Survival (adults)	Contact	2.4 (apples and berries)	5.76 μg a.i./bee	LD_{50} = 12.1 (1752901)	0.48	YES
				LD_{50} >200 (1752899, 1347732)	<0.03	NO
Individual Survival (adults)	Diet		69.6 μg a.i./bee	LD_{50} >236 (1752899, 1347732)	<0.29	NO

[a]For contact exposure, the exposure estimate = (2.4 μg a.i./bee)*(application rate in kg a.i./ha);
for dietary exposure, the exposure estimate = (29 μg a.i./bee)*(application rate in kg a.i./ha).
LOC is 0.4 for acute pollinator studies.
+ use currently not supported by PMRA.

Table 5 Risk Assessment for Earthworms from Direct Applications and Off-Site Spray Drift of Folpet

Exposure	Crop	Folpet Appl. Rate g a.i./ha × No. of appl[1]	Minimum day interval between application	Spray technology	EEC in soil Direct Overspray mg a.i./kg soil[4]	Endpoint (mg a.i./kg soil)[5]	Acute RQ = EEC/Tox Endpoint	LOC exceeded
Acute	Cranberries	5000 × 2	10	GB[2]	2.41	> 500	< 0.005	No
	Cucurbits and tomatoes	4000 × 6	7	GB	2.16		< 0.004	No
	Apples	2400 × 6	10	AB[3]	1.16		< 0.002	No
Reproduction	Cranberries	5000 × 2	10	GB	2.41	5.18	0.470	No
	Cucurbits and tomatoes	4000 × 6	7	GB	2.16		0.417	No
	Apples	2400 × 6	10	AB	1.16		0.224	No

[1] No. of appl = number of application
[2] GB = Groundboom
[3] AB = Airblast
[4] EEC is based on an aerobic soil DT_{50} of 2.8 days, cumulative rates of application and a soil depth of 15 cm
[5] Toxicity endpoint for folpet acute 14 d-LD_{50} × ½ = 400 mg a.i./kg of soil and reproduction NOEC = 5.18 mg a.i./kg soil.

Table 6 Risk Assessment for Predators and Parasites from Direct Applications and Off-Site Spray Drift of Folpet

Organisms	Crop	Folpet appl. Rate g a.i./ha × No. of appl.[1]	Minimum day interval between appl.	Spray technology	EEC direct overspray kg a.i./ha[2]	Endpoint LR/ER_{50} or ER_{50} (kg a.i./ha)	Acute RQ = EEC/tox endpoint[3]	EEC spray drift[4] kg a.i./ha	Off-site Acute RQ = spray drift / tox endpoint	LOC exceeded
Predatory arthropods										
T. pyri; C. septempunctata and *C. carnea*[5]	Cranberries	5000 × 2	10	GB	7.295	>5.250	**< 1.39**	0.438	< 0.08	No
	Cucurbits and tomatoes	4000 × 6	7	GB	9.158		**< 1.74**	0.549	< 0.10	No
	Apples	2400 × 6	10	AB	5.494		**< 1.05**	4.065	< 0.77	No
Parasitic arthropods										
A.Rhopalosiphi[6]	Apples	2400 × 6	10	AB	3.600[7]	>3.380	**< 1.74**	2.100	<0.62	No

[1]appl = application
[2]umulative soil application
[3]Toxicity Endpoint to predatory arthropods: acute LR/ER_{50} >5250 g a.i./ha and to parasitic arthropods: ER_{50} >3380 g a.i./ha
[4]Spray drift 6% ground boom applications; 74% early season airblast applications
[5] *T. pyri = Typhlodromus pyri , C. septempunctata = Coccinella septempunctata, C. carnea = Chrysoperla carnea*
[6] *A. rhopalosiphi = Aphidius rhopalosiphi*

[7]EEC values obtained from EFSA, 2006 for apple crops; Shaded values indicate that RQ is above the LOC.

Screening Level and Refined Risk Assessment for Birds and Mammals

Table 7 Parameters Used in Screening and Refined Risk Assessment of Birds and Mammals Exposed to Folpet

Crop scenario	RA Type[1]	Tech[2]	Rate (g a.i./ha)	Droplet size	Timing[3]	No. applic	Time Interval (d)	Foliage DT_{50} (d)	Off field Drift (%)	Mean nomog[4]	Comments
Tomatoes and cucurbits	Screening	GB	4000	Medium	Anytime	6	7	8.9	6	No, only Max	This is assuming a continuous application of folpet at each 7 days. This worst case scenario is not recommended by agronomists and other field specialists and most of the time it is never used by growers because of increased risk of fungicide resistance in fields.
	Refined	GB	4000	Medium	Late according to standard practice in fields	6	14	3	6	Yes, with LOEL for mammals	Some studies suggest a foliar DT_{50} of 3-d and reasonable time interval of 14 days to avoid fungicide resistance in field. One or many other class of fungicide should be applied between two folpet applications if possible.
Apple orchard	Screening	AB	2400	Fine	Anytime	6	10	8.9	74	No, only Max	This is assuming a continuous application of folpet at each 10 days. This worst case scenario is not recommended by agronomists and other field specialists and most of the time it is never used by growers because of increased risk of fungicide resistance in fields
	1st Refined	AB	2400	Fine	Late according to standard practice in fields	6	20	3	74	Yes with LOEL for mammals	Some studies suggest a foliar DT_{50} of 3-d and reasonable time interval of 20 days to avoid fungicide resistance in field. One or many other class of fungicide should be applied between two folpet applications if possible. According to labels, folpet can be used early during the growing season
	2nd Refined	AB	2400	Fine	Late according to standard practice in fields	6	20	3	59	Yes	Some studies suggest a foliar DT_{50} of 3-d and reasonable time interval of 20 days to avoid fungicide resistance in field. One or many other class of fungicide should be applied between two folpet applications if possible. Agronomically speaking, treatments are normally expected to start at the flowering stage of crops when full canopy development stage occurs because many other existing fungicides may be more efficient than folpet, at early stage development of apples, to prevent fungal diseases.

[1] RA = Risk Assessment
[2] GB = groundboom sprayer
Ab = Airblast sprayer
[4] Mean nomog = mean nomogram

Table 8 Screening Level Risk Assessment for Birds from Contaminated Food Consumption Following Six Groundboom Applications of Folpet at 4000 g a.i./ha in Tomatoes and Cucurbits[1]

Bird size / Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Acute	134.0	Insectivore	745.4	**5.6**	44.7	0.3	514.7	**3.8**	30.9	0.2
	134.0	Granivore (grain and seeds)	115.4	0.9	6.9	0.1	55.0	0.4	3.3	0.0
	134.0	Frugivore (fruit)	230.7	**1.7**	13.8	0.1	110.0	0.8	6.6	0.0
Reproduction	78.3	Insectivore	745.4	**9.5**	44.7	0.6	514.7	**6.6**	30.9	0.4
	78.3	Granivore (grain and seeds)	115.4	**1.5**	6.9	0.1	55.0	0.7	3.3	0.0
	78.3	Frugivore (fruit)	230.7	**2.9**	13.8	0.2	110.0	**1.4**	6.6	0.1
Medium Sized Bird (0.1 kg)										
Acute	134.0	Insectivore	581.7	**4.3**	34.9	0.3	401.7	**3.0**	24.1	0.2
	134.0	Granivore (grain and seeds)	90.0	0.7	5.4	0.0	42.9	0.3	2.6	0.0
	134.0	Frugivore (fruit)	180.1	**1.3**	10.8	0.1	85.9	0.6	5.2	0.0
Reproduction	78.3	Insectivore	581.7	**7.4**	34.9	0.4	401.7	**5.1**	24.1	0.3
	78.3	Granivore (grain and seeds)	90.0	**1.1**	5.4	0.1	42.9	0.5	2.6	0.0
	78.3	Frugivore (fruit)	180.1	**2.3**	10.8	0.1	85.9	**1.1**	5.2	0.1
Large Sized Bird (1 kg)										
Acute	134.0	Insectivore	169.8	**1.3**	10.2	0.1	117.3	0.9	7.0	0.1
	134.0	Granivore (grain and seeds)	26.3	0.2	1.6	0.0	117.3	0.9	0.8	0.0
	134.0	Frugivore (fruit)	52.6	0.4	3.2	0.0	25.1	0.2	1.5	0.0
	134.0	Herbivore (short grass)	375.8	2.8	22.5	0.2	133.4	1.0	8.0	0.1
	134.0	Herbivore (long grass)	229.4	1.7	13.8	0.1	74.9	0.6	4.5	0.0
	134.0	Herbivore (Broadleaf plants)	347.7	2.6	20.9	0.2	114.9	0.9	6.9	0.1
Reproduction	78.3	Insectivore	169.8	2.2	10.2	0.1	117.3	**1.5**	7.0	0.1
	78.3	Granivore (grain and seeds)	26.3	0.3	1.6	0.0	117.3	1.5	0.8	0.0
	78.3	Frugivore (fruit)	52.6	0.7	3.2	0.0	25.1	0.3	1.5	0.0
	78.3	Herbivore (short grass)	375.8	**4.8**	22.5	0.3	133.4	**1.7**	8.0	0.1
	78.3	Herbivore (long grass)	229.4	**2.9**	13.8	0.2	74.9	1.0	4.5	0.1
	78.3	Herbivore (Broadleaf plants)	347.7	**4.4**	20.9	0.3	114.9	**1.5**	6.9	0.1

[1] Foliar DT_{50} = 8.9 days; Interval between applications = 7 days; *Bold values and shaded cells indicate that the level of concern (LOC) is exceeded;
EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:
Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$
All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822
Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]
Nagy, K.A. (1987)

Table 9 Refined Risk Assessment for Birds from Contaminated Food Consumption Following Six Groundboom Applications of Folpet at 4000 g a.i./ha in Tomatoes and Cucurbits Scenario[1]

