Proposed Re-evaluation Decision PRVD2018-15

Fomesafen 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.

Fomesafen is a herbicide for weed management in a range of agricultural crops. It provides post-emergence control of a wide spectrum of broadleaf weeds with residual activity in certain pulse crops (dry and succulent beans and peas), soybean, cucumber, strawberry, and potato. The end-use products are applied using ground application equipment only and are registered for use in Eastern Canada, the Red River Valley of Manitoba, or in British Columbia, depending on the specific use.

This document presents the proposed regulatory decision for the re-evaluation of fomesafen including the 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 fomesafen 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 the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA Publications Section. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

With respect to human health, the risks were found to be acceptable. Exposure from the labelled uses is unlikely to affect human health when used according to the proposed label updates.

Fomesafen enters the environment when used to control specified weeds on various agricultural field crops. Risks to the environment were found to be acceptable when fomesafen is used according to the proposed label updates.

Fomesafen contributes to weed management in a range of agricultural crops. It provides post-emergence control of a wide spectrum of broadleaf weeds with residual activity in certain pulse crops (dry and succulent beans and peas), soybeans, cucumber, strawberry, and potato. It is the primary and most widely used herbicide on snap beans for which there are limited alternative herbicides.

Proposed Regulatory Decision for Fomesafen

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing that products containing fomesafen are acceptable for continued registration in Canada, provided that the proposed risk mitigation measures are in place.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of fomesafen, further risk mitigation measures for product labels, as summarized below, are being proposed.

Human Health

Label updates to meet current standards

- A label statement prohibiting aerial application.
- A label statement prohibiting application in greenhouses.
- A label statement prohibiting application when there is potential drift to areas of human habitation or areas of human activity.

Proposed risk mitigation

To protect workers entering treated areas:

- A 12-hour Restricted-Entry Interval (REI) is required for all crops.

Environment

To protect the environment:

- Standard environmental precaution statements to inform the users of the potential for toxicity to terrestrial vascular plants and aquatic organisms.
- Spray buffer zones to protect sensitive terrestrial habitats from spray drift.
- Precautionary label statements informing users how to reduce the potential for runoff.
- Label statements informing users of the potential for carryover of fomesafen from one season to the next.

International Context

Fomesafen is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, Mexico and Israel. Fomesafen is currently under registration review by the United States Environmental Protection Agency.

No decision by an OECD member country to prohibit all uses of fomesafen for health or environmental reasons has been identified.

Although fomesafen is currently listed as “not approved” by the European Commission, no health or environmental reasons were identified in the European Union decision.

Next Steps

The public including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document[2], which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with the PMRA’s responses.

1 “Consultation statement” as required by subsection 28(2) of the *Pest Control Products Act*.

2 “Decision statement” as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

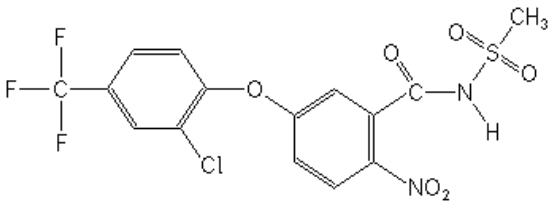
Fomesafen contributes to weed management in a range of agricultural crops. It provides post-emergence control of a wide spectrum of broadleaf weeds with residue activity. It is the primary and most widely used herbicide on snap beans for which there are limited alternative herbicides. It is the only alternative to bentazon for post-emergence in-crop use to control broadleaf weeds in dry and snap beans which has been identified as one of key issues facing Canadian pulse crop growers. It is a tool to manage resistant weeds in soybeans by providing an alternative mode of action to acetolactate synthase (ALS) inhibitors and glyphosate herbicides, to which a number of resistant weed biotypes have been reported.

Appendix I, Table 1 lists all fomesafen products that are registered under the authority of the *Pest Control Products Act* as of July 2018. A total of seven products contain fomesafen including two Technical Grade Active Ingredients, two Manufacturing Concentrates and three Commercial Class end-use products.

Appendix I, Table 2 lists all of the Commercial Class uses for which fomesafen is presently registered. All uses were supported by the registrant at the time of initiation of the re-evaluation and were, therefore, considered in the health and environmental risk assessments.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name	Fomesafen
Function	Herbicide
Chemical Family	Diphenyl ether
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	5-(2-chloro-α,α,α-trifluoro-*p*-tolyloxy)-*N*-mesyl-2-nitrobenzamide
2 Chemical Abstracts Service (CAS)	5-[2-chloro-4-(trifluoromethyl)phenoxy]-*N*-(methylsulfonyl)-2-nitrobenzamide
CAS Registry Number	72178-02-0
Molecular Formula	$C_{15}H_{10}ClF_3N_2O_6S$
Structural Formula	

Molecular Weight	438.8

Registration Number	**Purity of the Technical Grade Active Ingredient (%)**
28133	98
28828	99.8

2.2 Physical and Chemical Properties

Property	**Result**	**Interpretation**
Vapour pressure at 20°C	$< 4 \times 10^{-3}$ mPa	Non-volatile under field conditions
Ultraviolet (UV)/visible spectrum	No absorption at $\lambda > 400$ nm	Absorption within the range for possible photodegradation; however, no data to confirm
Solubility in water at 20°C	50.0 mg/L in distilled water < 10.0 mg/L (pH 1-2) 10 000 mg/L (pH 9)	Soluble at neutral pH but very soluble at alkaline pH
n-Octanol/water partition coefficient	Log K_{ow} = 3.4 (pH 4)	Potential for bioaccumulation under acidic conditions; unlikely under neutral conditions
Dissociation constant at 20–25°C	2.83	Anion at environmentally relevant pH range

3.0 Human Health Assessment

3.1 Toxicology Summary

A detailed review of the toxicological database for fomesafen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Two forms of fomesafen are registered: an acid form herein referred to as fomesafen, and a sodium salt form. Both forms were assessed for acute toxicity. Short- and long-term toxicity studies on the acid form are relevant for assessing the toxicity of the sodium form. The scientific quality of the data is acceptable and the database is considered adequate to define the majority of the toxic effects that may result from exposure to fomesafen. The database was supplemented with more recently conducted studies assessing acute toxicity, neurotoxicity and immunotoxicity. The published scientific literature was also examined.

Oral gavage toxicokinetic studies in rats and other mammals with radiolabelled fomesafen indicated rapid absorption and excretion. In rats, sex and dose level influenced the route of excretion. With a single low dose, fecal/biliary excretion was the main route of elimination in males, while urinary excretion was the main route in females. With a single high dose, urinary excretion was predominant in both sexes. The majority of the radiolabel was eliminated within 72 hours in both males and females; however, elimination in males was significantly less than in

females. Negligible amounts of radiolabel were released in expired air. There were also sex differences in the rat with regard to elimination of the administered radiolabel from tissues, with higher tissue radioactivity in males. The largest amount of radioactivity was found in the liver, with lower amounts found in the gastrointestinal tract, carcass and kidneys. The majority of the radioactivity in urine, feces, bile and liver was unchanged fomesafen. Other metabolites were minor with no single metabolite comprising more than 5% of the administered dose. In mice, dogs and marmosets treated with a single low dose, there were no pronounced excretion differences between the sexes. In dogs and marmosets, urinary excretion was the main route of elimination, while in mice fecal excretion predominated. In mice, the amount of radioactivity was highest in the liver, reflecting the primary route of biliary excretion in the mouse.

Fomesafen was of slight acute toxicity in rats by the oral route. Clinical signs included subdued behaviour, dehydration, upward curvature of the spine, piloerection, urinary and fecal incontinence and ungroomed appearance. Fomesafen was also of slight acute toxicity in rabbits by the dermal route. It was mildly irritating to rabbit eyes and slightly irritating to rabbit skin. It was a dermal sensitizer in guinea pigs, when assessed by the Maximization method. An aqueous solution of the sodium salt of fomesafen (technical grade, 48%) was of slight acute oral toxicity and of low acute dermal and inhalation toxicity in rats. It was severely irritating to the eyes and moderately irritating to the skin in rabbits, and did not cause an allergic skin reaction in a local lymph node assay in mice.

There were no treatment-related systemic effects observed in a rabbit 21-day dermal toxicity study at the limit dose for testing.

Repeat-dose toxicity studies, by the oral (diet, capsule, or gavage) route, were conducted in the mouse, rat, dog and marmoset. In these studies, the liver was the major target organ with males more sensitive than females.

In short-term rat and dog toxicity studies and a mouse immunotoxicity study, liver weight was increased. Additionally, in the rat and dog, there were increases in the number of liver peroxisomes and liver enzymes, as well as reductions in cholesterol and triglycerides. Rats also showed hepatocytic hyalinization, and dogs showed hepatocytic cytoplasmic eosinophilia. The liver effects in rats largely disappeared following a recovery period on control diet. Kidney weights were increased in both the rat and the dog. In the dog, other findings included slight increases in urinary protein, as well as slight reductions in hemoglobin, hematocrit, and ovary weight. In mice, at dose levels considerably higher than those in the rat and dog studies, body weight was reduced. In a two-week gavage study in marmosets, hepatotoxicity was observed, characterized by increased severity of focal inflammation, slight increases in peroxisomes and the degree of swelling of the endoplasmic reticulum (ER), and a slight decrease in palmitoyl CoA oxidation enzyme. Overall, the rat was the most sensitive species to the short-term toxicological effects of fomesafen.

Following chronic dosing in rodents, liver effects increased in incidence and severity compared to shorter-term studies. In the two-year dietary rat chronic toxicity/oncogenicity study, in addition to the liver effects seen in the short-term rat studies, effects in the liver of male rats included hepatocytic cystic degeneration, increased lipofuscin content, proteinaceous deposits,

Kupffer cell and macrophage infiltration, and focal necrosis. Males also showed reduced body weight gain, and increased incidences of adrenal fatty degeneration and cystic degeneration in the lymph nodes. Females showed increased dilatation and calcification of the pelvic epithelium of the kidney. In the two-year dietary mouse oncogenicity study, in addition to increases in liver weight, liver enzymes and hyalinization noted in the shorter-term studies, effects included discoloration of the liver, enlarged hepatocytes, pigmented Kupffer cells and macrophages, and an increased incidence of single cell necrosis. Peroxisome proliferation was not examined in this study. Decreased survival was noted in both sexes at the highest dose level. The mouse, following two years of exposure, and the dog, following six months of exposure, were the most sensitive to the long-term toxicological effects of fomesafen, with each establishing a no-observed adverse effect level (NOAEL) of 1.0 mg/kg bw/day.

The assessment of the oncogenic potential of fomesafen was informed by a battery of in vivo and in vitro genotoxicity studies, as well as the long-term dietary studies in rats and mice. Genotoxicity studies included in vivo chromosome aberration, unscheduled deoxyribonucleic acid (DNA) synthesis, in vitro chromosome aberration, dominant lethal, Ames reverse mutation and mammalian cell transformation tests. One in vivo chromosome aberration test with rat bone marrow was positive; however, the results could not be repeated in a second test. All other genotoxicity tests were negative. Overall, the weight of evidence suggests that fomesafen is not genotoxic. There was no evidence of oncogenicity in the rat. In the mouse, significant increases in hepatic adenomas and carcinomas were observed following treatment with fomesafen at the two highest dose levels.