Bird size/ Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Acute	134.0	Insectivore	338.9	**2.5**	20.3	0.2	234.0	**1.7**	14.0	0.1
	134.0	Granivore (grain and seeds)	52.5	0.4	3.1	0.0	25.0	0.2	1.5	0.0
	134.0	Frugivore (fruit)	104.9	0.8	6.3	0.0	50.0	0.4	3.0	0.0
Reproduction	78.3	Insectivore	338.9	**4.3**	20.3	0.3	234.0	**3.0**	14.0	0.2
	78.3	Granivore (grain and seeds)	52.5	0.7	3.1	0.0	25.0	0.3	1.5	0.0
	78.3	Frugivore (fruit)	104.9	**1.3**	6.3	0.1	50.0	0.6	3.0	0.0
Medium Sized Bird (0.1 kg)										
Acute	134.0	Insectivore	264.5	**2.0**	15.9	0.1	182.6	**1.4**	11.0	0.1
	134.0	Granivore (grain and seeds)	40.9	0.3	2.5	0.0	19.5	0.1	1.2	0.0
	134.0	Frugivore (fruit)	81.9	0.6	4.9	0.0	39.0	0.3	2.3	0.0
Reproduction	78.3	Insectivore	264.5	**3.4**	15.9	0.2	182.6	**2.3**	11.0	0.1
	78.3	Granivore (grain and seeds)	40.9	0.5	2.5	0.0	19.5	0.2	1.2	0.0
	78.3	Frugivore (fruit)	81.9	**1.0**	4.9	0.1	39.0	0.5	2.3	0.0
Large Sized Bird (1 kg)										
Acute	134.0	Insectivore	77.2	0.6	4.6	0.0	53.3	0.4	3.2	0.0
	134.0	Granivore (grain and seeds)	12.0	0.1	0.7	0.0	53.3	0.4	0.3	0.0
	134.0	Frugivore (fruit)	23.9	0.2	1.4	0.0	11.4	0.1	0.7	0.0
	134.0	Herbivore (short grass)	170.9	**1.3**	10.3	0.1	60.7	0.5	3.6	0.0
	134.0	Herbivore (long grass)	104.3	0.8	6.3	0.0	34.1	0.3	2.0	0.0
	134.0	Herbivore (Broadleaf plants)	158.1	**1.2**	9.5	0.1	52.3	0.4	3.1	0.0
Reproduction	78.3	Insectivore	77.2	1.0	4.6	0.1	53.3	0.7	3.2	0.0

Bird size/ Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	78.3	Granivore (grain and seeds)	12.0	0.2	0.7	0.0	53.3	0.7	0.3	0.0
	78.3	Frugivore (fruit)	23.9	0.3	1.4	0.0	11.4	0.1	0.7	0.0
	78.3	Herbivore (short grass)	170.9	**2.2**	10.3	0.1	60.7	0.8	3.6	0.0
	78.3	Herbivore (long grass)	104.3	**1.3**	6.3	0.1	34.1	0.4	2.0	0.0
	78.3	Herbivore (Broadleaf plants)	158.1	**2.0**	9.5	0.1	52.3	0.7	3.1	0.0

[1] Foliar DT_{50} = 3.0days; Interval between applications = 14 days; Bold values and shaded cells are above LOC

EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$

All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]

Nagy, K.A. (1987).

Table 10 Percentage Contamination (1/RQ × 100) of Bird Diet Required to Reach the LOC (i.e. Risk Quotient = 1) From the Refined Risk Assessment

Toxicity endpoint (mg a.i./kg bw/d)		Food Guild	Application number × rate (g a.i./ha) of folpet							
			Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off-field (6%)		On-field (100%)		Off-field (6%)	
			RQ*	1/RQ x100**	RQ	1/RQ x100	RQ	1/RQ x100	RQ	1/RQ x100
Small Bird (0.02 kg)										
Acute	134	Insectivore	**2.5**	**40**	0.2		**1.7**	**59**	0.1	
	134	Granivore (grain and seeds)	0.4	-	0.0		0.2	-	0.0	
	134	Frugivore (fruit)	0.8	-	0.0		0.4	-	0.0	
Reproduction	78.3	Insectivore	**4.3**	**23**	0.3		**3.0**	**33**	0.2	
	78.3	Granivore (grain and seeds)	0.7	-	0.0		0.3	-	0.0	
	78.3	Frugivore (fruit)	**1.3**	**77**	0.1		0.6	-	0.0	
Medium Sized Bird (0.1 kg)										
Acute	134	Insectivore	**2.0**	**50**	0.1		**1.4**	**71**	0.1	-
	134	Granivore (grain and seeds)	0.3	-	0.0		0.1	-	0.0	-
	134	Frugivore (fruit)	0.6	-	0.0		0.3	-	0.0	-

Toxicity endpoint (mg a.i./kg bw/d)		Food Guild	Application number × rate (g a.i./ha) of folpet							
			Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off-field (6%)		On-field (100%)		Off-field (6%)	
			RQ*	1/RQ x100**	RQ	1/RQ x100	RQ	1/RQ x100	RQ	1/RQ x100
Reproduction	78.3	Insectivore	**3.4**	**29**	0.2		**2.3**	**44**	0.1	-
	78.3	Granivore (grain and seeds)	0.5	-	0.0		0.2	-	0.0	-
	78.3	Frugivore (fruit)	**1.0**	**> 99**	0.1		0.5	-	0.0	-
Large Sized Bird (1 kg)										
Acute	134	Insectivore	0.6	-	0.0	-	0.4	-	0.0	-
	134	Granivore (grain and seeds)	0.1	-	0.0	-	0.4	-	0.0	-
	134	Frugivore (fruit)	0.2	-	0.0	-	0.1	-	0.0	-
	134	Herbivore (short grass)	**1.3**	**77**	0.1	-	0.5	-	0.0	-
	134	Herbivore (long grass)	0.8	-	0.0	-	0.3	-	0.0	-
	134	Herbivore (broadleaf plants)	**1.2**	**83**	0.1	-	0.4	-	0.0	-
Reproduction	78.3	Insectivore	1.0	-	0.1	-	0.7	-	0.0	-
	78.3	Granivore (grain and seeds)	0.2	-	0.0	-	0.7	-	0.0	-
	78.3	Frugivore (fruit)	0.3	-	0.0	-	0.1	-	0.0	-
	78.3	Herbivore (short grass)	**2.2**	**45**	0.1	-	0.8	-	0.0	-
	78.3	Herbivore (long grass)	**1.3**	-	0.1	-	0.4	-	0.0	-
	78.3	Herbivore (broadleaf plants)	**2.0**	**50**	0.1	-	0.7	-	0.0	-

* Bold values and shaded cells indicate that the level of concern (LOC) is exceeded.

** Percentage contamination of food was calculated for RQs above the level of concern.

Table 11 Screening Level Risk Assessment for Birds from Contaminated Food Consumption Following Six Airblast Applications of Folpet at 2400 g a.i./ha in Apple Orchards[1]

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (74%)		On-field (100%)		Off Field (74%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Acute	134.0	Insectivore	357.7	**2.7**	264.7	**2.0**	247.0	**1.8**	182.8	**1.4**
	134.0	Granivore (grain and seeds)	55.4	0.4	41.0	0.3	26.4	0.2	19.5	0.1
	134.0	Frugivore (fruit)	110.7	0.8	81.9	0.6	52.8	0.4	39.1	0.3

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (74%)		On-field (100%)		Off Field (74%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Reproduction	78.3	Insectivore	357.7	**4.6**	264.7	**3.4**	247.0	**3.2**	182.8	**2.3**
	78.3	Granivore (grain and seeds)	55.4	0.7	41.0	0.5	26.4	0.3	19.5	0.2
	78.3	Frugivore (fruit)	110.7	**1.4**	81.9	**1.0**	52.8	0.7	39.1	0.5
Medium Sized Bird (0.1 kg)										
Acute	134.0	Insectivore	279.2	**2.1**	206.6	**1.5**	192.8	**1.4**	142.6	**1.1**
	134.0	Granivore (grain and seeds)	43.2	0.3	32.0	0.2	20.6	0.2	15.2	0.1
	134.0	Frugivore (fruit)	86.4	0.6	63.9	0.5	41.2	0.3	30.5	0.2
Reproduction	78.3	Insectivore	279.2	**3.6**	206.6	**2.6**	192.8	**2.5**	142.6	**1.8**
	78.3	Granivore (grain and seeds)	43.2	0.6	32.0	0.4	20.6	0.3	15.2	0.2
	78.3	Frugivore (fruit)	86.4	**1.1**	63.9	0.8	41.2	0.5	30.5	0.4
Large Sized Bird (1 kg)										
Acute	134.0	Insectivore	81.5	0.6	60.3	0.5	56.3	0.4	41.6	0.3
	134.0	Granivore (grain and seeds)	12.6	0.1	9.3	0.1	56.3	0.4	4.5	0.0
	134.0	Frugivore (fruit)	25.2	0.2	18.7	0.1	12.0	0.1	8.9	0.1
	134.0	Herbivore (short grass)	180.3	**1.3**	133.4	1.0	64.0	0.5	47.4	0.4
	134.0	Herbivore (long grass)	110.1	0.8	81.5	0.6	36.0	0.3	26.6	0.2
	134.0	Herbivore (Broadleaf plants)	166.8	**1.2**	123.5	0.9	55.2	0.4	40.8	0.3
Reproduction	78.3	Insectivore	81.5	**1.0**	60.3	0.8	56.3	0.7	41.6	0.5
	78.3	Granivore (grain and seeds)	12.6	0.2	9.3	0.1	56.3	0.7	4.5	0.1
	78.3	Frugivore (fruit)	25.2	0.3	18.7	0.2	12.0	0.2	8.9	0.1
	78.3	Herbivore (short grass)	180.3	2.3	133.4	**1.7**	64.0	0.8	47.4	0.6
	78.3	Herbivore (long grass)	110.1	1.4	81.5	**1.0**	36.0	0.5	26.6	0.3
	78.3	Herbivore (Broadleaf plants)	166.8	2.1	123.5	**1.6**	55.2	0.7	40.8	0.5

[1] Foliar dissipation DT_{50} = 8.9 days; Interval between applications = 10 days; Early season airblast with fine droplet size; Bold values and shaded cells indicate that the LOC is exceeded.

EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most

conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:
Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$
All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$
All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822
Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]
Nagy, K.A. (1987).