The mode of action (MOA) for the development of liver tumours in the mouse is purported to be non-genotoxic, involving the activation of peroxisome proliferator-activated receptor alpha (PPARα). Activation of these receptors leads to an increase in the expression of peroxisomal genes and peroxisome proliferation. This in turn causes an increase in DNA synthesis, enlargement of the liver and, eventually, liver tumours. This MOA is well described in the published literature (PMRA# 2817364, 2817365, 2817366). Peroxisome proliferation-induced tumour development in mice is considered specific to mice and the mechanism by which it occurs is not considered to lead to carcinogenicity in humans.

Evidence for this MOA in mice is supported by the observation, in 28- and 56-day dietary studies, of increased liver weights and liver hypertrophy as early as one week after dosing, and at subsequent time points. An increase in DNA synthesis and peroxisome proliferation was also observed after 1, 4 and 8 weeks. In the 2-year dietary study in mice significantly increased tumour responses occur at the two highest dose levels (100 and 1000 ppm) which were also the concentrations at which a significant increase in mean absolute liver weight and enlargement of the liver were observed. In the 28- and 56-day studies, the key events, peroxisome proliferation and increased liver weight and size, also occurred at these same doses. Overall, the data support dose and temporal concordance. Other potential MOAs (cytotoxicity, genotoxicity) are not supported by the available data. Fomesafen was not considered genotoxic in a battery of in vivo and in vitro assays.

Radioactive tracer experiments on the interaction of fomesafen with mouse liver in vivo showed no covalent interaction between fomesafen or its metabolites and liver DNA, and very limited binding to hepatic protein. Although the PPARα MOA is plausible in humans, quantitative species differences in PPARα activation and toxicokinetics render tumour production in humans unlikely.

In a dietary two-generation reproductive toxicity study in rats, effects were noted only at the highest dose level of 50 mg/kg bw/day. Findings in parental animals included hepatotoxicity (diffuse hepatocyte hyalinization, increased biliary hyperplasia, pigmented Kupffer cells, and focal necrosis). There was also a slight reduction in body weight and body weight gain in parental males, and a slight reduction in body weight gain in females during pregnancy. Effects in the pups included slightly decreased body weight and body weight gain, and in males, slightly increased renal pelvic dilatation and hepatocytic hyalinization. No adverse effects on reproductive parameters were noted at any dose level. There was no indication of sensitivity of the young.

In the gavage developmental toxicity studies in rats, fetal effects at the high dose level included an increase in post-implantation loss (early and late resorptions) and a decrease in litter weight, establishing a NOAEL of 100 mg/kg bw/day. Maternal effects at the same dose level also included reductions in body weight gain, gravid uterine weight and food consumption, and an increase in staining of genital/ventral fur. In the gavage developmental toxicity study in rabbits, no treatment-related fetal effects were noted. Maternal toxicity at the high dose included some animals appearing thin, and increased incidences of stomach mucosa erosion and mucus around the nose. There was no evidence of malformations in either study.

A dietary 90-day neurotoxicity study in rats did not reveal evidence of neurotoxicity; however, effects on the liver were apparent. In a gavage acute neurotoxicity study in rats, conducted with higher dose levels, a number of effects were noted at, and above, 250 mg/kg bw including reduced motor activity, hunched posture, piloerection, abnormal gait, reduced righting response, and decreased female body temperature. These responses occurred largely on the day of dosing and were not considered evidence of selective neurotoxicity. No treatment-related neurohistopathology was identified.

There was some evidence for suppression of the immune response in the 28-day dietary immunotoxicity study in mice with a reduction in immunoglobulin M (IgM) levels at 176 mg/kg bw/day, and, at higher dose levels, a reduction in spleen and thymus weights.

Results of the toxicology studies conducted on laboratory animals with fomesafen are summarized in Appendix II, Table 1. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix II, Table 2.

3.1.1 *Pest Control Products Act* (PCPA) 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 database as it pertains to the toxicity to infants and children, the standard complement of required studies were available including gavage developmental toxicity studies in rats and rabbits and a dietary reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the two-generation reproductive toxicity study. Both parents and offspring demonstrated hepatic effects and effects on bodyweight at the same dose level. In a developmental toxicity study in rats, fetal effects included increased post-implantation loss and a reduction in litter weight in the presence of maternal toxicity (decreased body weight, reduced food consumption, staining of genital/ventral fur). In the rabbit developmental toxicity study, there were no treatment-related effects in the fetuses at a dose level which produced maternal toxicity (clinical signs, increased incidence of stomach mucosa erosion).

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well-characterized. Post-implantation loss in the rat developmental toxicity study was considered a serious effect. However, concern for this finding was tempered because it occurred in the presence of maternal toxicity. Therefore, the PCPA factor was reduced to threefold when using the rat developmental toxicity study to establish the point of departure for assessing risk to women of child-bearing age. For exposure scenarios involving other sub-populations, the risk was considered well-characterized and the PCPA factor was reduced to onefold.

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 fomesafen 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 value. The PMRA's Science Policy Note SPN2003-03 *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute and chronic risk assessment procedures.

Sufficient information was available to adequately assess the dietary exposure and risk from fomesafen. Acute and chronic dietary (food and drinking water) exposure and risk assessments for fomesafen 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 for the years 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 the PMRA's Science Policy Note SPN 2014-01 *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on the dietary risk estimates or the residue chemistry information used in the dietary assessment, see Appendix III and Appendix IV, respectively.

3.2.1 Determination of Acute Reference Dose (ARfD)

Females 13-49 Years of Age

To estimate acute dietary risk, the rat gavage developmental toxicity study with a developmental NOAEL of 100 mg/kg bw/day was selected for risk assessment. At the developmental lowest observed adverse effect level (LOAEL) of 200 mg/kg bw/day, there was an increase in post-implantation loss. This effect could result from a single dose and is therefore considered relevant to an acute risk assessment. The maternal toxicity noted in the rabbit developmental toxicity study, consisting of minor clinical effects and an increased incidence of stomach mucosa erosion, was not considered relevant to an acute risk assessment. 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 PCPA factor was reduced to threefold. Thus, the composite assessment factor (CAF) is 300.

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{300} = 0.3 \text{ mg/kg bw}$$

General Population (excluding females 13-49 years of age)

To estimate acute dietary risk, the acute gavage neurotoxicity study in rats with a NOAEL of 100 mg/kg bw was selected for risk assessment. A reduction in body weight gain, food consumption and motor activity occurred at the LOAEL of 250 mg/kg bw. These effects were the result of a single exposure and are therefore considered relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intra-species variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to onefold. Thus, the CAF is 100.

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{100} = 1.0 \text{ mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of residues of fomesafen 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 estimated exposure is less than the ARfD, the acute dietary exposure is not of concern.

The assessment was conducted using Canadian Maximum Residue Limits (MRLs), American Tolerance levels or anticipated residues, and assuming all food commodities were 100% treated, including imports. Theoretical processing factors were used, where available. Drinking water contribution to the exposure was accounted for by direct incorporation of the acute estimated environmental concentration (EEC) value obtained from water modelling (see Section 3.3), into the dietary exposure evaluation model (DEEM).

The acute dietary exposure estimates (from food and drinking water) at the 95th percentile were at or below 2% of the ARfD for the general population and all other sub-populations, including females 13–49 years of age, and thus, are not of concern.

3.2.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk from repeat dietary exposure, the 26-week capsule study in the dog and the 2-year dietary study in the mouse, each with a NOAEL of 1.0 mg/kg bw/day, were co-critical studies selected for risk assessment. At the LOAEL of 25 mg/kg bw/day in the dog study, effects on liver and clinical chemistry were observed. At the LOAEL of 10 mg/kg bw/day in the mouse study, liver effects were observed. These studies provide the lowest NOAEL in the database. 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 PCPA factor was reduced to onefold. The CAF is thus 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{1.0 mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day}$$

The ADI provides a margin of 20,000 to the dose level which resulted in post-implantation loss in the rat developmental toxicity study.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using average consumption of different foods and drinking water, and food and drinking water residue values. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The assessment was conducted using Canadian MRLs, American Tolerance levels or anticipated residues, and assuming all food commodities were 100% treated, including imports. Theoretical processing factors were used, where available. Drinking water contribution to the exposure was accounted for by direct incorporation of the chronic EEC value obtained from modelling (see Section 3.3) into DEEM.

The chronic dietary exposure estimates (from food and drinking water) were at or below 92% of the ADI for the general population and all other sub-populations and thus, are not of concern.

3.2.5 Cancer Assessment

Fomesafen was not considered genotoxic in a battery of in vivo and in vitro assays. No treatment related tumours were noted in the rat chronic/oncogenicity study. In the mouse oncogenicity study, a significant increase in liver tumours was observed following treatment with fomesafen. Based on studies submitted to the PMRA, and additional studies submitted to, and summarized by the USEPA (PMRA# 2817364), the overall weight of evidence supports a hepatocarcinogenic MOA in mice based on activation of PPARα. This MOA is considered specific to mice and the mechanism by which it occurs is not considered to lead to carcinogenicity in humans. Therefore, no cancer risk assessment is necessary.

3.3 Exposure from Drinking Water

Residues of fomesafen in potential drinking water sources were estimated from water modelling.

3.3.1 Concentrations in Drinking Water

EECs of fomesafen were calculated using the Pesticides in Water Calculator (PWC) model. The use pattern modelled was one application of 240 g a.i./ha, applied every other year. Modelling used initial application dates between 11 May and 26 June. EECs in groundwater were calculated by selecting the highest EEC from several selected scenarios representing different regions of Canada. All scenarios were run for 50 years.

The highest groundwater daily EEC value of 119 ppb and groundwater yearly EEC value of 120 ppb were used in acute and chronic exposure assessments, respectively.

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. The risks were found to be acceptable. Please refer to Sections 3.2.2 and 3.2.4 for details.

3.4 Occupational Risk Assessment

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 sub-population. 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 Toxicological Endpoint Selection for Residential and Occupational Exposure

3.4.1.1 Short-term Dermal and Inhalation Exposure

The two-generation reproductive study in the rat with a parental/offspring NOAEL of 13 mg/kg bw/day was selected for risk assessment. At the LOAEL of 50 mg/kg bw/day, liver effects and a slight decrease in body weight/body weight gain were observed in parents and pups. An oral study was used for dermal and inhalation risk assessments because the available short-term dermal toxicity study did not consider developmental effects and no route-specific inhalation toxicity studies were available. For the dermal and inhalation routes of exposure, a target MOE of 100 was selected. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The selection of this point of departure and MOE is considered protective of sensitive sub-populations, such as women of reproductive age, pregnant women, and unborn children.

3.4.1.2 Dermal Absorption

Various in vivo and in vitro studies were submitted to the PMRA or available in the literature for the re-evaluation of fomesafen. Using a weight-of-evidence from physical/chemical properties of fomesafen, observations from toxicological studies and qualitative observations, a decreased dermal absorption value from 100% to 50% is supported and was used in this risk assessment.

3.4.2 Non-Occupational Exposure and Risk Assessment

A residential assessment was not required since there are no domestic-class products containing fomesafen and, based on the registered use pattern, commercial application to residential areas is not expected.

A standardized statement is proposed to prohibit application when there is potential drift to areas of human habitation or areas of human activity.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to fomesafen through mixing, loading, or applying the pesticide, and when entering a treated site to conduct postapplication activities such as scouting.

3.4.3.1 Mixer, Loader, and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators. The following scenarios were assessed:

- Open mixing/loading of liquids and;
- Open cab groundboom liquid application.

Based on the number of applications and the timing of application, workers applying fomesafen would generally have a short (<30 days) duration of exposure.

Handler exposure was estimated based on the following personal protection:

Baseline personal protective equipment (PPE): Long sleeved shirt and long pants and chemical-resistant gloves.

Dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database Version 1.1 (PHED). The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data which are used for scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems, and level of PPE.

Route specific MOEs for mixer/loader and applicators for agricultural crops are outlined in Appendix V, Table 1. Calculated dermal, inhalation, and combined (total exposure from dermal and inhalation routes) MOEs for mixers/loaders and applicators of fomesafen exceeded target MOEs for all scenarios and are not of concern.

3.4.3.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, scouting). Based on the use pattern, there is potential for short-term (<30 days) postapplication exposure to fomesafen residues for workers.

Activity-specific transfer coefficients (TC) from the Agricultural Re-entry Task Force (ARTF) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard clothing worn by adult workers. Postapplication exposure activities include: scouting and weeding.

Dislodgeable foliar residues (DFR) refer to the amount of residue that can be dislodged or transferred from a surface, such as the leaves of a plant. There were no chemical specific DFR studies submitted to the PMRA for the re-evaluation of fomesafen; therefore the following defaults were used:

A default peak value of 25% of the application rate with a dissipation rate of 10% per day was used for DFR.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before people can safely enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE.

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 fomesafen, inhalation exposure is not likely to be of concern provided that the minimum 12-hour REI is followed.

Calculated dermal MOEs for worker postapplication exposure to fomesafen in commercial crops exceeded target MOEs and are not of concern. REIs were set at the standard minimum value of 12 hours for all postapplication activities. The postapplication exposure assessment is outlined in Appendix V, Table 2.

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).

For fomesafen, the aggregate assessment consisted of combining food and drinking water exposure only (for which the risks were found to be acceptable, see Sections 3.2.2 and 3.2.4), since residential exposure is not expected to occur.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative effects of pest control products that have a common mechanism of toxicity. For the current re-evaluation, the PMRA did not identify information indicating that fomesafen shares a common mechanism of toxicity with other pest control products. Additionally, fomesafen does not appear to produce a toxic metabolite produced by other pest control products. Therefore, a cumulative assessment is not required at this time.

3.7 Incident Reports

As of 17 January 2018, the PMRA received one human and two domestic animal incident reports involving fomesafen. All incidents occurred in the United States and were classified as death. In the human incident, a man was exposed to a herbicide containing multiple active ingredients. Although fomesafen was listed as one of the active ingredients, it is not a component of the product. No exposure details pertaining to fomesafen were outlined in the report. In the domestic animal incidents, cows and chickens were exposed as a result of drift of various herbicide products, including one containing fomesafen, which were applied to nearby fields. Four young chickens and two cows were reported to have died. Given the limited exposure details in these serious American incidents, as well as the low number of reported incidents, no mitigation measures are recommended as a result of these reports.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

Fomesafen enters the terrestrial environment when used as a herbicide on a variety of crops. Fomesafen does not readily hydrolyse under typical environmental pH conditions. Fomesafen slowly phototransforms on soil surfaces (half-life approximately 40 days) and in aqueous solutions (half-life of 30 to 289 days), and photolysis is not expected to be an important route of dissipation in the environment. No major transformation products were detected that could be attributed exclusively to hydrolysis or phototransformation processes.

Based on laboratory studies, fomesafen is slightly persistent to persistent in soil, depending on soil type, under aerobic conditions (DT_{50} of 3 to 99 weeks). Dissipation is more rapid under anaerobic conditions where it is considered to be slightly persistent (DT_{50} of less than 3 weeks) in flooded soils. Dissipation of fomesafen in soils was also studied under aerobic flooded conditions. This information indicated that, in general, degradation of fomesafen in soil is more rapid under flooded conditions (DT_{50}, 8.7 to 19.9 weeks). It should be noted, however, that, generally, unextractable residues increased over time (approximately 30% to 60%). The bioavailability of these residues is unknown, but they could contribute to the carryover of the pesticide to the following season. No major transformation products were detected in soil under aerobic conditions, whereas Compound XV (5-(2-chloro-α-α-α-trifluoro-p-tolyloxy)-N-methylsulphonyl-anthranilamide) was the major transformation product in soil under anaerobic conditions. Compound XV peaked at 23 weeks into the study and had dissipated to less than 10% by 52 weeks. Limited data from one study were available to address aquatic biotransformation in natural water/sediment systems. Fomesafen dissipated from the whole system with an estimated DT_{50} of 5 to 10 days. However, it was not clear in the study report if the test systems were maintained as aerobic or anaerobic. In addition, only a small number samples were taken and unextractable residues from the sediment increased over time. Based on this, these study results and the dissipation half-life were considered as supplemental information only. Biotransformation is, however, an important route of transformation for fomesafen.

In general, fomesafen was found to be slightly to moderately persistent in soil under field conditions (DT_{50} <1 to >4 months) at recommended pre-emergent and post-emergent application rates. In most cases and for most soil types, minimal or no amounts of fomesafen leached below the 15 cm depth. The rate of dissipation in some cases appeared to be rapid at first (within the first few weeks), but then decreased over the next several months. Transformation products were not measured; therefore, it is unknown what transformation products, and levels, may occur under field conditions. Results indicate that, depending on soil type, residues of fomesafen could be carried over to the next growing season. Aquatic field study data were not available.

Laboratory data from adsorption/desorption, soil column-leaching and soil thin-layer chromatography studies indicated that fomesafen is moderately mobile to very highly mobile and has a potential to leach in soils, especially in coarse-textured (sandy) soils. However, field data indicated limited mobility beyond the top soil layers. This could be explained, in part, by the fact that in field studies, dissipation occurs through various processes which would reduce the amount of residues available to leach through soil. All the criteria of Cohen et al. were met;

based on the Groundwater Ubiquity Score (GUS) of Gustafson, fomesafen would be considered to be a pesticide with the potential to leach to groundwater. No groundwater monitoring data were available to determine levels in groundwater, but water modelling results predicted that fomesafen may be found in groundwater. Therefore, based on a weight of evidence, there is a potential for fomesafen to leach to groundwater. In addition, fomesafen has low potential for volatilization from water and moist soil surfaces.

The log K_{ow} for fomesafen at pH 7 is -1.4, which indicates fomesafen has low potential for bioaccumulation in biota. Studies reported bioconcentration factors from 0.7 to 2.8 in whole fish tissue. After a 14-day depuration period, residues in fish decreased to background concentrations. This information indicates that fomesafen has a low potential to bioaccumulate in biota.

Summaries of fate data for fomesafen in the terrestrial and aquatic environments are presented in Appendix VI, Tables 1 and 2.

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. 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).

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 RQ is below the LOC, 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 LOC, 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

A summary of terrestrial toxicity endpoints and the associated screening level risk assessment can be found in Appendix VI, Tables 3 and 4. For the environmental risk assessment, the toxicity endpoints from the most sensitive species within each taxonomic group were used as representative values for a wide range of organisms that can be potentially exposed to fomesafen through label use. At the screening level, the proposed maximum application rate of 240 g a.i./L (applied once per season) was used to determine conservative EECs to each taxonomic group.

Terrestrial invertebrates

The RQ for earthworms resulting from chronic exposure to fomesafen in soil was < 1 and, therefore, did not exceed the LOC at the screening level.

Bees

Pollinators, as represented by honey bees in the following risk assessment, can be exposed to the active ingredient via both the contact and oral route.

Risk from contact exposure

During spray application of the proposed foliar end-use products; adult forager bees may be exposed to spray droplets during flight. Acute contact exposure to fomesafen did not result in mortality in honey bees at rates tested in the laboratory. Based on the lowest contact LD_{50} value of > 100 µg a.i./bee and an exposure estimate of 0.576 µg a.i./bee, the RQ value of 0.006 does not exceed the level of concern for adult bees.

Risk from oral exposure

Fomesafen may be found on pollen and nectar as spray droplets are deposited onto open flowers during application. Acute oral exposure to fomesafen did not result in mortality in honey bees at rates tested in the laboratory. Based on the lowest oral LD_{50} value of (>) 50 µg a.i./bee and an exposure estimate of 6.96 µg a.i./bee, the RQ value of 0.14 does not exceed the level of concern for adult bees.

As the risks were found to be acceptable as a result of the Tier I risk assessment, higher tier (Tier II semi-field, and Tier III field studies) studies were not required.

Beneficial arthropods

Limited information, from a review conducted by the USEPA, was available to address the effects of fomesafen on non-target arthropods. Eight species of terrestrial invertebrates (from orders Acarina, Hemiptera, Diptera, Lepidoptera, Coleoptera, Nemotoda) were exposed to 250 to 500 ppm fomesafen at various life-stages. Details were not provided and it is unknown if the tests were conducted for dietary exposure, or if the exposure concentrations are representative of typical application rates. Results indicated limited toxicity and that the greatest level of mortality occurred with aphids, which was 9%. As toxicity to other arthropod species, such as bees and

aquatic invertebrates, was low when exposed to fomesafen, it is reasonable to assume that toxicity would be low towards other non-target arthropods, and that the risks are expected to be acceptable.

Terrestrial vascular plants

Using the most sensitive endpoint for vegetative vigour (0.0022 kg a.i./ha, or 2.2 g a.i./ha) and seedling emergence (0.0056 kg a.i./ha, or 5.6 g a.i./ha), and a maximum application rate of 240 g a.i./ha, the RQs were determined to be 109 and 43, respectively. Therefore, risks to terrestrial plants based on the screening level scenario were not shown to be acceptable.

A refinement to the risk assessment was conducted by calculating an EEC based on the spray drift deposition (ASAE medium spray quality) for ground applications (i.e., 6% of the applied rate) at 1 metre downwind from the site of application. Using the same endpoints as for the screening level, the RQs for seedling emergence and vegetative vigour based on this EEC are 6.5 and 2.6, respectively, and exceed the LOC. To mitigate the potential exposure of fomesafen to non-target plants, spray buffer zones are required to protect sensitive terrestrial habitats from spray drift.