Table 12 Refined Risk Assessment for Birds from Contaminated Food Consumption Following Six Airblast Applications of Folpet at 2400 g a.i./ha in Apple Orchards[1]

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Acute	134.0	Insectivore	197.3	**1.5**	146.0	1.1	136.2	**1.0**	100.8	0.8
	134.0	Granivore (grain and seeds)	30.5	0.2	22.6	0.2	14.6	0.1	10.8	0.1
	134.0	Frugivore (fruit)	61.1	0.5	45.2	0.3	29.1	0.2	21.6	0.2
Reproduction	78.3	Insectivore	197.3	**2.5**	146.0	**1.9**	136.2	**1.7**	100.8	**1.3**
	78.3	Granivore (grain and seeds)	30.5	0.4	22.6	0.3	14.6	0.2	10.8	0.1
	78.3	Frugivore (fruit)	61.1	0.8	45.2	0.6	29.1	0.4	21.6	0.3
Medium Sized Bird (0.1 kg)										
Acute	134.0	Insectivore	154.0	**1.1**	113.9	0.9	106.3	0.8	78.7	0.6
	134.0	Granivore (grain and seeds)	23.8	0.2	17.6	0.1	11.4	0.1	8.4	0.1
	134.0	Frugivore (fruit)	47.7	0.4	35.3	0.3	22.7	0.2	16.8	0.1
Reproduction	78.3	Insectivore	154.0	**2.0**	113.9	**1.5**	106.3	**1.4**	78.7	1.0
	78.3	Granivore (grain and seeds)	23.8	0.3	17.6	0.2	11.4	0.1	8.4	0.1
	78.3	Frugivore (fruit)	47.7	0.6	35.3	0.5	22.7	0.3	16.8	0.2
Large Sized Bird (1 kg)										
Acute	134.0	Insectivore	45.0	0.3	33.3	0.2	31.0	0.2	23.0	0.2

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	134.0	Granivore (grain and seeds)	7.0	0.1	5.1	0.0	31.0	0.2	2.5	0.0
	134.0	Frugivore (fruit)	13.9	0.1	10.3	0.1	6.6	0.0	4.9	0.0
	134.0	Herbivore (short grass)	99.5	0.7	73.6	0.5	35.3	0.3	26.1	0.2
	134.0	Herbivore (long grass)	60.7	0.5	44.9	0.3	19.8	0.1	14.7	0.1
	134.0	Herbivore (Broadleaf plants)	92.0	0.7	68.1	0.5	30.4	0.2	22.5	0.2
Reproduction	78.3	Insectivore	45.0	0.6	33.3	0.4	31.0	0.4	23.0	0.3
	78.3	Granivore (grain and seeds)	7.0	0.1	5.1	0.1	31.0	0.4	2.5	0.0
	78.3	Frugivore (fruit)	13.9	0.2	10.3	0.1	6.6	0.1	4.9	0.1
	78.3	Herbivore (short grass)	99.5	**1.3**	73.6	0.9	35.3	0.5	26.1	0.3
	78.3	Herbivore (long grass)	60.7	0.8	44.9	0.6	19.8	0.3	14.7	0.2
	78.3	Herbivore (Broadleaf plants)	92.0	**1.2**	68.1	0.9	30.4	0.4	22.5	0.3

[1] Foliar dissipation DT_{50} = 3.0 days; Interval between applications = 20 days; Early season airblast with fine droplet size; Bold values and shaded cells indicate that the level of concern (LOC) is exceeded.

EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$

All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]

Nagy, K.A. (1987).

Table 13 Percentage Contamination (1/RQ × 100) of Bird Diet Required to Reach the LOC (i.e. Risk Quotient = 1) From the Refined Risk Assessment

Percentage of the diet to reach refined LOC for birds			Application number × rate (g a.i./ha) of folpet							
			Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off-field (74%)		On-field (100%)		Off-field (74%)	
Toxicity endpoint (mg a.i./kg bw/d)		Food Guild	RQ*	1/RQ x100**	RQ	1/RQ x100	RQ	1/RQ x100	RQ	1/RQ x100
Small Bird (0.02 kg)										
Acute	134	Insectivore	**1.5**	**67**	1.1	-	**1.0**	**99**	0.8	-
	134	Granivore (grain and seeds)	0.2	-	0.2	-	0.1	-	0.1	-
	134	Frugivore (fruit)	0.5	-	0.3	-	0.2	-	0.2	-
Reproduction	78.3	Insectivore	**2.5**	**40**	**1.9**	**53**	**1.7**	**59**	**1.3**	**77**
	78.3	Granivore (grain and seeds)	0.4	-	0.3	-	0.2	-	0.1	-
	78.3	Frugivore (fruit)	0.8	-	0.6	-	0.4	-	0.3	-
Medium Sized Bird (0.1 kg)										
Acute	134	Insectivore	**1.1**	**91**	0.9	-	0.8	-	0.6	-
	134	Granivore (grain and seeds)	0.2	-	0.1	-	0.1	-	0.1	-
	134	Frugivore (fruit)	0.4	-	0.3	-	0.2	-	0.1	-
Reproduction	78.3	Insectivore	**2.0**	**50**	**1.5**	**67**	**1.4**	**71**	1.0	-
	78.3	Granivore (grain and seeds)	0.3	-	0.2	-	0.1	-	0.1	-
	78.3	Frugivore (fruit)	0.6	-	0.5	-	0.3	-	0.2	-
Large Sized Bird (1 kg)										
Acute	134	Insectivore	0.3	-	0.2	-	0.2	-	0.2	-
	134	Granivore (grain and seeds)	0.1	-	0.0	-	0.2	-	0.0	-
	134	Frugivore (fruit)	0.1	-	0.1	-	0.0	-	0.0	-
	134	Herbivore (short grass)	0.7	-	0.5	-	0.3	-	0.2	-
	134	Herbivore (long grass)	0.5	-	0.3	-	0.1	-	0.1	-
	134	Herbivore (broadleaf plants)	0.7	-	0.5	-	0.2	-	0.2	-
Reproduction	78.3	Insectivore	0.6	-	0.4	-	0.4	-	0.3	-
	78.3	Granivore (grain and seeds)	0.1	-	0.1	-	0.4	-	0.0	-
	78.3	Frugivore (fruit)	0.2	-	0.1	-	0.1	-	0.1	-
	78.3	Herbivore (short grass)	**1.3**	**77**	0.9	-	0.5	-	0.3	-
	78.3	Herbivore (long grass)	0.8	-	0.6	-	0.3	-	0.2	-
	78.3	Herbivore (broadleaf plants)	**1.2**	**83**	0.9	-	0.4	-	0.3	-

* Shaded cells indicate that the level of concern (LOC) is exceeded.

** Percentage contamination of food was calculated for RQs above the level of concern.

Table 14 Screening Level Risk Assessment for Mammals from Contaminated Food Consumption Following Six Groundboom Applications of Folpet at 4000 g a.i./ha in Tomatoes and Cucurbits[1]

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Acute	244.0	Insectivore	428.7	**1.8**	25.7	0.1	296.0	**1.2**	17.8	0.1
	244.0	Granivore (grain and seeds)	66.4	0.3	4.0	0.0	31.6	0.1	1.9	0.0
	244.0	Frugivore (fruit)	132.7	0.5	8.0	0.0	63.3	0.3	3.8	0.0
Reproduction	14.0	Insectivore	428.7	**30.6**	25.7	**1.8**	296.0	**21.1**	17.8	**1.3**
	14.0	Granivore (grain and seeds)	66.4	**4.7**	4.0	0.3	31.6	**2.3**	1.9	0.1
	14.0	Frugivore (fruit)	132.7	**9.5**	8.0	0.6	63.3	**4.5**	3.8	0.3
Medium Sized Mammal (0.035 kg)										
Acute	244.0	Insectivore	375.8	**1.5**	22.6	0.1	259.5	**1.1**	15.6	0.1
	244.0	Granivore (grain and seeds)	58.2	0.2	3.5	0.0	27.7	0.1	1.7	0.0
	244.0	Frugivore (fruit)	116.3	0.5	7.0	0.0	55.5	0.2	3.3	0.0
	244.0	Herbivore (short grass)	831.5	**3.4**	49.9	0.2	295.3	**1.2**	17.7	0.1
	244.0	Herbivore (long grass)	507.7	**2.1**	30.5	0.1	165.8	0.7	9.9	0.0
	244.0	Herbivore (forage crops)	769.3	**3.2**	46.2	0.2	254.3	**1.0**	15.3	0.1
Reproduction	14.0	Insectivore	375.8	**26.8**	22.6	**1.6**	259.5	**18.5**	15.6	**1.1**
	14.0	Granivore (grain and seeds)	58.2	**4.2**	3.5	0.2	27.7	**2.0**	1.7	0.1
	14.0	Frugivore (fruit)	116.3	**8.3**	7.0	0.5	55.5	**4.0**	3.3	0.2
	14.0	Herbivore (short grass)	831.5	**59.4**	49.9	**3.6**	295.3	**21.1**	17.7	**1.3**
	14.0	Herbivore (long grass)	507.7	**36.3**	30.5	**2.2**	165.8	**11.8**	9.9	0.7
	14.0	Herbivore (Broadleaf plants)	769.3	**55.0**	46.2	**3.3**	254.3	**18.2**	15.3	**1.1**
Large Sized Mammal (1 kg)										
Acute	244.0	Insectivore	200.8	0.8	12.0	0.0	138.7	0.6	8.3	0.0
	244.0	Granivore (grain and seeds)	31.1	0.1	1.9	0.0	14.8	0.1	0.9	0.0
	244.0	Frugivore (fruit)	62.2	0.3	3.7	0.0	29.6	0.1	1.8	0.0
	244.0	Herbivore (short grass)	444.3	**1.8**	26.7	0.1	157.8	0.6	9.5	0.0
	244.0	Herbivore (long grass)	271.3	**1.1**	16.3	0.1	88.6	0.4	5.3	0.0
	244.0	Herbivore (Broadleaf plants)	411.1	**1.7**	24.7	0.1	135.9	0.6	8.2	0.0
Reproduction	14.0	Insectivore	200.8	**14.3**	12.0	0.9	138.7	**9.9**	8.3	0.6

Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	14.0	Granivore (grain and seeds)	31.1	**2.2**	1.9	0.1	14.8	**1.1**	0.9	0.1
	14.0	Frugivore (fruit)	62.2	**4.4**	3.7	0.3	29.6	**2.1**	1.8	0.1
	14.0	Herbivore (short grass)	444.3	**31.7**	26.7	**1.9**	157.8	**11.3**	9.5	0.7
	14.0	Herbivore (long grass)	271.3	**19.4**	16.3	**1.2**	88.6	**6.3**	5.3	0.4
	14.0	Herbivore (Broadleaf plants)	411.1	**29.4**	24.7	**1.8**	135.9	**9.7**	8.2	0.6

[1] Foliar DT_{50} = 8.9 days; Interval between applications = 7 days; *Bold values and shaded cells indicate that the LOC is exceeded
EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:
Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) 0.850
All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) 0.651
All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822
Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]
Nagy, K.A. (1987).

Table 15 Refined Risk Assessment for Mammals from Contaminated Food Consumption Following Six Groundboom Applications of Folpet at 4000 g a.i./ha in Tomatoes and Cucurbits[1]

Mammal size/ Endpoints[2]	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Acute	244.0	Insectivore	194.9	0.8	11.7	0.0	134.6	0.6	8.1	0.0
	244.0	Granivore (grain and seeds)	30.2	0.1	1.8	0.0	14.4	0.1	0.9	0.0
	244.0	Frugivore (fruit)	60.3	0.2	3.6	0.0	28.8	0.1	1.7	0.0
Reproduction (LOEL)	70.0	Insectivore	194.9	**2.8**	11.7	0.2	134.6	**1.9**	8.1	0.1
	70.0	Granivore (grain and seeds)	30.2	**0.4**	1.8	0.0	14.4	0.2	0.9	0.0
	70.0	Frugivore (fruit)	60.3	**0.9**	3.6	0.1	28.8	**0.4**	1.7	0.0
Medium Sized Mammal (0.035 kg)										
Acute	244.0	Insectivore	170.9	0.7	10.3	0.0	118.0	0.5	7.1	0.0
	244.0	Granivore (grain and seeds)	26.4	0.1	1.6	0.0	12.6	0.1	0.8	0.0
	244.0	Frugivore (fruit)	52.9	0.2	3.2	0.0	25.2	0.1	1.5	0.0

Mammal size/ Endpoints[2]	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (6%)		On-field (100%)		Off Field (6%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	244.0	Herbivore (short grass)	378.1	**1.5**	22.7	0.1	134.3	0.6	8.1	0.0
	244.0	Herbivore (long grass)	230.9	0.9	13.9	0.1	75.4	0.3	4.5	0.0
	244.0	Herbivore (forage crops)	349.8	**1.4**	21.0	0.1	115.6	0.5	6.9	0.0
Reproduction (LOEL	70.0	Insectivore	170.9	**2.4**	10.3	0.1	118.0	**1.7**	7.1	0.1
	70.0	Granivore (grain and seeds)	26.4	**0.4**	1.6	0.0	12.6	0.2	0.8	0.0
	70.0	Frugivore (fruit)	52.9	**0.8**	3.2	0.0	25.2	**0.4**	1.5	0.0
	70.0	Herbivore (short grass)	378.1	**5.4**	22.7	**0.3**	134.3	**1.9**	8.1	0.1
	70.0	Herbivore (long grass)	230.9	**3.3**	13.9	0.2	75.4	**1.1**	4.5	0.1
	70.0	Herbivore (Broadleaf plants)	349.8	**5.0**	21.0	**0.3**	115.6	**1.7**	6.9	0.1
Large Sized Mammal (1 kg)										
Acute	244.0	Insectivore	91.3	0.4	5.5	0.0	63.1	0.3	3.8	0.0
	244.0	Granivore (grain and seeds)	14.1	0.1	0.8	0.0	6.7	0.0	0.4	0.0
	244.0	Frugivore (fruit)	28.3	0.1	1.7	0.0	13.5	0.1	0.8	0.0
	244.0	Herbivore (short grass)	202.0	0.8	12.1	0.0	71.7	0.3	4.3	0.0
	244.0	Herbivore (long grass)	123.4	0.5	7.4	0.0	40.3	0.2	2.4	0.0
	244.0	Herbivore (Broadleaf plants)	186.9	0.8	11.2	0.0	61.8	0.3	3.7	0.0
Reproduction (LOEL)	70.0	Insectivore	91.3	**1.3**	5.5	0.1	63.1	**0.9**	3.8	0.1
	70.0	Granivore (grain and seeds)	14.1	**0.2**	0.8	0.0	6.7	0.1	0.4	0.0
	70.0	Frugivore (fruit)	28.3	**0.4**	1.7	0.0	13.5	0.2	0.8	0.0
	70.0	Herbivore (short grass)	202.0	**2.9**	12.1	0.2	71.7	**1.0**	4.3	0.1
	70.0	Herbivore (long grass)	123.4	**1.8**	7.4	0.1	40.3	**0.6**	2.4	0.0
	70.0	Herbivore (Broadleaf plants)	186.9	**2.7**	11.2	0.2	61.8	**0.9**	3.7	0.1

[1] Foliar DT_{50} = 3.0 days; Interval between applications = 14 days; *Bold values and shaded cells indicate that the LOC is exceeded

EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) 0.850

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) 0.651

All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]

Nagy, K.A. (1987).

Table 16 Screening Level Risk Assessment for Mammals from Contaminated Food Consumption Following Six Airblast Applications of Folpet at 2400 g a.i./ha in Apple Orchard[1]

Mammal size / Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Acute	244.0	Insectivore	205.8	0.8	152.3	0.6	142.1	0.6	105.1	0.4
	244.0	Granivore (grain and seeds)	31.8	0.1	23.6	0.1	15.2	0.1	11.2	0.0
	244.0	Frugivore (fruit)	63.7	0.3	47.1	0.2	30.4	0.1	22.5	0.1
Reproduction	14.0	Insectivore	205.8	**14.7**	152.3	**10.9**	142.1	**10.1**	105.1	**7.5**
	14.0	Granivore (grain and seeds)	31.8	**2.3**	23.6	**1.7**	15.2	**1.1**	11.2	0.8
	14.0	Frugivore (fruit)	63.7	**4.5**	47.1	**3.4**	30.4	**2.2**	22.5	**1.6**
Medium Sized Mammal (0.035 kg)										
Acute	244.0	Insectivore	180.4	0.7	133.5	0.5	124.5	0.5	92.2	0.4
	244.0	Granivore (grain and seeds)	27.9	0.1	20.7	0.1	13.3	0.1	9.9	0.0
	244.0	Frugivore (fruit)	55.8	0.2	41.3	0.2	26.6	0.1	19.7	0.1
	244.0	Herbivore (short grass)	399.1	**1.6**	295.3	**1.2**	141.7	0.6	104.9	0.4
	244.0	Herbivore (long grass)	243.7	1.0	180.3	0.7	79.6	0.3	58.9	0.2
	244.0	Herbivore (forage crops)	369.2	**1.5**	273.2	**1.1**	122.1	0.5	90.3	0.4
Reproduction	14.0	Insectivore	180.4	**12.9**	133.5	**9.5**	124.5	**8.9**	92.2	**6.6**
	14.0	Granivore (grain and seeds)	27.9	**2.0**	20.7	**1.5**	13.3	1.0	9.9	0.7
	14.0	Frugivore (fruit)	55.8	**4.0**	41.3	**3.0**	26.6	**1.9**	19.7	**1.4**
	14.0	Herbivore (short grass)	399.1	**28.5**	295.3	**21.1**	141.7	**10.1**	104.9	**7.5**
	14.0	Herbivore (long grass)	243.7	**17.4**	180.3	**12.9**	79.6	**5.7**	58.9	**4.2**
	14.0	Herbivore (Broadleaf plants)	369.2	**26.4**	273.2	**19.5**	122.1	**8.7**	90.3	**6.5**
Large Sized Mammal (1 kg)										
Acute	244.0	Insectivore	96.4	0.4	71.3	0.3	66.5	0.3	49.2	0.2
	244.0	Granivore (grain and seeds)	14.9	0.1	11.0	0.0	7.1	0.0	5.3	0.0
	244.0	Frugivore (fruit)	29.8	0.1	22.1	0.1	14.2	0.1	10.5	0.0
	244.0	Herbivore (short grass)	213.2	0.9	157.8	0.6	75.7	0.3	56.0	0.2
	244.0	Herbivore (long grass)	130.2	0.5	96.3	0.4	42.5	0.2	31.5	0.1
	244.0	Herbivore (Broadleaf plants)	197.3	0.8	146.0	0.6	65.2	0.3	48.3	0.2
Reproduction	14.0	Insectivore	96.4	**6.9**	71.3	**5.1**	66.5	**4.8**	49.2	**3.5**
	14.0	Granivore (grain and seeds)	14.9	**1.1**	11.0	0.8	7.1	0.5	5.3	0.4
	14.0	Frugivore (fruit)	29.8	**2.1**	22.1	**1.6**	14.2	**1.0**	10.5	0.8
	14.0	Herbivore (short grass)	213.2	**15.2**	157.8	**11.3**	75.7	**5.4**	56.0	**4.0**

Mammal size / Endpoint	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
	14.0	Herbivore (long grass)	130.2	**9.3**	96.3	**6.9**	42.5	**3.0**	31.5	**2.2**
	14.0	Herbivore (Broadleaf plants)	197.3	**14.1**	146.0	**10.4**	65.2	**4.7**	48.3	**3.4**

[1] Foliar DT_{50} = 8.9 days; Interval between applications = 10 days; * Bold values and shaded cells indicate that the LOC is exceeded
EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:
Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) 0.850
All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) 0.651
All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822
Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]
Nagy, K.A. (1987).

Table 17 Refined Risk Assessment for Mammals from Contaminated Food Consumption Following Six Airblast Applications of Folpet at 2400 g a.i./ha in Apple Orchard

Mammal size/ Endpoint[2]	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (74%)		On-field (100%)		Off Field (74%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Acute	244.0	Insectivore	113.5	0.5	84.0	0.3	78.4	0.3	58.0	0.2
	244.0	Granivore (grain and seeds)	17.6	0.1	13.0	0.1	8.4	0.0	6.2	0.0
	244.0	Frugivore (fruit)	35.1	0.1	26.0	0.1	16.8	0.1	12.4	0.1
Reproduction (LOEL)	70.0	Insectivore	113.5	**1.6**	84.0	**1.2**	78.4	**1.1**	58.0	0.8
	70.0	Granivore (grain and seeds)	17.6	0.3	13.0	0.2	8.4	0.1	6.2	0.1
	70.0	Frugivore (fruit)	35.1	0.5	26.0	0.4	16.8	0.2	12.4	0.2
Medium Sized Mammal (0.035 kg)										
Acute	244.0	Insectivore	99.5	0.4	73.6	0.3	68.7	0.3	50.8	0.2
	244.0	Granivore (grain and seeds)	15.4	0.1	11.4	0.0	7.3	0.0	5.4	0.0
	244.0	Frugivore (fruit)	30.8	0.1	22.8	0.1	14.7	0.1	10.9	0.0
	244.0	Herbivore (short grass)	220.1	0.9	162.9	0.7	78.2	0.3	57.8	0.2
	244.0	Herbivore (long grass)	134.4	0.6	99.4	0.4	43.9	0.2	32.5	0.1
	244.0	Herbivore (forage crops)	203.6	0.8	150.7	0.6	67.3	0.3	49.8	0.2