The screening level and refined risk assessments for non-target terrestrial plants are summarised in Appendix VI, Table 4.

Terrestrial Vertebrates

Birds and mammals may be exposed to fomesafen through the ingestion of food items that have received spray from the product through direct application or from spray drift. The level of risk is assessed by considering the estimated daily exposure (EDE), which takes into account the estimated amount of chemical on various food items immediately after the last application in conjunction with the food ingested per day, or the food ingestion rate (FIR), by different sized birds and mammals (small, medium, and large size classes).

The screening level risk assessment is based on simple methods, conservative exposure scenarios, and the most sensitive toxicity endpoints. For this assessment, EDEs are based on EECs that were calculated with the upper bound of the maximum residue concentrations on various food items, based on a nomogram developed by the USEPA. At the screening level, only one feeding guild for each category of bird and mammal weights is selected. The selected feeding guilds are relevant to each specific size of bird or mammal and based on the most conservative residue values.

For the bird and mammal screening level assessments, the most sensitive endpoints from acute and reproductive toxicity studies were used. In the case of birds, the endpoint used was the highest concentration tested, and no effects were observed. Therefore, this is conservative. The LOC was not exceeded for acute effects; however, the LOC was exceeded for all sizes of birds and medium-sized mammals for reproductive effects.

Given the conservative assumptions made in the screening level assessment, an expanded assessment was conducted to further characterize the reproductive risk to birds and mammals for those size classes where the RQs exceeded the LOC. In addition to considering upper bound maximum residue values as were used in the screening level risk assessment, the expanded assessment considers the mean residue values for calculating EECs and EDEs for all food guilds at the maximum single application rate. The risk associated with the consumption of food items contaminated from spray drift immediately adjacent to the treated field (off-field) is also assessed taking into consideration the spray drift deposition (ASAE medium spray quality) for ground applications (i.e., 6% of the applied application rate) at 1 metre downwind from the site of application.

The results of the expanded risk assessment for reproductive effects on birds and wild mammals are presented in Appendix I, Tables 5 and 6, respectively. RQs for all off-field exposures were below the LOC for maximum and mean residue values.

When considering on-field exposure for birds, RQs exceeded the LOC for maximum residues for insectivores (all sizes), frugivores (small and medium birds), and herbivores (large sized birds). All RQs for exposure to birds on-field were < 5. When considering mean residues or birds, RQs exceeded the LOC only for small and medium insectivorous birds for on-field sites.

Several conservative assumptions are made in this risk assessment, such as: animals are being exposed to residues on food items at levels equivalent to those present immediately after application, that these levels remain constant over time, and that animals would feed exclusively on a single food item (for example, small insects) from within the treated area. In cases where RQs exceed the LOC, an additional analysis can be conducted to determine the amount of contaminated food, expressed as a percentage of the daily diet that, if consumed, would reach the LOC (calculated as 1/RQ×100). For insectivore birds, 20% of the diet of small-sized animals, 26% for medium-sized animals, and 91% for large-sized animals, would need to be consumed as contaminated food at the maximum residue levels to reach the LOC; for mean residue levels 30% of the diet for small-sized birds and 38% for medium-sized birds would need to be consumed to reach the LOC. For frugivore birds, 67% of the diet of small-sized animals and 83% for medium-sized animals would need to be consumed as contaminated food items at the maximum residue levels to reach the LOC. For large-sized herbivore birds, 40–67% of their diet as contaminated food items at the maximum residue levels would need to be consumed to reach the LOC. Birds would be expected to forage over a large range where exposure to contaminated food exclusively is not likely and the probability of consuming enough contaminated food to reach the LOCs would be low. In addition, the reproductive endpoint (NOEC) used in the risk assessment is based on an absence of effect, and was the highest concentration tested in the study. This also adds to the conservative nature of the assessment.

For mammals, the only RQs that exceed the LOC are for medium-sized herbivores exposed on-field, and these RQs were < 2. In the case of herbivorous wild mammals where the LOC was exceeded, 58–94% of their diet, using maximum residues, would need to be consumed from contaminated food sources on-field to reach the LOC.

As with birds, mammals would also be expected to forage over a large range where exposure to contaminated food exclusively is not likely and the probability of consuming enough contaminated food to reach the LOCs would be low.

In conclusion, the off-field risk to birds and mammals through the use of fomesafen is expected to be minimal, as all RQs were below the LOC for acute toxicity and reproductive effects. Acute effects on-field are also not of concern. Considering the conservatisms and assumptions for the on-field assessment for both birds and mammals (i.e., low RQ values, reproductive endpoint is based on a no-effect level and was the highest concentration tested, birds and mammals will forage over a larger range and they are unlikely to consume all of their diet from a treated field), risks are expected to be acceptable for birds and small mammals.

4.2.2 Risks to Aquatic Organisms

Acute laboratory toxicity studies indicated that fomesafen is practically non-toxic to slightly toxic to fish and aquatic invertebrates (marine and freshwater). Data indicate that fomesafen can have toxic effects on aquatic plants including green algae. This is expected as the intended use of fomesafen is as an herbicide. Blue-green algae, however, are less sensitive than green algae. Results of a mesocosm study (summary provided by USEPA, PMRA# 2821594) indicated that short-term effects on phytoplankton abundance and production were not anticipated for concentrations of fomesafen in water < 0.06 mg/L. Effects of fomesafen on aquatic organisms are summarized in Appendix VI, Table 7.

The initial conservative screening level EEC calculations for aquatic systems were based on a direct application to waterbodies with depths of 15 and 80 cm following the maximum single application at 240 g a.i./ha. The 15 cm depth was chosen to represent a seasonal body of water that could be inhabited by amphibians. The 80 cm depth was chosen to represent a typical permanent water body for applications of pest control products in agriculture (for freshwater and marine habitats). Data for the most sensitive fish species is used as a surrogate to conduct a risk assessment for aquatic stages of amphibians.

Appendix VI, Table 8 summarizes the screening level risk assessment of fomesafen for aquatic organisms. The LOC was not exceeded for any freshwater or estuarine/marine taxa at the highest application rate. Therefore, no further refinement to the aquatic risk assessment is necessary and risks to aquatic organisms are expected to be acceptable. An aquatic mesocosm study indicated that short term effects on abundance and growth of algae is not anticipated for water concentrations < 0.06 mg/L. The EEC for water is below this concentration; thus, this further supports that risks to the aquatic environment are expected to be acceptable. In addition, the highest concentration of fomesafen reported in available surface water monitoring data was 0.8737 µg/L, which is considerably lower that the EEC determined for the screening level risk assessment (see Appendix VII for more information). Precautionary label statements will however, be required due to the inherent toxicity (<1 mg/L) of fomesafen to green algae and aquatic vascular plants.

4.2.3 Environmental Incident Reports

As of 17 January 2018, no Canadian environmental incidents involving fomesafen had been submitted to the PMRA.

The United States Ecological Incident Information System (EIIS) was also searched for environmental incidents involving fomesafen. There were 78 incidents in the EIIS database. Plant damage or mortality was reported in 76 incidents. The causalities of all of these incidents were considered to be possible, probable, or highly probable in relation to the use of fomesafen. In most cases, the organisms affected were agricultural crops, and the plants were directly treated with a pesticide containing fomesafen sodium using a broadcast application. In some cases the crop damage was due to spray drift, carryover or accidental misuse. In one case, the reported damage was to an unknown species of tree that had been affected by drift. Based on the current review, these incident reports do not impact the environmental risk assessment.

One incident involving mortality of freshwater fish as a result of runoff from a treated site had a certainty index of unlikely. One other incident was reported where bee hives were exposed through an aerial application, causing bees to be lethargic and vacate the hives. No mortality was recorded. The certainty index was considered possible. Therefore, these incidents also did not impact the environmental risk assessment and outcomes.

5.0 Value Assessment

Fomesafen contributes to weed management in a range of agricultural crops. It is registered for use on certain pulse crops (dry and succulent beans and peas), soybean, cucumber, strawberry, and potato. It provides post-emergence control of a wide spectrum of broadleaf weeds with residual activity. The use of fomesafen is restricted to Eastern Canada, Red River Valley of Manitoba, or British Columbia. Nevertheless, these areas are typically the major production regions for the registered crops.

Fomesafen is one of the main herbicides used for weed control in pulse crops. It is the primary and most widely used herbicide for snap beans for which there are limited alternative herbicides. It is the only alternative to bentazon for post-emergence in-crop use to control broadleaf weeds in dry and snap beans, which has been identified as one of the key issues facing Canadian pulse crop growers. It also provides a control option for volunteer broadleaf crops (crops not deliberately planted) such as canola, which is another issue facing Canadian pulse crop growers.

Fomesafen helps manage weed (population and species) shifts occurring in soybeans and is one of the few residual herbicides registered for use in soybeans. When co-formulated with glyphosate, fomesafen provides residual control of broadleaf weeds to address the weed shifts occurring in soybean.

Fomesafen use on cucumber and potatoes is an important component of an overall weed control program in these crops.

Fomesafen is a tool to manage resistant weeds in soybeans. Acetolactate synthase (ALS) inhibitors used to be the main herbicides used in soybean but at least eight species of weeds (for example, green foxtail, pigweed, ragweed and nightshade) resistant to this group of herbicides have been reported. These resistant weeds are increasingly becoming a challenge to the agricultural production system. Fomesafen provides an alternative mode of action to ALS inhibitor and glyphosate herbicides to mitigate the risk of herbicide resistance development and combat the resistant weed populations.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[3] the assessment of fomesafen against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

Fomesafen does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix VI, Table 9)

Fomesafen does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[4] The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[6] 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 fomesafen and its associated end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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3 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

4 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

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

6 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

7.0 Conclusion of Science Evaluation

7.1 Human Health

With respect to human health, the risks were found to be acceptable for the supported uses of fomesafen when used according to the proposed label updates.

7.2 Environment

Fomesafen is non-volatile and is not expected to be subject to long-range transport. It is slightly persistent to persistent in the terrestrial environment, and breaks down primarly through biotic processes. Depending on soil type, fomesafen can be expected to carryover in soil to the next season. Persistence in water is not well defined but is likely slightly less persistant than in the terrestrial environment, and transformation is expected to be primarily through biotic means. Although fomesafen has properties associated with chemicals that may leach to groundwater, field studies indicate that fomesafen is unlikely to move below 15 cm depth in soil. Precautionary label statements are required to avoid application where soils are permeable (for example, coarse or sandy soils), particularly where the water table is shallow to reduce the potential for groundwater contamination.

Based on the current use pattern, fomesafen may pose a risk to non-target terrestrial vascular plants, however, risks to other non-target terrestrial organisms or to aquatic organisms are not expected from fomesafen, nor is it expected to bioaccumulate in the tissues of aquatic organisms. Spray buffer zones will be required on the label to mitigate risks to non-target terrestrial plants.

7.3 Value

Fomesafen contributes to weed management in a range of agricultural crops. It provides post-emergence control of a wide spectrum of broadleaf weeds with residue activity in certain pulse crops (dry, snap and lima beans), soybeans, cucumber and potatoes. It is the primary and most widely used herbicide on snap beans for which there are limited alternative herbicides. It is the only alternative to bentazon for post-emergence in-crop use to control broadleaf weeds in dry and snap beans which has been identified as one of key issues facing Canadian pulse crop growers. It is a tool to manage resistant weeds in soybeans by providing an alternative mode of action to ALS inhibitors and glyphosate herbicides, to which a number of resistant weed biotypes have been reported.

List of Abbreviations

♂	male
♀	female
↑	increase
↓	decrease
AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ALS	acetolactate synthase
ALT	alanine aminotransferase
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
ASAE	American Society of Agricultural Engineers
AST	aspartate aminotransferase
ATPD	area treated per day
BUN	blood urea nitrogen
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CN	cyanide ion
CoA	Coenzyme A
conc.	concentration
d	day(s)
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
EIIS	Ecological Incident Information System
ER	endoplasmic reticulum
F_0	original parent generation
F_1	first generation
fc	food consumption
FCID™	Food Commodity Intake Database™
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
GI	gastro-intestinal
GUS	Groundwater Ubiquity Score

h	hour(s)
ha	hectare
hct	hematocrit
hgb	hemoglobin
IgM	immunoglobulin M
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	octanol water partition coefficient
K_{oc}	adsorption quotient normalized to organic carbon
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOEC	lowest-observed-effect-concentration
M/L/A	mixer, loader and applicator
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)
MIS	maximum irritation score
MOA	mode of action
MOE	margin of exposure
MRL	Maximum Residue Limit
NCHS	National Center for Health Statistics
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
PCP	Pest Control Product
PCPA	*Pest Control Products Act*
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPARα	peroxisome proliferator-activated receptor alpha
ppb	parts per billion
ppm	parts per million
PWC	Pesticides in Water Calculator
REI	restricted-entry interval
rel.	relative
RQ	risk quotient
TC	transfer coefficient
TSMP	Toxic Substances Management Policy
µg	micrograms
µL	micro litre
USEPA	United States Environmental Protection Agency
URMULE	User Requested Minor Use Label Expansion
wk	week(s)
wt	weight

Appendix I

Table 1 Fomesafen Products Registered in Canada as of 16 February 2018 Excluding Discontinued Products or Products with a Submission for Discontinuation Based on the PMRA's Electronic Pesticide Regulatory System (e-PRS) database

Registration Number	Marketing Class	Registrant	Product Name	Guarantee	Formulation
28133	Technical	Syngenta Canada Inc.	Fomesafen Technical Active Ingredient Herbicide	98%	Solid
28828	Technical	Syngenta Canada Inc.	Fomesafen Technical Grade Herbicide	99.8%	Solid
28134	Manufacturing Concentrate	Syngenta Canada Inc.	Fomesafen Sodium Salt Aqueous Concentrate Herbicide	48%	Solution
28827	Manufacturing Concentrate	Syngenta Canada Inc.	Fomesafen Technical Grade Manufacturing Use Product Herbicide	49.7%	Solution
24779	Commercial	Syngenta Canada Inc.	Reflex Liquid Herbicide	240 g/L	Solution
29644	Commercial	Syngenta Canada Inc.	Flexstar Herbicide	79 g/L fomesafen; 315 g/L glyphosate	Solution
30412	Commercial	Syngenta Canada Inc.	Flexstar GT Herbicide	67 g/L fomesafen; 271 g/L glyphosate	Solution

Table 2 Registered Commercial Class uses of fomesafen in Canada as of 21 February 2017. Uses from discontinued products or products with a submission for discontinuation are excluded[1]

Use-Site Category	Sites[2]		Weeds[3]	Application Method and Equipment	Maximum Application Rate (g a.i./ha)[4]		Maximum Number of Applications Per Year
					Single	Cumulative Per Year	
Industrial oil seed crops and fibre crops Terrestrial feed crops Terrestrial food crops	Soybean including glyphosate -tolerant	Eastern Canada only	A	Ground	240	240	Once per year
		Red River Valley of Manitoba only	B		140.7	140.7	Once every second year to a field

Use-Site Category	Sites[2]		Weeds[3]	Application Method and Equipment	Maximum Application Rate (g a.i./ha)[4]		Maximum Number of Applications Per Year
					Single	Cumulative Per Year	
Terrestrial food crops	Dry edible beans	Eastern Canada only	B		240	240	
		Red River Valley of Manitoba only			139.2	139.2	
		Ontario only - Otebo beans	B		240	240	
Terrestrial food crops	Snap common beans (yellow and green)	Eastern Canada only	B		240	240	
Terrestrial food crops	Lima beans	Eastern Canada only	B		240	240	
Terrestrial food crops	Cucumber	Eastern Canada and British Columbia only	B		240	240	
Terrestrial food crops	Potatoes	Eastern Canada only	B		240	240	

1. Formulation types: Solution for all products.
2. Sites are as either stated on the label or interpreted by the PMRA so as to achieve consistency in naming.
3. The weed list includes:

   A = alone use - Redroot pigweed, common ragweed, wild mustard, velvetleaf (suppression only), lady's-thumb, lamb's-quarters (suppression only), eastern black nightshade, cocklebur, volunteer canola, tall waterhemp (minor use)

   Co-formulated with glyphosate - alfalfa, barnyard grass, blue grass (Canada), blue grass (Kentucky), bluegrass (annual), bromegrass (smooth), cattail (common), chickweed, common, chickweed, mouse-eared, cleavers, clover, white, cocklebur, colt's-foot, corn spurry, cottontop, cow cockle, crabgrass (large, smooth), curled dock, dandelion (common), dodder, downy brome, fall panicum, field bindweed, fleabane (Canada), flixweed, foxtail barley, giant foxtail, goldenrod (Canada), green foxtail, green smartweed, hairy galinsoga, hemp dogbane, hemp nettle, hoary cress, horsetail, Jerusalem artichoke, knotweed (Japanese), kochia, lady's-thumb, lamb's-quarters, low cudweed, milkweed (common), narrow-leaved hawk's-beard, narrow-leaved vetch, night-flowering catchfly, nightshade, eastern black, non-glyphosate tolerant volunteer canola, orchard grass, Pennsylvania smartweed, Persian darnel, plantain, broad-leaved, poison ivy, prickly lettuce, proso millet, prostrate knotweed, purple loosestrife, quack grass, ragweed (common), redroot pigweed, redtop, round-leaved mallow, Russian thistle, rye, tame, sheep sorrel, shepherd's-purse, smooth bedstraw, smooth pigweed, sowthistle (annual), sow-thistle (perennial), stinkweed, stitchwort, grass-leaved, stork's-bill, thistle (Canada), velvetleaf, volunteer barley, volunteer corn, volunteer flax, volunteer wheat, wild buckwheat, wild carrot, wild grape, wild mustard, wild oats, wild tomato, wirestem muhly, wormwood (absinth), yellow foxtail, yellow nutsedge, yellow toadflax.

   B = Redroot pigweed, common ragweed, wild mustard, velvetleaf (suppression only), lady's-thumb, lamb's-quarters (suppression only), eastern black nightshade, cocklebur, volunteer canola

4. Rates of active ingredient (a.i.) were calculated by the PMRA.

Appendix II Toxicological Information for Health Risk Assessment

Table 1 Toxicity Profile of Technical Fomesafen

(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 #	Study Results
Toxicokinetic Studies	
Absorption, Distribution, Metabolism and Excretion Wistar rats; CD-1 mice; Beagle dogs; Marmosets PMRA# 1258744 –1258748; 1258752 (rats); 1258754 (mice); 1258753 (dogs); 1258756 (marmosets) **Absorption:** Rats: Plasma conc. not measured. Dogs: Rapid, peak plasma conc. at 3 h from a single oral dose (5 mg/kg bw); Marmosets: Peak plasma conc. at 4 h from a single oral dose (50 mg/kg bw)	**Distribution:** Rats: With a single low dose of 5 mg/kg bw, residues are > in ♂s than in ♀s: 10–19% (♂), 0.3–0.6% (♀) at 7 days; 25–28% (♂), < 1% (♀) at 72 h. With a single high dose of 500 mg/kg bw, the difference is less: 1.5% (♂), 0.6% (♀) at 7 days. Highest tissue residues occurred in the liver. In low dose ♂s: liver (7.1%) > GI tract (1.68%) > carcass (1.4%) > kidneys (0.17%) Dogs: Tissue residue levels are low following a single oral dose (5 mg/kg bw) with adipose (0.12–0.15%) and liver (0.2–0.4%) having the highest residue levels; Mice: Highest tissue levels in liver following a single oral dose (5 mg/kg bw): 30%/20% (♂/♀) at 7 days; 41–51%/19–35% (♂/♀) at 72 h **Metabolism:** Rats: Majority of residues in the urine, feces, and liver were unchanged fomesafen after a single oral dose (5 mg/kg bw); in the urine unchanged fomesafen accounted for 60% (♂) and 90% (♀) of recovered radioactivity; other metabolites were minor with no single metabolite more than 5% of the AD. Dogs: Predominate radioactivity in urine and bile was unchanged fomesafen; Mice: Predominate radioactivity in urine and bile was unchanged fomesafen, > 90% of recovered activity; Marmosets: Majority of residues in the urine were unchanged fomesafen (>80%); other metabolites were less than 5% of the AD. **Excretion:** Rats: With a single low dose of 5 mg/kg bw, there is a sex difference in the ratio of radioactivity in urine and feces: in ♂s urinary/fecal is 34%/55%; in ♀s urinary/fecal is 75%/23% at 7 days. Biliary excretion predominates in ♂s, while urinary excretion predominates in ♀s. With a single high dose of 500 mg/kg bw, excretion in both sexes is similar (74–79% urinary, 21–23% fecal at 7 days post-dosing). In females the decline in radioactivity in the liver and kidney was biexponential, initially rapid, followed by a slower terminal portion; male tissue residue declines were exponential. Dogs: 46–82% in urine, 12–46% in feces; Mice: 4–7% in urine, 42–59% in feces; Marmosets: 30–75% in urine, 8–25% in feces. Little sex difference in excretion pattern.