Mammal size/ Endpoint[2]	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field (100%)		Off Field (74%)		On-field (100%)		Off Field (74%)	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Reproduction (LOEL)	70.0	Insectivore	99.5	**1.4**	73.6	**1.1**	68.7	**1.0**	50.8	0.7
	70.0	Granivore (grain and seeds)	15.4	0.2	11.4	0.2	7.3	0.1	5.4	0.1
	70.0	Frugivore (fruit)	30.8	0.4	22.8	0.3	14.7	0.2	10.9	0.2
	70.0	Herbivore (short grass)	220.1	**3.1**	162.9	**2.3**	78.2	**1.1**	57.8	0.8
	70.0	Herbivore (long grass)	134.4	**1.9**	99.4	**1.4**	43.9	0.6	32.5	0.5
	70.0	Herbivore (Broadleaf plants)	203.6	**2.9**	150.7	**2.2**	67.3	**1.0**	49.8	0.7
Large Sized Mammal (1 kg)										
Acute	244.0	Insectivore	53.2	0.2	39.3	0.2	36.7	0.2	27.2	0.1
	244.0	Granivore (grain and seeds)	8.2	0.0	6.1	0.0	3.9	0.0	2.9	0.0
	244.0	Frugivore (fruit)	16.5	0.1	12.2	0.0	7.8	0.0	5.8	0.0
	244.0	Herbivore (short grass)	117.6	0.5	87.0	0.4	41.8	0.2	30.9	0.1
	244.0	Herbivore (long grass)	71.8	0.3	53.1	0.2	23.4	0.1	17.4	0.1
	244.0	Herbivore (Broadleaf plants)	108.8	0.4	80.5	0.3	36.0	0.1	26.6	0.1
Reproduction (LOEL)	70.0	Insectivore	53.2	0.8	39.3	0.6	36.7	0.5	27.2	0.4
	70.0	Granivore (grain and seeds)	8.2	0.1	6.1	0.1	3.9	0.1	2.9	0.0
	70.0	Frugivore (fruit)	16.5	0.2	12.2	0.2	7.8	0.1	5.8	0.1
	70.0	Herbivore (short grass)	117.6	**1.7**	87.0	**1.2**	41.8	0.6	30.9	0.4
	70.0	Herbivore (long grass)	71.8	1.0	53.1	0.8	23.4	0.3	17.4	0.2
	70.0	Herbivore (Broadleaf plants)	108.8	**1.6**	80.5	**1.2**	36.0	0.5	26.6	0.4

[1] Foliar DT_{50} = 3.0 days; Interval between applications = 20 days; *Bold values and shaded cells indicate that the LOC is exceeded

[2] LOEL = 70 mg a.i./kg bw/d

EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) 0.850

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) 0.651

All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g et/day)]

Nagy, K.A. (1987).

Screening Level and Refined Risk Assessment on Non-Target Aquatic Species

Table 18 Toxicity Effects of Folpet and Transformation Products to Aquatic Organisms Following Groundboom Application in Cucurbit and Tomato Productions (6 × 4000 g a.i./ha; 7 days Interval Between Applications and a DT_{50} in Water of 0.06 day for Folpet)

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
Freshwater species						
Invertebrate: *Daphnia magna*	Folpet	Acute	Formulation 90.3%	48-hr EC_{50} = 20 µg a.i./L ÷ 2 = 10	500	**50.0**
		Chronic	TGAI	NOEC > 1880 µg a.i./L 1880	500	0.27
	Phthalimide	Acute	TGAI	48-hr EC_{50} = 39 000 µg a.i./L÷ 2 = 19500	250	0.01
	Phthalic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	526	0.01
	Phthalamic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	501	0.01
	Benzamide	Acute	TGAI	48-hr $EC_{50} \geq$ 102 000 µg a.i./L÷ 2 = 50000	216	0.004
	2-cyanobenzoic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	250	0.005
Invertebrate: *Gammarus fasciatus*	Folpet	Acute	TGAI	96-hour EC_{50} >2500 µg a.i./L÷2 = 1250	500	0.4
Cold fish: Rainbow trout: *Onchorynchus mykiss*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	500	**333.3**
		Chronic	Folpan 500 SC	NOEC = 19.5 µg a.i./L 19.5	500	**25.64**
	Phthalamic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	501	0.05
	Benzamide	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	216	0.02
	2-cyanobenzoic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	250	0.03
Cold fish: Brown trout: *Salmo trutta lacustris*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 29 µg a.i./L÷ 10 = 2.9	500	**172.4**
Cold fish: Coho salmon: *Onchor.kisutch*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 106 µg a.i./L÷ 10 = 10.6	500	**47.17**
Cold fish: Lake trout: *Salmo trutta sp.*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 24.0 µg a.i./L÷ 10 = 2.4	500	**208.3**
Warm fish: Bluegill sunfish: *Lepomis macrochirus*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 47.0 µg a.i./L÷ 10 = 4.7	500	**106.4**
	Phthalimide	Acute	TGAI	96-hour LC_{50} = 38 000 µg a.i./L÷ 10 = 3800	250	0.07
Channel catfish: *Ictalurus punctatus*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 108 µg a.i./L÷ 10 = 10.8	500	**46.3**
Smallmouth bass: *Micropterus dolomieu*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 91 µg a.i./L÷ 10 = 9.1	500	**55.0**
Yellow perch: *Perca flavescens*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 177 µg a.i./L÷ 10 = 17.7	500	**28.3**
Fathead minnow: *Pimephales promelas*	Folpet	ELS*	TGAI	NOEC = 8.81	500	**56.8**
Amphibians: 15 cm water depth Surrogate: Rainbow trout: *Onchor. mykiss*	Folpet	Acute	TGAI	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	2667	**1778**
Green algae: *Scenedesmus subspicatus*	Folpet	Acute	TGAI	72-hr EC_{50} = 100 µg a.i./L÷ 2 = 50.0	500	**10.0**
Green algae: *Selenastrum capricornutum*	Folpet	Acute	Folpan 80 WDG	96-hr ErC_{50} = 1400 µg a.i./L÷ 2 = 700	500	0.71

	Phthalic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	526	0.01
	Phthalamic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	501	0.01
	Benzamide	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	216	0.004
	2-cyanobenzoic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 mg a.i./L÷ 2 = 50 000	250	0.005
Algae: *Navicula pelliculosa*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 40.3 µg a.i./L÷ 2 = 20.1	500	**24.88**
Algae: *Anabaena flos aquae*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 900 µg a.i./L÷ 2 = 450	500	**1.11**
Vascular plant: *Lemna gibba*	Folpet	Dissolved	Folpan 80 WDG	7-day EC_{50} > 2900 µg a.i./L÷ 2 = 1450	500	0.34
Marine/Estuarine species						
Shell deposition, Eastern oyster, *Crassostrea virginica*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50} =120 µg a.i./L÷ 2 = 60	500	**8.33**
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour LC_{50} = 65 µg a.i./L÷ 10 = 6.5	500	**76.92**
Algae: diatom *Skeletonema costatum*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50}= 180 µg a.i./L÷ 2 = 90	500	**5.56**

* Bold values and shaded cells indicate that the LOC is exceeded with RQ>1

Table 19 Toxicity Effects of Folpet and Transformation Products to Aquatic Organisms Following 6 Airblast Applications in Apple Production (6 × 2400 g a.i./ha, 10 Days Interval between Applications and DT_{50} in Water of 0.06 days for Folpet)

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
Freshwater species						
Invertebrate: *Daphnia magna*	Folpet	Acute	Formulation 90.3%	48-hr EC_{50} = 20 µg a.i./L ÷ 2 = 10	300	**30**
		Chronic	TGAI	NOEC > 1880 µg a.i./L 1880	300	0.16
	Phthalimide	Acute	TGAI	48-hr EC_{50} = 39 000 µg a.i./L÷ 2 = 19500	150	0.008
	Phthalic acid	Acute	TGAI	48-hr EC_{50} ≥ 100 000 µg a.i./L÷ 2 = 50000	256	0.005
	Phthalamic acid	Acute	TGAI	48-hr EC_{50} ≥ 100 000 µg a.i./L÷ 2 = 50000	245	0.005
	Benzamide	Acute	TGAI	48-hr EC_{50} ≥ 102 000 µg a.i./L÷ 2 = 51000	125	0.002
	2-cyanobenzoic acid	Acute	TGAI	48-hr EC_{50} ≥ 100 000 µg a.i./L÷ 2 = 50000	150	0.003
Invertebrate: *Gammarus fasciatus*	Folpet	Acute	TGAI	96-hour EC_{50} >2500 µg a.i./L÷2 = 1250	300	0.24
Cold fish: Rainbow trout: *Onchorynchus mykiss*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	300	**200**
		Chronic	Folpan 500 SC	NOEC = 19.5 µg a.i./L 19.5	300	**15.4**
	Phthalamic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	245	0.025
	Benzamide	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	125	0.013
	2-cyanobenzoic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	150	0.015
Cold fish: Brown trout: *Salmo trutta lacustris*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 29 µg a.i./L÷ 10 = 2.9	300	**103.5**
Cold fish: Coho salmon: *Onchorynchus .kisutch*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 106 µg a.i./L÷ 10 = 10.6	300	**28.3**

Cold fish: Lake trout: *Salmo trutta sp.*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 24.0 µg a.i./L÷ 10 = 2.4	300	**125**
Warm fish: Bluegill sunfish: *Lepomis macrochirus*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 47.0 µg a.i./L÷ 10 = 4.7	300	**63.8**
	Phthalimide	Acute	TGAI	96-hour LC_{50} = 38 000 µg a.i./L÷ 10 = 3800	150	0.04
Channel catfish: *Ictalurus punctatus*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 108 µg a.i./L÷ 10 = 10.8	300	**27.8**
Smallmouth bass: *Micropterus dolomieu*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 91 µg a.i./L÷ 10 = 9.1	300	**33.0**
Yellow perch: *Perca flavescens*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 177 µg a.i./L÷ 10 = 17.7	300	**17.0**
Fathead minnow: *Pimephales promelas*	Folpet	ELS*	TGAI	NOEC = 8.81	300	**34.1**
Amphibians: 15 cm water depth Surrogate: Rainbow trout: *Onchoynchus. mykiss*	Folpet	Acute	TGAI	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	1600	**1066.7**
Green algae: *Scenedesmus subspicatus*	Folpet	Acute	TGAI	72-hr EC_{50} = 100 µg a.i./L÷ 2 = 50.0	300	**6.0**
Green algae: *Selenastrum capricornutum*	Folpet	Acute	Folpan 80 WDG	96-hr ErC_{50} = 1400 µg a.i./L÷ 2 = 700	300	0.43
	Phthalic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	256	0.005
	Phthalamic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	245	0.005
	Benzamide	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	125	0.002
	2-cyanobenzoic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 mg a.i./L÷ 2 = 50 000	150	0.003
Algae: *Navicula pelliculosa*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 40.3 µg a.i./L÷ 2 = 20.1	300	**14.9**
Algae: *Anabaena flos aquae*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 900 µg a.i./L÷ 2 = 450	300	0.67
Vascular plant: *Lemna gibba*	Folpet	Dissolved	Folpan 80 WDG	7-day EC_{50} > 2900 µg a.i./L÷ 2 = 1450	300	0.21
Marine/Estuarine species						
Shell deposition, Eastern oyster, *Crassostrea virginica*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50} =120 µg a.i./L÷ 2 = 60	300	**5.0**
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour LC_{50} = 65 µg a.i./L÷ 10 = 6.5	300	**46.2**
Algae: diatom *Skeletonema costatum*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50}= 180 µg a.i./L÷ 2 = 90	300	**3.33**