Study Type/Animal/PMRA #	Study Results
Acute Toxicity Studies: Fomesafen acid	
Oral toxicity Wistar-derived Alderley Park Rat PMRA# 1249210	**LD_{50} = 1250-2000 mg/kg bw (♂); 1595 mg/kg bw (♀)** **Clinical Signs:** included subdued behaviour, dehydration, upward curvature of the spine, piloerection, urinary and fecal incontinence and ungroomed appearance. **Slightly toxic**
Dermal toxicity New Zealand White Rabbit PMRA# 1249211	**LD_{50} >1000 mg/kg bw (♂/♀)** no adverse systemic effects were observed **Slightly toxic**
Primary Eye Irritation New Zealand White Rabbit PMRA# 1249210	MAS (24, 48, 72 h) = 9; MIS (1h) = 16 **Mildly irritating**
Primary Skin Irritation New Zealand White Rabbit PMRA# 1249210	MIS (0 h) = 0.67; MIS (48 h) = 0.33 **Slightly irritating**
Dermal sensitization (Magnusson and Kligman Maximization test) Dunkin-Hartley Guinea Pig PMRA# 1249212	**Sensitizer**
Acute Toxicity Studies: Fomesafen Sodium Salt (48%)	
Oral toxicity (Up and down procedure) Sprague-Dawley Rat PMRA# 2413803	**LD_{50} = 2000 mg/kg bw (♀)** **Clinical Signs:** hypoactivity, piloerection, anogenital staining, reduced fecal volume, hunched posture **Slightly toxic**

Study Type/Animal/PMRA #	Study Results
Dermal toxicity Sprague-Dawley Rat PMRA# 2324789	**LD_{50} > 2000 mg/kg bw (♂/♀)** Slight dermal irritation (erythema and edema) noted at the dose site of all ♀s between days 1 and 3 **Low toxicity**
Inhalation toxicity (nose only) Wistar Rat PMRA# 2324791	**LC_{50} > 2.28 mg/L** No deaths and no significant adverse effects **Low toxicity**
Primary Eye Irritation New Zealand White Rabbit PMRA# 2324794	MAS (24, 48, 72 h) = 39; MIS at 24 and 48h = 41. Group mean score at 7 days = 24 **Severely irritating**
Primary Skin Irritation New Zealand White Rabbit PMRA# 2324795	MAS (24, 48, 72 h) = 2; MIS (1h) = 4 **Moderately irritating**
Dermal sensitization (Local lymph node assay) CBA/Ca/Ola/Hsd Mouse PMRA# 2324797	**Non-sensitizer**
Short-Term Toxicity Studies	
21-day dermal toxicity New Zealand White Rabbit PMRA# 1258626	**Systemic NOAEL = 1000 mg/kg bw/day** There were no treatment-related systemic adverse effects. Dose-dependent slight to moderate skin irritation was noted in treated areas.
2-week oral (gavage) toxicity Marmoset PMRA# 1258627	**50 mg/kg bw/day:** slight hepatotoxicity (↑ severity of focal inflammation (♂/♀); slight ↑ peroxisomes, slight ↑ in degree of swelling of smooth and rough endoplasmic reticulum (♂); slight ↓ CN-insensitive palmitoyl-CoA oxidation enzyme (♀) **Supplementary – single dose level tested**

Study Type/Animal/PMRA #	Study Results
4-week oral (dietary) toxicity Wistar-derived Alderley Park Rat PMRA# 1199936; 1258631	**50 mg/kg bw/day:** at 4 wks: ↓ cholesterol, ↓ triglycerides, ↓ free fatty acids, ↓ aminopyrine demethylase, moderate hepatocyte hyalinization, ↑ liver wt. After 1 wk of recovery (control diet) these effects resolved) with the exception of the ↑ liver wt which remained higher than controls. Affected livers showed ↓ density of smooth ER, ↑ size and number of peroxisomes, but no evidence of degenerative change. **Supplementary – single dose level tested**
13-week oral (dietary) toxicity Wistar Rat PMRA# 1249214; 1249222	**NOAEL = 0.25 mg/kg bw/day (♂)** **LOAEL = 5.0 mg/kg bw/day (♂):** ↑ liver wt, hepatocyte hyalinization, ↑ peroxisomes in liver, ↓ cholesterol, ↓ triglycerides (♂) **NOAEL ≥ 50.0 mg/kg bw/day (♀)** **LOAEL > 50.0 mg/kg bw/day (♀)**
26-week oral (capsule) toxicity Beagle Dog PMRA# 1258630	**NOAEL = 1.0 mg/kg bw/day** **LOAEL = 25 mg/kg bw/day:** slightly ↓ hgb, slightly ↓ hct, ↓ cholesterol, ↓ triglycerides, slightly ↑ urinary protein, ↑ liver wt, ↑ kidney wt, ↑ cytoplasmic eosinophilia of centrilobular hepatocytes, ↓ cytoplasmic eosinophilia of periportal hepatocytes, ↑ number of peroxisomes in the hepatocytes (♂/♀); ↓ ALP, ↑ BUN (♂); slight ↓ ovary wt (♀)
Chronic Toxicity/Oncogenicity Studies	
24-month oral (dietary) chronic toxicity/carcinogenicity Wistar-derived, Alderley Park Rat PMRA# 1258312; 1258313	**NOAEL = 5.0 mg/kg bw/day** **LOAEL = 50 mg/kg bw/day:** ↓ cholesterol, ↓ triglycerides, ↑ albumin, ↑ liver wt, ↑ hepatocyte hyalinization, ↑ peroxisomes in liver (♂/♀); ↓ bwg, ↑ ALP, ↑ ALT, ↑ AST, ↑ cystic degeneration of hepatocytes, ↑ lipofuscin content and proteinaceous deposits in liver, ↑ Kupffer cells and macrophages infiltration in liver, ↑ focal necrosis in liver, ↑ fatty degeneration in adrenals, ↑ cystic degeneration in lymph nodes (♂); ↑ dilatation and calcification of the pelvic epithelium of the kidney (♀) **No evidence of oncogenicity**
24-month oral (dietary) carcinogenicity CD-1 Mouse PMRA# 1258327; 1258328; 1258737; 1258897	**NOAEL = 1.0 mg/kg bw/day** **LOAEL = 10 mg/kg bw/day:** ↑ ALP*, ↑ ALT*, liver enlargement, ↑ liver wt, discolouration of liver with irregular surfaces and/or masses, enlarged hepatocytes with hyalinization, pigmented Kupffer cells and macrophages in liver (♂/♀); ↑ incidence of combined adenomas and carcinomas in the liver (♀)[Incidence: ♂(adenomas) = 13/128, 19/63, 6/64, 14/64, 14/64; ♂(carcinomas) = 17/128, 7/63, 11/64, 13/64, 28/64; ♀(adenomas) = 3/128, 1/64, 1/64, 8/63, 11/64; ♀(carcinomas) = 0/128, 1/64, 2/64, 2/64, 17/64 at 0, 0.1, 1.0, 10, 115 mg/kg bw/day] *measured at 52 wks only *peroxisome proliferation not measured in this study. **Evidence of oncogenicity**

Study Type/Animal/PMRA #	Study Results
Genotoxicity Studies	
In vivo chromosome aberration Rat bone marrow PMRA# 1199901; 1258636	**Positive** No effect was noted after 6 h with either multiple or single dosing. However, after 24 h there were significant increases in chromosomal abnormalities, including gaps, breaks, and fragments at the two high doses (125 and 250 mg/kg bw). These positive findings may be related to the relatively high, toxic levels of fomesafen with systemic toxicity being realized at 24 h but not at 6 hrs post-dose; however, no independent measure of systemic toxicity was made.
In vivo chromosome aberration Rat bone marrow PMRA# 1258322	**Negative** At 250 mg/kg bw, there was a slight ↑ (<twofold) in chromosome/chromatid gaps and a slightly ↓ mitotic index (no effects at 125 mg/kg bw). Cyclophosphamide caused a significant ↑ (10-fold) in chromosome/chromatid gaps and a threefold ↑ in mitotic index. **Thus, fomasafen was not considered clastogenic.** The abnormal chromosome effects noted in the study directly above could not be repeated in the present study suggesting the effects may have been due to systemic toxicity.
In vitro unscheduled DNA synthesis HeLa cells PMRA# 1222978; 1258898	**Negative**
In vitro chromosome aberration Human lymphocytes PMRA# 1258899	**Negative**
Dominant lethal (gavage) CD-1 Mouse PMRA# 1199900; 1258634	**Negative**

Study Type/Animal/PMRA #	Study Results
Ames reverse mutation Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538 PMRA# 1199899; 1258633	**Negative**
Mammalian cell transformation Syrian Hamster kidney fibroblasts PMRA# 1199899; 1258633	**Negative**
Reproductive/Developmental Toxicity Studies	
2-generation oral (dietary) reproductive toxicity Wistar Rat PMRA# 1258315; 1258324	**Parental NOAEL = 13 mg/kg bw/day** **Parental (F_0) LOAEL = 50 mg/kg bw/day:** diffuse hyalinization of the hepatocytes, ↑ biliary hyperplasia (♂/♀); pigmented Kupffer cells, focal necrosis in liver, slight ↓ bw/bwg (♂); slight ↓ bwg during pregnancy (♀) **Parental (F_1) LOAEL = 50 mg/kg bw/day:** diffuse and centrilobular hyalinization of the hepatocytes (♂/♀); slight ↑ basophil vacuolation of the pituitary (♂); ↑ incidence colloid cysts within pars distalis of the pituitary, slight ↓ bwg during pregnancy (♀) **Offspring NOAEL = 13 mg/kg bw/day** **Offspring LOAEL = 50 mg/kg bw/day:** slight ↓ pup bw/bwg (♂/♀); slight ↑ hepatocyte hyalinization and renal pelvic dilatation (♂). **Reproductive NOAEL ≥ 50 mg/kg bw/day** No adverse effects noted **No evidence of sensitivity of the young**
Developmental toxicity (gavage) Wistar Rat PMRA# 1258319	**Maternal NOAEL = 100 mg/kg bw/day** **Maternal LOAEL = 200 mg/kg bw/day:** ↓ bwg, ↓ fc, ↑ staining of genital/ventral fur, ↑ post-implantation loss (early and late resorptions), ↓ mean gravid uterine wt, ↓ litter wt. **Developmental NOAEL = 100 mg/kg bw/day** **Developmental LOAEL = 200 mg/kg bw/day:** ↑ post-implantation loss (early and late resorptions), ↓ litter wt. **No evidence of malformations** **No evidence of sensitivity of the young**

Study Type/Animal/PMRA #	Study Results
Developmental toxicity (gavage) Wistar Rat PMRA# 1258320	**Maternal/Developmental NOAEL ≥ 50 mg/kg bw/day (HDT)** **Maternal/Developmental LOAEL > 50 mg/kg bw/day** No adverse effects noted **No evidence of malformations** **No evidence of sensitivity of the young**
Developmental toxicity (capsule) Dutch Rabbit PMRA# 1258318	**Maternal NOAEL = 10 mg/kg bw/day** **Maternal LOAEL = 40 mg/kg bw/day:** ↑ incidence of stomach mucosa erosion, clinical signs (thin, ↑ incidence of animals with mucus around the nose) **Developmental NOAEL ≥ 40 mg/kg bw/day** **Developmental LOAEL > 40 mg/kg bw/day** No adverse effects noted **No evidence of malformations** **No evidence of sensitivity of the young**
Neurotoxicity Studies	
Acute oral (gavage) neurotoxicity RccHan:WIST Rat PMRA# 2324799	**NOAEL = 100 mg/kg bw** **LOAEL = 250 mg/kg bw:** ↓ bwg, ↓ fc (♂/♀); ↓ motor activity on day 1 (♂) **800 mg/kg bw:** Hunched posture, piloerection, ↓ righting response, abnormal gait, ↓ motor activity on day 1 (♂/♀); ↓ temperature (♀) Treatment-related FOB effects were essentially limited to the high dose males and females at the 4–7 h (day 1) post-dose interval. No treatment-related signs of neuropathology were noted.
13-week oral (dietary) neurotoxicity RccHan:WIST Rat PMRA# 2324803	**NOAEL (♂) = 20 mg/kg bw/day** **LOAEL (♂) = 67 mg/kg bw/day:** ↓ bwg (♂) **NOAEL (♀) = 74 mg/kg bw/day** **LOAEL (♀) = 233 mg/kg bw/day):** enlarged liver, hepatocellular hypertrophy (♂); ↓ bwg, ↑ rel. liver wt (>25%) (♀) No evidence of selective neurotoxicity
Immunotoxicity Studies	
28-day oral (dietary) immunotoxicity CD-1 Mouse PMRA# 2413804	**NOAEL =16 mg/kg bw/day** **LOAEL = 176 mg/kg bw/day:** ↑ rel. liver wt, diffuse or centrilobular hepatocytic hypertrophy, ↓ IgM levels **791 mg/kg bw/day:** ↓ bw/bwg, ↓ spleen wt, ↓ thymus wt Evidence of slight suppression of the immune response.

Study Type/Animal/PMRA #	Study Results
Special Studies	
Interaction of fomesafen with liver macromolecules Wistar-derived, Alderley Park Rat PMRA# 1258321	Dosed with 500 mg/kg bw of ^{14}C-ring-nitrophenyl labelled fomesafen. Sacrificed 6, 12 or 24 h after dosing. **No binding of fomesafen to tissue macromolecules was demonstrated.**
Interaction of fomesafen with liver macromolecules CD-1 Mouse PMRA# 1222989; 1258902	Dosed with 500 mg/kg bw of ^{14}C-ring-nitrophenyl labelled fomesafen. Sacrificed 6, 12 or 24 h after dosing. **No binding of fomesafen to tissue macromolecules was demonstrated.** Significant ↓ in plasma triglyceride levels

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

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Rat acute neurotoxicity	NOAEL = 100 mg/kg bw based on reduced body weight gain and motor activity	100
	ARfD = 1.0 mg/kg bw		
Acute dietary females ages 13–49 years	Rat developmental toxicity	NOAEL = 100 mg/kg bw based on increased post-implantation loss	300
	ARfD = 0.3 mg/kg bw		
Repeated dietary	Co-critical studies: Dog 26-week toxicity and Mouse 2-year oncogenicity	NOAEL = 1.0 mg/kg bw/day based on liver toxicity (dog and mouse) and clinical chemistry findings (dog)	100
	ADI = 0.01 mg/kg bw/day		
Short-term dermal[2]	Rat 2-generation reproduction	NOAEL = 13 mg/kg bw/day based on liver toxicity, decreased body weight/body weight gain	100
Short-term inhalation[3]	Rat 2-generation reproduction	NOAEL = 13 mg/kg bw/day based on liver toxicity, decreased body weight/body weight gain	100
Cancer	No evidence of oncogenicity relevant to a human health risk assessment		

[1]CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments
[2]Since an oral NOAEL was selected, a dermal absorption factor (50%) was used in a route-to-route extrapolation.
[3]Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Appendix III Dietary Exposure and Risk Assessments

Table 1 Dietary Chronic Exposure and Risk Assessments

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw/day)	%ADI[1]	Exposure (mg/kg bw/day)	%ADI[1]
General Population	0.000108	1.1	0.002532	25.3
All Infants (<1 year old)	0.000167	1.7	0.009223	92.2
Children 1–2 years old	0.000305	3.1	0.003640	36.4
Children 3–5 years old	0.000251	2.5	0.002964	29.6
Children 6–12 years old	0.000152	1.5	0.002169	21.7
Youth 13–19 years old	0.000093	0.9	0.001802	18.0
Adults 20–49 years old	0.000089	0.9	0.002498	25.0
Adults 50+ years old	0.000084	0.8	0.002427	24.3
Females 13–49 years old	0.000087	0.9	0.002455	24.5

[1]Acceptable Daily Intake (ADI) of 0.01 mg/kg bw/day.

Table 2 Dietary Acute Exposure and Risk Assessments

Population Subgroup	Food only		Food and Drinking Water	
	Exposure (mg/kg bw)	%ARfD[1]	Exposure (mg/kg bw)	%ARfD[1]
General Population	N/A	N/A	N/A	N/A
All Infants (<1 year old)	0.000530	0.05	0.021876	2.19
Children 1–2 years old	0.000790	0.08	0.009610	0.96
Children 3–5 years old	0.000703	0.07	0.007459	0.75
Children 6–12 years old	0.000427	0.04	0.005848	0.58
Males 13–19 years old	0.000262	0.02	0.005078	0.51
Males 20–49 years old	0.000249	0.03	0.005990	0.60
Adults 50+ years old	0.000229	0.02	0.005493	0.55
Females 13–49 years old	0.000240	0.08	0.006387	2.13

N/A: Not applicable.
[1]Acute Reference Dose (ARfD) of 0.3 mg/kg bw for females 13–49 years old and 1.0 mg/kg bw for all other populations (including children).

Appendix IV Food Residue Chemistry Summary

The nature of the residue in livestock and plant commodities is adequately understood based on metabolism studies in lactating goats, laying hens, tomatoes, cotton, soybeans and potatoes. The residue definition in plant commodities for enforcement of MRLs is fomesafen. No change is proposed to this residue definition as a result of the re-evaluation. Since finite/detectable residues are not expected to occur in livestock based on the currently registered uses, no MRLs have been established for livestock commodities. Therefore, a residue definition in animal commodities for enforcement purposes is not required at this time.

Available enforcement analytical methods for fomesafen in plant matrices are deemed adequate. No enforcement analytical method is currently required for fomesafen in animal matrices.

The available crop field trial data are sufficient to support the current MRLs specified in Canada.

Currently, plant-back intervals are specified as 4 months for winter wheat and 10 months for spring wheat, soybeans, dry edible beans, field corn and potatoes. The established plant back intervals are required due to phytotoxicity. The Canadian label also allows plant-back of all other crops following a bioassay to determine phytotoxicity. No change is proposed to the existing plant-back intervals as a result of the re-evaluation

Product labels contain grazing restrictions; therefore, no pre-grazing intervals are required at this time.

Overall, sufficient information was available to adequately assess the dietary exposure and risk from fomesafen.

Appendix V Commercial Mixer/Loader/Applicator and Postapplication Risk Assessment

Table 1 Occupational Dermal and Inhalation Exposure Risk Assessment

Crop	Formulation	Application Equipment	Max Rate (kg a.i./ha)	ATPD (ha/day)	Dermal Exposure[a] (mg/kg bw/day)	Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[c]	Combined MOE[d]
Soybean	SN	GB Farmer	0.24	107	1.35E-02	8.20E-04	930	15211	873
		GB Custom		360	4.54E-02	2.76E-03	275	4521	259
Soybean, glyphosate tolerant	SN	GB Farmer	0.2345	107	1.35E-02	8.00E-04	926	15211	873
		GB Custom		360	4.54E-02	2.70E-03	275	4521	259
Dry edible beans	SN	GB Farmer	0.24	107	1.35E-02	8.20E-04	926	15211	873
		GB Custom		360	4.54E-02	2.76E-03	275	4521	259
Snap common beans (yellow and green)	SN	GB Farmer	0.24	107	1.35E-02	8.20E-04	926	15211	873
		GB Custom		360	4.54E-02	2.76E-03	275	4521	259
Lima beans	SN	GB Farmer	0.24	107	1.35E-02	8.20E-04	926	15211	873
		GB Custom		360	4.54E-02	2.76E-03	275	4521	259
Otebo beans	SN	GB Farmer	0.24	107	1.35E-02	8.20E-04	926	15211	873
		GB Custom		360	4.54E-02	2.76E-03	275	4521	259
Cucumber	SN	GB Farmer	0.24	26	3.28E-03	2.00E-04	3810	62600	3592
Potatoes	SN	GB Farmer	0.24	107	1.35E-02	2.76E-03	926	15211	873
		GB Custom		360	4.54E-02	8.20E-04	275	4521	259

Baseline PPE: single layer, CR gloves (no gloves in groundboom application)
ATPD = area treated per day, MOE = margin of exposure, SN = solution, GB = groundboom
[a] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × 50% dermal absorption)/80 kg body weight
[b] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight
[c] Based on a NOAEL of 12.5 mg/kg bw/day, target MOE = 100
[d] Combined MOE = NOAEL/(EXP_{derm}+EXP_{inh})

Table 2 Postapplication Risk Assessment

Crop[a]	Activity	TC (cm^2/hr)[b]	App rate (kg a.i./ha)	Dermal Exposure (mg/kg/day)[c]	Dermal MOE[d]	REI (hours)[e]
Soybean, soybean glyphosate tolerant, dry edible beans, snap common beans, lima beans,[f] otebo beans[f]	Scouting[g]	210	0.24	0.0126	1964	12

TC = Transfer coefficient, DFR = Dislodgeable Foliar Residue, MOE = Margin of Exposure, REI = restricted-entry interval
[a] Fomesafen is applied to potatoes and cucumbers pre-emergent to the crop. Foliar residues are not expected for potatoes and cucumbers.
[b] The TC values are from the PMRA Transfer Coefficient Memo (PMRA, 2012). The TC value for maximum foliage density was considered as a worst case scenario for the risk assessment.
[c] Dermal exposure (mg/kg bw/day) = DFR (ug/cm^2) × TC (cm^2/hr) × work duration (8 hr) x DA / BW (80kg). Since no DFR studies were submitted, a peak default DFR value of 25% of the application rate and a dissipation rate value of 10% were used. 1 application per year for all scenarios.
[d] Based on the short-term oral NOAEL of 12.5 mg/kg bw/day and a target MOE of 100

[e] If the target MOE is met, the REI is set at 12 hours.
[f] Surrogate TC values from dry, edible beans used for lima beans and otebo beans
[g] Minimal exposure is anticipated for weeding activity for soybeans, soybean glyphosate tolerant, dry edible beans, snap common beans, lima beans, and otebo beans since fomesafen applied at very early crop stage of plant (1–2 trifoliate leaf stage).