* Bold values and shaded cells indicate that the LOC is exceeded with RQ>1

Table 20 Risk Quotient for Aquatic Organism after Refinement Using a Groundboom Spray Drift of 6% for Folpet and Transformation Products at Maximum Rate of Application (4000 g a.i./ha) in Cucurbit and Tomato Productions

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
Freshwater species						
Invertebrate: *Daphnia magna*	Folpet	Acute	Formulation 90.3%	48-hr EC_{50} = 20 µg a.i./L ÷ 2 = 10	30	**3.0**
		Chronic	TGAI	NOEC > 1880 µg a.i./L 1880	30	0.02
	Phthalimide	Acute	TGAI	48-hr EC_{50} = 39 000 µg a.i./L÷ 2 = 19500	15	0.0008
	Phthalic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 0000	31.6	0.0006
	Phthalamic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	30.1	0.0006

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
	Benzamide	Acute	TGAI	48-hr $EC_{50} \geq$ 102 000 µg a.i./L÷ 2 = 50000	13	0.0003
	2-cyanobenzoic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	15	0.0003
Invertebrate: *Gammarus fasciatus*	Folpet	Acute	TGAI	96-hour EC_{50} >2500 µg a.i./L÷2 = 1250	30	0.024
Cold fish: Rainbow trout: *Onchorynchus mykiss*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	30	**20.0**
		Chronic	Folpan 500 SC	NOEC = 19.5 µg a.i./L 19.5	30	**1.5**
	Phthalamic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	30.1	0.003
	Benzamide	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	13	0.001
	2-cyanobenzoic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	15	0.002
Cold fish: Brown trout: *Salmo trutta lacustris*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 29 µg a.i./L÷ 10 = 2.9	30	**10.3**
Cold fish: Coho salmon: *Onchor.kisutch*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 106 µg a.i./L÷ 10 = 10.6	30	**2.8**
Cold fish: Lake trout: *Salmo trutta sp.*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 24.0 µg a.i./L÷ 10 = 2.4	30	**12.5**
Warm fish: Bluegill sunfish: *Lepomis macrochirus*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 47.0 µg a.i./L÷ 10 = 4.7	30	**6.4**
	Phthalimide	Acute	TGAI	96-hour LC_{50} = 38 000 µg a.i./L÷ 10 = 3800	15	0.004
Channel catfish: *Ictalurus punctatus*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 108 µg a.i./L÷ 10 = 10.8	30	**2.8**
Smallmouth bass: *Micropterus dolomieu*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 91 µg a.i./L÷ 10 = 9.1	30	**3.3**
Yellow perch: *Perca flavescens*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 177 µg a.i./L÷ 10 = 17.7	30	**1.7**
Fathead minnow: *Pimephales promelas*	Folpet	ELS*	TGAI	NOEC = 8.81	30	**3.4**
Amphibians: 15 cm water depth Surrogate: Rainbow trout: *Onchor. mykiss*	Folpet	Acute	TGAI	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	160.0	**106.7**
Green algae: *Scenedesmus subspicatus*	Folpet	Acute	TGAI	72-hr EC_{50} = 100 µg a.i./L÷ 2 = 50.0	30	0.6
Green algae: *Selenastrum capricornutum*	Folpet	Acute	Folpan 80 WDG	96-hr ErC_{50} = 1400 µg a.i./L÷ 2 = 700	30	0.4
	Phthalic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	31.6	0.0006
	Phthalamic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	30.1	0.0006
	Benzamide	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	13	0.0003
	2-cyanobenzoic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 mg a.i./L÷ 2 = 50 000	15	0.0003
Algae: *Navicula pelliculosa*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 40.3 µg a.i./L÷ 2 = 20.1	30	**1.5**
Algae: *Anabaena flos aquae*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 900 µg a.i./L÷ 2 = 450	30	0.07
Vascular plant: *Lemna gibba*	Folpet	Dissolved	Folpan 80 WDG	7-day EC_{50} > 2900 µg a.i./L÷ 2 = 1450	30	0.02
Marine/Estuarine species						
Shell deposition, Eastern oyster, *Crassostrea virginica*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50} =120 µg a.i./L÷ 2 = 60	30	0.5
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour LC_{50} = 65 µg a.i./L÷ 10 = 6.5	30	**4.6**
Algae: diatom *Skeletonema costatum*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50}= 180 µg a.i./L÷ 2 = 90	30	0.3

* Bold values and shaded cells indicate that the LOC is exceeded with RQ>1

Table 21 Risk Quotient for Aquatic Organism after Refinement Using an Airblast Spray Drift of 74% for Folpet and Transformation Products at 2400 g Folpet/ha in Apple Production

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
Freshwater species						
Invertebrate: *Daphnia magna*	Folpet	Acute	Formulation 90.3%	48-hr EC_{50} = 20 µg a.i./L ÷ 2 = 10	222	**22.2**
		Chronic	TGAI	NOEC > 1880 µg a.i./L 1880	222	0.12
	Phthalimide	Acute	TGAI	48-hr EC_{50} = 39 000 µg a.i./L÷ 2 = 19500	111	0.006
	Phthalic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	189.4	0.004
	Phthalamic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	181.3	0.004
	Benzamide	Acute	TGAI	48-hr $EC_{50} \geq$ 102 000 µg a.i./L÷ 2 = 51000	92.5	0.002
	2-cyanobenzoic acid	Acute	TGAI	48-hr $EC_{50} \geq$ 100 000 µg a.i./L÷ 2 = 50000	111	0.006
Invertebrate: *Gammarus fasciatus*	Folpet	Acute	TGAI	96-hour EC_{50} >2500 µg a.i./L÷2 = 1250	222	0.18
Cold fish: Rainbow trout: *Onchorynchus mykiss*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	222	**148**
		Chronic	Folpan 500 SC	NOEC = 19.5 µg a.i./L 19.5	222	**11.4**
	Phthalamic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	181.3	0.004
	Benzamide	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	92.5	0.002
	2-cyanobenzoic acid	Acute	TGAI	96-hr LC_{50} > 100 000 µg a.i./L ÷ 10 = 10 000	111	0.01
Cold fish: Brown trout: *Salmo trutta lacustris*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 29 µg a.i./L÷ 10 = 2.9	222	**76.6**
Cold fish: Coho salmon: *Onchorynchus .kisutch*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 106 µg a.i./L÷ 10 = 10.6	222	**20.9**
Cold fish: Lake trout: *Salmo trutta sp.*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 24.0 µg a.i./L÷ 10 = 2.4	222	**92.5**
Warm fish: Bluegill sunfish: *Lepomis macrochirus*	Folpet	Acute	Formulation 90.3%	96-hour LC_{50} = 47.0 µg a.i./L÷ 10 = 4.7	222	**47.2**
	Phthalimide	Acute	TGAI	96-hour LC_{50} = 38 000 µg a.i./L÷ 10 = 3800	111	0.006
Channel catfish: *Ictalurus punctatus*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 108 µg a.i./L÷ 10 = 10.8	222	**20.6**
Smallmouth bass: *Micropterus dolomieu*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 91 µg a.i./L÷ 10 = 9.1	222	**24.4**
Yellow perch: *Perca flavescens*	Folpet	Acute	Formulation 88%	96-hour LC_{50} = 177 µg a.i./L÷ 10 = 17.7	222	**12.5**
Fathead minnow: *Pimephales promelas*	Folpet	ELS*	TGAI	NOEC = 8.81	222	**25.2**
Amphibians: 15 cm water depth Surrogate: Rainbow trout: *Onchoynchus. mykiss*	Folpet	Acute	TGAI	96-hour LC_{50} = 15 µg a.i./L ÷ 10 = 1.5	222	**148**
Green algae: *Scenedesmus subspicatus*	Folpet	Acute	TGAI	72-hr EC_{50} = 100 µg a.i./L÷ 2 = 50.0	222	**4.44**
Green algae: *Selenastrum capricornutum*	Folpet	Acute	Folpan 80 WDG	96-hr ErC_{50} = 1400 µg a.i./L÷ 2 = 700	222	0.3
	Phthalic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	189.4	0.004
	Phthalamic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	181.3	0.004

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (µg a.i./L) ÷ safety factor	EEC (µg a.i./L)	RQ*
	Benzamide	Acute	TGAI	96-hr EbC_{50} > 100 000 µg a.i./L÷ 2 = 50 000	92.5	0.002
	2-cyanobenzoic acid	Acute	TGAI	96-hr EbC_{50} > 100 000 mg a.i./L÷ 2 = 50 000	111	0.006
Algae: *Navicula pelliculosa*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 40.3 µg a.i./L÷ 2 = 20.1	222	**11.0**
Algae: *Anabaena flos aquae*	Folpet	Acute	Folpan 80 WDG	96-hr EC_{50} = 900 µg a.i./L÷ 2 = 450	222	0.5
Vascular plant: *Lemna gibba*	Folpet	Dissolved	Folpan 80 WDG	7-day EC_{50} > 2900 µg a.i./L÷ 2 = 1450	222	0.15
Marine/Estuarine species						
Shell deposition, Eastern oyster, *Crassostrea virginica*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50} =120 µg a.i./L÷ 2 = 60	222	**3.7**
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour LC_{50} = 65 µg a.i./L÷ 10 = 6.5	222	**34.2**
Algae: diatom *Skeletonema costatum*	Folpet	Acute	TGAI (90.3% a.i.)	96-hour EC_{50}= 180 µg a.i./L÷ 2 = 90	222	**2.5**

* Bold values and shaded cells indicate that the LOC is exceeded with RQ>1

Table 22 Acute and Chronic Risks to Aquatic Organisms from Folpet in Runoff

Organisms	Exposure	Scenario	Folpet appl. rate g a.i./ha	No. of appl.	Spray techno	Water Depth m	EEC Runoff at 96-hour µg a.i./L	Most conservative endpoint values (µg a.i./L) ÷ safety factor	RQ EEC/endpoint
Freshwater Species									
Invertebrate: *Daphnia magna*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	10	**3.70**
	Acute	BC apples	2400	6	AB	0.80	0.39	10	0.04
	Chronic	Prairie pumpkins	4000	6	GB	0.80	37.00	1880	0.02
	Chronic	BC apples	2400	6	AB	0.80	0.39	1880	0.0002
Fish: Rainbow trout: *Onchorynchus mykiss*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	1.5	**24.70**
	Acute	BC apples	2400	6	AB	0.80	0.39	1.5	0.30
Fish: Fathead minnow: *Pimephales promelas*	Chronic	Prairie pumpkins	4000	6	GB	0.80	37.00	8.81	**4.20**
	Chronic	BC apples	2400	6	AB	0.80	0.39	8.81	0.04
Amphibians:	Acute	Prairie pumpkins	4000	6	GB	0.15	195.00	1.5	**130.00**
	Acute	BC apples	2400	6	AB	0.15	2.10	1.5	**1.40**
Algae: *Navicula pelliculosa*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	20.1	**1.80**
	Acute	BC apples	2400	6	AB	0.80	0.39	20.1	0.02
Vascular plant: *Lemna gibba*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	1450	0.03
	Acute	BC apples	2400	6	AB	0.80	0.39	1450	0.0003

Organisms	Exposure	Scenario	Folpet appl. rate g a.i./ha	No. of appl.	Spray techno	Water Depth m	EEC Runoff at 96-hour µg a.i./L	Most conservative endpoint values (µg a.i./L) ÷ safety factor	RQ EEC/endpoint
Marine/Estuarine Species									
Shell deposition, Eastern oyster, *Crassostrea virginica*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	60	0.60
	Acute	BC apples	2400	6	AB	0.80	0.39	60	0.007
Fish: Sheepshead minnow, *Cyprinodon variegatus*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	6.5	**5.70**
	Acute	BC apples	2400	6	AB	0.80	0.39	6.5	0.06
Algae: diatom *Skeletonema costatum*	Acute	Prairie pumpkins	4000	6	GB	0.80	37.00	90	0.40
	Acute	BC apples	2400	6	AB	0.80	0.39	90	0.004

* Bold values and shaded cells indicate that the LOC is exceeded with RQ>1
AB = Airblast; GB = Groundboom

Appendix XI Water Modelling and Monitoring Data

Water Monitoring Data

A search for Canadian water monitoring data on folpet revealed that routine analysis for folpet is not conducted. The Federal Provincial and Territorial representatives from the provinces and territories in Canada were contacted requesting water monitoring data for folpet. In addition, requests were submitted to Environment Canada, the Department of Fisheries and Oceans and the Health Canada drinking water subcommittee. No monitoring data were obtained for this compound.

Given the lack of data available in Canada for residues of folpet in water, United States (US) databases were searched for detections in water. Data on residues present in water samples taken in the US are important to consider in the Canadian drinking water assessment given the extensive monitoring programs that exist in the US. Local weather patterns, runoff events, circumstantial hydrogeology as well as testing and reporting methods are probably more important influences on residue data than Northern versus Southern climate. As for climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and inputs may be more numerous and frequent. No detections of folpet were found in the USGS NAWQA database or other databases from the US.

Discussions and Conclusions

The limited amount of monitoring data available to the PMRA did not allow for an estimation of the residues of folpet (and folpet and transformation product PI) in both surface and drinking water using monitoring data. The concentrations of folpet (and folpet and transformation product PI) in surface and drinking water that should be considered in the risk assessment are the EECs determined by water modelling.

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Surface water and groundwater modelling of both parent only, and the transformation product phthalimide (PI) and folpet as a combined chemical was requested for drinking water. Estimated environmental concentrations (EECs) in potential drinking water sources (groundwater and surface water) were estimated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of folpet and combined residues in groundwater were calculated using the LEACHM model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using LEACHM are based on the flux, or movement, of pesticide into shallow groundwater with time. EECs of folpet and its transformation products in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Table 1 lists the

application information and main environmental fate characteristics used in the simulations. Twelve for surface water and four for groundwater initial application dates between April and June were modelled. The models were run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 2 below.

Table 1 Major groundwater and surface water model inputs for Level 1 assessment of folpet and its transformation product

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Pumpkin/apple
	Maximum allowable application rate per year (g a.i./ha)	24000/18000
	Maximum rate each application (g a.i./ha)	4000/3000
	Maximum number of applications per year	6
	Minimum interval between applications (days)	7
	Method of application	Ground foliar (CAM2)
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	0.039 (parent) 0.34 (combined)
	Photolysis half-life in water (days)	0 (stable)
	Adsorption K_{oc} (mL/g)	11.3 (20th percentile of K_{oc} values for "folpet")
	Aerobic soil biotransformation half-life (days)	2.8 (parent) (80th percentile of half-life values) 5.8 (combined) (80th percentile of half-life values)
	Aerobic aquatic biotransformation half-life (days)	0 (stable) short study value was assumed to be due to hydrolysis
	Anaerobic aquatic biotransformation half-life (days)	0 (stable) no data available

Table 2 Level 1 estimated environmental concentrations of folpet and its transformation product PI in potential drinking water sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Folpet (parent only)	0	0	404	1.1	308	0.72
Folpet (and transformation product phthalimide)	0	0	413	1.5	373	1.0

Notes:
[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

Estimated Concentrations in Water for the Ecological Assessment

Application Information and Model Inputs

Folpet is a fungicide used on fruits and vegetables. The maximum annual application rate is 6 applications of 4 kg a.i./ha, at 7-day intervals, for use on pumpkins, cucumbers, squash, zucchini, melon and tomatoes. The second highest rate is 6 applications of 2.4 kg a.i./ha, at 7-day intervals, for use on apples. The ecoscenario modelling included only the parent (folpet) in both 80-cm and 15-cm water bodies. Application information and the main environmental fate characteristics used in the models are summarized in Table 1

Aquatic Ecoscenario Assessment: Level 1 Modelling

The level 1 aquatic ecoscenario assessment estimated environmental concentrations (EECs) of folpet from runoff into a receiving water body were simulated using the Pesticide in Water Calculator (PWC). The PWC model simulates pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the Level 1 assessment, the water body consists of a 1-ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level. This water body is essentially a scaled-down version of the permanent water body noted above, but having a water depth of 0.15 m.

Six standard regional scenarios were modelled to represent different regions of Canada. More than 20 initial application dates between April and November were modelled. Table 2.1-1 lists the application information and the main environmental fate characteristics used in the simulations. The EECs are for the portion of the pesticide that enters the water body via runoff only; deposition from spray drift is not included. The models were run for 50 years for all scenarios.

The EECs are calculated from the model output from each run as follows. For each year of the simulation, PWC calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day, and 1 year). The 90th percentiles over each averaging period are reported as the EECs for that period.

The modelled EECs in 15-cm and 80-cm water bodies of all selected runs of all given use pattern/regional scenario are reported in Table 3 and Table 4 (the largest EECs are in bold), respectively.

Table 3 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for folpet in a water body 0.15 m deep, excluding spray drift

Scenario	Peak	96 hr	21 d	60 d	90 d	Yearly	Peak pore water	Yearly pore water
Pumpkin rate: 6x4000 g a.i./ha, at 7-day intervals								
British Columbia	301	4.3	1.0	0.37	0.26	0.060	0.1	0.003
Prairies	1700	24	6.6	2.4	1.6	0.39	6.7	0.062

Scenario	Peak	96 hr	21 d	60 d	90 d	Yearly	Peak pore water	Yearly pore water
Ontario	2330	37	9.1	3.8	2.5	0.63	1.9	0.032
Quebec	**2630**	40	7.9	3.1	2.1	0.51	4.6	0.051
Atlantic Region	2590	42	11	4.4	3.4	**0.72**	1.1	0.033
Apple rate: 6x2400 g a.i./ha, at 14-day intervals								
British Columbia	36	0.50	0.096	0.034	0.027	0.007	0.0005	0.0002
Ontario	502	7.1	1.6	0.66	0.50	0.11	0.038	0.004
Quebec	543	7.6	1.9	0.70	0.53	0.12	0.023	0.004
Atlantic Region	**555**	7.8	1.7	0.80	0.56	**0.13**	0.080	0.004

Table 4 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for folpet in a water body 0.80 m deep, excluding spray drift

Scenario	Peak	96 hr	21 d	60 d	90 d	Yearly	Peak pore water	Yearly pore water
Pumpkin rate: 6x4000 g a.i./ha, at 7-day intervals								
British Columbia	56	0.80	0.19	0.069	0.049	0.011	0.1	0.001
Prairies	318	4.5	1.3	0.44	0.30	0.073	6.7	0.051
Ontario	437	6.9	1.7	0.71	0.48	0.12	1.9	0.017
Quebec	**493**	7.5	1.5	0.58	0.38	0.095	4.6	0.039
Atlantic Region	486	7.8	2.1	0.83	0.64	**0.14**	1.1	0.013
Apple rate: 6x2400 g a.i./ha, at 14-day intervals								
British Columbia	6.7	0.094	0.018	0.006	0.005	0.001	0.0005	0.00004
Ontario	94	1.3	0.29	0.12	0.095	0.020	0.038	0.0009
Quebec	102	1.4	0.35	0.13	0.099	0.022	0.023	0.0009
Atlantic Region	**104**	1.5	0.32	0.15	0.11	**0.025**	0.080	0.001

Appendix XII Toxic Substances Management Policy

Table 1 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints*	Transformation Products Endpoints
CEPA toxic or CEPA toxic equivalent	Yes		-	-
Predominantly anthropogenic	Yes		-	-
Persistence	Soil	Half-life ≥ 182 days	3.8 days (aerobic soil) 9 days (anaerobic soil)	Phthalimide, Phthalic acid, phthalamic acid: 0.4 – 17.2 days (aerobic soil)
	Water	Half-life ≥ 182 days	0.27 days (hydrolysis) 0.04 days (aerobic water[5])	Phthalimide: 0.08 – 0.31 days (hydrolysis
	Sediment	Half-life ≥ 365 days	Not available	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	The Henry's law constant (2.96×10^{-3} Atm.m^3/mol) indicates that folpet has the potential to volatilize from surface water or moist soil under field conditions. However, the low vapour pressure of folpet (2.1×10^{-5} Pa) suggests a low volatility potential of the compound. No volatility studies were available to confirm that long-range atmospheric transport of folpet would occur.	Not expected to be volatile due to high hydrolysis rate and low vapour pressure
Bioaccumulation	Log $K_{OW} \geq 5$		The Log K_{ow} is 3.1	Not available
	BCF ≥ 5000		BCF 19 to 81 in bluegill sunfish	Not available
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, they do not meet TSMP Track 1 criteria.

Appendix XIII Label Amendments for End-Use Products Containing Folpet

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements. **Note:** The following information is divided according to product type. Please read each section carefully.

The following uses are proposed for cancellation. All references to these uses must be removed from all end-use product labels:

- Fungicidal additive vinyl plastics
- Azalea stem soak
- Greenhouse cut flowers
- Field cut flowers
- Cranberries

1. Label Amendments for Technical Grade Active Ingredients Containing Folpet

The current hazard symbol, signal word and hazard statement on the primary display panel should be modified from "Caution – Poison, Causes eye irritation" to "WARNING – POISON, EYE IRRITANT, POTENTIAL SKIN SENSITIZER" based on the acute inhalation toxicity, eye irritation and sensitization data on technical folpet. The precautionary statements on the secondary panel should be amended to include the following: May be fatal if inhaled. Avoid inhaling/breathing dusts or sprays. Causes eye irritation. Do not get in eyes. Potential skin sensitizer.

2. Health Label Amendments for Commercial Class End-use Products Containing Folpet

2.1 Wettable Powder or Wettable Granules in Water Soluble Packaging (WSP)[7]:

I) It is proposed that all folpet products currently formulated as wettable powders be reformulated in water soluble packaging. Label language would need to be clarified to indicate directions for the use of water soluble packaging. Registrants would need to ensure that the sizes of the water soluble packets are reconciled with the registered/required use-specific application rates.

2.2 PRECAUTIONS

2.2.1 General Label Improvements

[7] End use products registered for use in vinyl plastics (PCP# 15605; PCP# 32928) are proposed for cancellation due to occupational exposure issues. However, if any additional information received during the consulation period results in a reassessment and these uses being retained in the final re-evaluation decision, then additional label amendments would be required. Specifically, the following clarification would be required in the DIRECTIONS FOR USE section: "For treatment of vinyl used in the manufacture of gaskets, vinyl flooring backing, outdoor upholstery (seats for boats), coatings applied to tents, awnings and roof membranes."

The following label statements are added to the **PRECAUTIONS** of all commercial end-use product labels with agricultural uses (PCP#15654, 27733):

> "Apply only when the potential for drift to areas of human habitation or areas of human activity (houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

2.2.2 Personal Protective Equipment

Label statements must be amended (or added) to include the following directions to the appropriate labels, unless the current label mitigation is more restrictive:

2.2.2.1 Water Dispersible Granules (WDG) - PCP#27733

A. Mixing and Loading

"Wear chemical resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, goggles and, during mixing/loading, clean-up and repair, a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

B. Airblast Application

"If using an open cab, wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, goggles, chemical-resistant hat that covers the neck (e.g Sou'Wester) and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

"If using a closed cab, wear a long-sleeved shirt, long pants, and chemical-resistance gloves. The closed cab must have a chemical-resistant barrier that totally surrounds the occupant and prevents contact with pesticides outside the cab."

C. Groundboom Application

"Wear a long-sleeved shirt, long pants, shoes plus socks, goggles, and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides. Chemical-resistant gloves are not required to be worn during application but are required for clean-up, calibration and repair."

D. Handheld Application

"Wear a long-sleeved shirt, long pants, shoes plus socks, goggles, chemical-resistant gloves and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

"For mechanically-pressurized handguns: Also wear cotton coveralls."

2.2.2.2 Wettable Powders in Water Soluble Packages (WP in WSP)- PCP# 15654, but reformulated to be in water soluble packages

A Mixing and Loading (Water Soluble Packages)
"Wear long-sleeved shirt, long pants, chemical-resistant gloves during mixing/loading, clean-up and repair."

B. Airblast Application
"Wear cotton coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, chemical-resistant hat that covers the neck (e.g Sou'Wester) and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

C. Groundboom Application
"Wear a long-sleeved shirt, long pants, shoes plus socks. Chemical-resistant gloves are not required to be worn during application but are required for clean-up, calibration and repair."

D. Handheld Application
"Wear a long-sleeved shirt, long pants, shoes plus socks, and chemical-resistant gloves."

"For mechanically-pressured handguns: Also wear coveralls and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

2.3 DIRECTIONS FOR USE

2.3.1 Uses

The following statements are added to the agricultural product labels:

- "A minimum rotational crop plantback interval of 12 months must be observed for all crops other than those registered for use with folpet".

- For label clarification, product Reg. No. 15654 should be updated in accordance with the Regulatory Directive: Chemigation (DIR93-13); the following statement should be added to the product label:

  "DO NOT apply this product by chemigation or through any type of irrigation system"

- For greenhouse and field flower uses:

  "Only for use with potted plants. Not for use on cut flowers."

- For commercial products that have crops that may be found in greenhouses (*e.g.* cucumber, tomato):

"For outdoor use only."

2.3.2 Restricted Entry Interval

Table 1 lists the maximum number of applications, minimum interval and proposed restricted-entry intervals (REI) for folpet.

Where the REIs for hand harvesting are longer than the PHI, the PHI should be increased to correspond with the proposed REI, and vice versa. Apples/crabapples, field cucumber, pumpkin, melon, squash, and strawberries currently have a PHI of 1 day, which will need to be increased to be the same as the hand harvesting REI, unless mechanical harvesting is also possible. If this is the case, then the current label PHI should remain, with the current REI for hand-harvesting activities.

Table 1 Proposed REIs and Maximum Number of Application for Folpet

Crop	Activity	Maximum Rate	REI	Max Number of Apps	Min RTI
Greenhouse Poinsettia	All	1.13 kg a.i./1000 L (1000 L/ha dilution)	0.5 days	2	10
Greenhouse Carnations	All (non-cut flower)	1.0 kg/1000 L (1000 L/ha dilution)	0.5 days	5	14
Greenhouse Marigolds, Zinnias, Snapdragons	All (non-cut flower)		0.5 days	3	3
Greenhouse Roses, Asters, China Asters, Phloxes, Chrysanthemums	All (non-cut flower)		0.5 days	3	7
Greenhouse Irises	All (non-cut flower)		0.5 days	3	7
Apples, Crabapples	Thinning fruit	3.0 kg a.i./ha (WDG)	21 days	3	10
	Hand harvesting		3 days		
	All other activities		0.5 days		
	Thinning fruit	2.0 kg a.i./ha (WP)	3 days	3	10
	All other activities		0.5 days		
Grapes	Hand girdling and turning (table/ra.i.sin grapes only)	1.0 kg a.i./ha	32 days	1	N/A
	Hand harvesting, training/tying, leaf pulling		25 days		
	All other activities		0.5 days		
Strawberry	Hand harvesting	2.0 kg a.i./ha	12 days	1	N/A
	All other activities		0.5 days		
Field Cucumber, Pumpkin, Melon, Squash	Hand harvesting, mechanically-assisted harvesting, training, turning (pumpkin, melon only)	4.0 kg a.i./ha	12 days	1	N/A
	Moving irrigation pipes by hand		23 days		
	All other activities		0.5 days		
Field Tomato	Hand harvesting, tying/training	4.0 kg a.i./ha	18 days	1	N/A

Crop	Activity	Maximum Rate	REI	Max Number of Apps	Min RTI
	Scouting		3 days		
	All other activities		0.5 days		
Field Carnations	All (non-cut flower)	1.0 kg/1000 L (1000 L/ha dilution)	0.5 days	6	14
Field Marigolds, Zinnias, Snapdragons	All (non-cut flower)		1 day	6	3
Field Roses, Asters, China Asters, Phloxes, Chrysanthemums	All (non-cut flower)		0.5 days	6	7
Field Irises	All (non-cut flower)		0.5 days	4	7

REI= restricted entry interval; Max = maximum; Apps = applications; Min RTI = minimum retreatment interval (that is. shortest time between applications); N/A = not applicable

3.0 Environmental Label Statements for Commercial Class End-use Products Containing Folpet

The environmental risk assessment identified a potential hazard to small mammals, fish, amphibians, algae and aquatic invertebrates.

3.1 Add to ENVIRONMENTAL HAZARDS (or ENVIRONMENTAL PRECAUTIONS):

- **TOXIC** to small mammals and aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.

3.2 RUN-OFF AND LEACHING

- To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil or clay.

- Avoid application 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.

- Transformation products of folpet have the potential to leach and to reach groundwater. Avoid application where soils are permeable and/or the depth to the water table is shallow.

3.3 Add to DIRECTIONS FOR USE

3.3.1 The following statement is required for all agricultural and commercial pesticide products.

- As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests

- DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

- DO NOT apply by air.

3.3.2 For **field applications using conventional groundboom and airblast sprayers** (agricultural or commercial products), the following statements are required:

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 S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **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:

Spot treatments using hand-held equipment **DO NOT** require a buffer zone.

The buffer zones specified in the table 1 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	Crop		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Aster, carnation, China aster, chrysanthemum, iris, marigold, phlox, poinsettia, rose, snapdragon, zinnia		15	2	1	1
	Strawberry		25	3	2	1
	Cucumber, melon, pumpkin, squash, tomato		40	5	3	2
	Cranberry		50	5	4	2
Airblast	Grape	Early growth stage	50	25	15	10

Method of application	Crop		Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
		Late growth stage	40	15	10	4
	Apple, crabapple	Early growth stage	55	30	25	15
		Late growth stage	45	20	15	10

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

References

A. Information Considered in the Chemistry Assessment

A.1 List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
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B. Information Considered for the Toxicological Assessment

B.1 List of Studies/Information Submitted by Registrant

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C. Information Considered in the Dietary Assessment

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852160	1994. Folpet: Nature of Residue on Grapes. Report# R-6403a. Report# 93/0962, 12/21/94. 266 pages. Unpublished.
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