Appendix VI Environmental Assessment

Table 1 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	technical	pH 3 and 11, < 8% hydrolysis after 31 days; stable stable	Compound II (5-(2-chloro-α-α-α-trifluoro-p-tolyloxy)-2-nitrobenzoic acid) at < 2% not stated	Not an important route of transformation in the environment.	1258763 2821594
Phototransformation on soil	technical	Half life ~ 40 days	Compound XIX (Methanesulphonamide) accounted for up to 24% Compound II at 2%	Not an important route of transformatoin in the environment.	1258765
Phototransformation in air	No data available. Low potential to volatilize into air; therefore, phototransformation in air is not expected to be an important route of transformation				
Biotransformation					
Biotransformation in aerobic soil	technical	Sandy loam DT50 ~ 3 weeks Loamy sand and silty clay loam > 18 weeks USEPA-derived values: Silty clay loam DT_{50} = 29.7 weeks Loam DT_{50} = 99 weeks, loamy sand DT_{50} = 90 weeks, clay loam DT_{50} = 75.3 weeks PMRA-derived values: 90%	No transformation products measured. Compound II at 4.8%	Slightly to moderately persistent	1258766 1218641, USEPA DER for 1218641, 2821594

Property	Test substance	Value	Transformation products	Comments	PMRA#
		confidence bound on the mean representative half-lives for all four soils = 773 days Loam DT_{50} = 9 weeks, loamy sand DT_{50} = 27 weeks clay loam DT_{50} = 50 weeks	No details provided for transformation products		USEPA DER for 1218641, 2821594
Biotransformation in aerobic flooded soils	18 Acre sandy loam, Frensham loamy sand, Gore Hill calcareous clay loam, Wisborough Green Silty clay loam	DT_{50}s = 61, 139, 92 and 116 days, approximately	Reported in USEPA review. Neither data nor original studies were available to the PMRA; therefore, data were considered supplemental. As definitive data are not available, fomesafen was considered 'stable' for water modelling purposes.	NA	2821594
Biotransformation in anaerobic soil	Loam, loamy sand, silty clay loam, calcareous clay loam	All soils DT_{50} < 3 weeks	Compound XV, max of 19.3% Compound II and V – each < 2%	Slightly persitant	1212586 2821594
Mobility					
Property	Soil Type	K_{oc} Value	Comments		Reference
Adsorption/desorption in soil, K_{oc}	Blount (silt loam)	58.03564	Moderately mobile to very mobile		1218640 2821594
	Bryce (silty clay loam)	62.84046			
	Dickenson (loamy course sand)	37.89828			
	Drummer (silty clay loam)	46.90523			
	Flanagan (silt loam)	34.89879			
	Norfolk (coarse sandy	58.0913			

Property	Test substance	Value	Transformation products	Comments	PMRA#
	loam)				
	Onarga (coarse sand)	52.83226			
	Peotone (silty clay loam)	62.95104			
	Plano (silt loam)	55.168			
	Brazil (Terra rosa) (sandy clay)	168.5113			
	Brazil 1B (sandy clay loam)	121.6467			
	Peartree (sandy clay loam)	64.4855			
Soil leaching	75–85% remained in top 15 cm over a 9-week soil column leaching study; in sandy soil evenly distributed over a soil column and 17% found in leachate		Mobile and potential to leach in course-textured soils		1258769 1258768
Volatilization	No data available. Fomesafen is non-volatile and no further data required.				
Field studies, Canada					
Study Type	**Soil Type**	**DT_{50} value**	**Comments**		**Reference**
Terrestrial field dissipation	Clay loam; bare soil (Stoney Creek Road and 50 Road, Ontario)	Not provided	Slow but steady dissipation over 112 day study duration in the top layer (0–7.5 cm), accompanied by a slight increase in the 7.5–15 cm layer. In other soil types (not described) slight decreases in 0–7.5 and 7.5–15 cm layers were observed over the durationo the study. Low concentrations detected beyond 15 cm at 112 days. Relatively persistent in soils over the study period; minimal leaching below the 15 cm soil depth.		1258772
	Sandy clay loam; cropped plots (Stoney Creek, Ontario; application pre-plant and pre-emergent)	Not provided	Rates applied: 0.125, 0.25, and 0.5 kg a.i./ha. Soil samples were taken at 166 days (pre-emergent) and 169 days (pre-plant) after application, 0–7.5 cm and 7.5–15 cm. Test plots were cropped with soybean. No signifcant decrease between calculated starting concentration and concentration measured at 166 or 169 days for an application rate of 0.125 kg a.i./ha.		1258773
	Sandy loam (St. Anne de Bellevue, Quebec; application		Rate applied: 2.0 kg a.i./ha. Soil samples were taken 126 days after application, depth of 0–7.5 cm and 7.5–15 cm. Test plots were cropped with soybean. A decrease was noted between calculated		1258773

Property	Test substance	Value	Transformation products	Comments	PMRA#
	post-emergent)		initial residue and residues sampled after 126 days, but influence of weed cover at application would have contributed to this apparent dissipation.		
	Clay loam; sandy loam (Winona and Rodney, Ontario, respectively)	60 –128 days; > 128 days, clay loam 12 days, sandy loam (both rates)	Rate applied: 0.5 and 1.0 kg a.i./ha (both sites). Sampling occurred and remained in top 15 cm in clay and loam soils; slightly to moderately persistent in non-sandy soils; slightly persistent in sandy loam soil. No significant leaching in either soil.		1258774
	Sandy loam, silty clay loam (Rodney and St. Davids, Ontario)	28 days, sandy loam; not reported, silty clay loam	No evidence of leaching beyond 10 cm; slightly persistent.		1215404

Table 2 Fate and behaviour in the aquatic environment

Study type	Test material	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	technical	pH 3 and 11 < 8% hydrolysis after 31 days; stable stable	Compound II (5-(2-chloro-α-α-α-trifluoro-p-tolyloxy)-2-nitrobenzoic acid) at < 2% not stated	Not an important route of transformation in the environment.	1258763 2821594
Phototransformation in water	Technical Not stated	Half-life between 1 and 2 months Half-lives of 49 and 289 days	Transformation products detected but not identified. All < 10%. Not stated	Not an important route of transformation in the environment.	1258764 2821594
Biotransformation					
Biotransformation in aerobic water systems	DT_{50} = 5–10 days, where most of the degradation observed was attributed to microbially-mediated transformation and the remainder due to				1207907

	phototransformation processes. Study authors indicated this was under anaerobic conditions, but also stated aeration was conducted throughout the study. Oxygen measurements were not taken. Unextractable residues were high and increased over study duration. Few sampling times were included as the study was conducted over 30 days. Therefore, data were considered supplemental.	
	USEPA reported DT_{50}s in the range of 60.9 to 139.9 days. Neither data nor original studies were available to the PMRA; therefore, data were considered supplemental. As definitive data are not avialable, fomesafen is considered 'stable' for modelling purposes.	2821594
Field studies		
Field dissipation	No data available	
Bioaccumulation		
bluegill sunfish Bioconcentration factor (BCF) = 0.7, 0.2 and 5.2 in whole fish, muscles (lateral musculature including skin and bones) and viscera, respectively. Depurated to background levels after 14 days. Whole-fish BCF of 2.8 was reported in channel catfish (*Ictalurus punctatus*). Fomesafen has low potential to bioaccumulate.		1207911 2821594

Table 3 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Invertebrates					
Earthworm	12 months field chronic	End-use product, coverted to active	NOEC = 0.5 kg a.i./ha, coverted to 0.222 mg a.i./kg soil	N/A	1207914
Bee	48h-Oral	25% solution, converted to active for test range	LD_{50} > 50 µg a.i./bee	Relatively non-toxic	1207913
	48h-Contact		LD_{50} > 100 µg a.i./bee		
Predatory arthropod Parasitic arthropod	No screening level predator/parasite data were available assessing acute toxicity; however, based on information reviewed by the USEPA eight arthropod species (from orders Acarina, Hemiptera, Diptera, Lepidoptera, Coleoptera, Nemotoda), at 250 to 500 ppm fomesafen applied to various life stages, limited mortality was observed (highest was 9% for aphids);				2821594
Birds					
Bobwhite quail	Acute	No data available			
	5 d-Dietary	Active, 97.8% purity	LC_{50} > 20000 mg/kg diet, coverts to 2667 mg a.i./kg BW/day	Practically non-toxic	1258791 2821594
	31 week-Reproduction	Active, 97.8% purity	NOEC = 50 mg a.i./kg diet, converts to 4 mg a.i./kg BW/day (highest does tested)	N/A	1207910 2821594
Mallard duck	Acute	Active, 97.8% purity	LD_{50} > 5000 mg a.i./kg BW (14 day observation period)	Practically non-toxic	1258789 2821594
	5 d-Dietary	Active, 97.5% purity	LC_{50} > 20000 mg/kg diet, coverts to 2057	Practically non-toxic	1258790 2821594

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
			mg a.i./kg BW/day		
	23 week-Reproduction	Active, 97.8% purity	NOEC = 50 mg a.i./kg diet, converts to 6.4 mg a.i./kg BW/day (highest dose tested)	N/A	1207909 2821594
Mammals					
Rat	Acute	97.5% purity	LD_{50} = 1250–2000 mg/kg bw (♂); 1595 mg/kg bw (♀)	Slightly acutely toxic	1249210
		48.3% wt/wt purity	LD_{50} = 2000 mg/kg bw (♀)		2413803
		19.5% w/v Na salt in aqueous solution	LD_{50} = 1858 (1420–2546) mg/kg bw (♂); 1499 (1302–1748) mg/kg bw (♀)		1249211
Guinea pig		19.5% w/v Na salt in aqueous solution	LD_{50} = 487–975 mg/kg bw (♀)	Slighlty to moderately acutely toxic	
rabbit			LD_{50} ~ 487 mg/kg bw (♂)	Moderately acutely toxic	
rat	Reproduction	97.5% purity	Parental NOAEL($\underline{F_0}$ and $\underline{F_1}$) = 12.5 mg/kg bw/day Offspring NOAEL(F_1A/F_1B and F_2A/F_2B), = 12.5 mg/kg bw/day Reproductive NOAEL ≥ 50 mg/kg bw/day	N/A	1258315 1258324
Vascular plants					
Vascular plant	EC25-Seedling emergence	Based on active	0.0056 kg/ha	N/A	2821594
	EC25-Vegetative vigour	Based on active	0.0022 kg/ha	N/A	2821594

a Atkins *et al.*(1981) for bees and USEPA classification for others, where applicable.
N/A: Not applicable.

Table 4 Risk to terrestrial organisms other than birds and mammals

Organism	Exposure	Endpoint value	EEC	RQ	LOC exceeded?
Invertebrates					
Earthworm	Acute	0.222 mg a.i./kg soil	0.1067 mg a.i./kg soil	0.5	No
Bee	Oral	LD_{50} > 0.50 µg a.i./bee	6.96 µg a.i./bee	0.14	No

Organism	Exposure	Endpoint value	EEC	RQ	LOC exceeded?
	Contact	LD_{50} >100 µg a.i./bee	0.576 µg a.i./bee	0.006	No
Predatory arthropod	Contact	No endpoint data available. Based on low toxicity to bees, other invertebrates such as aquatic species, and information in USEPA review indicating limited mortality to various life stages of other terrestrial invertebrates, risks to non-target arthropods are expected to be acceptable.			
Parasitic arthropod	Contact				
Vascular plants – screening level					
	Seedling emergence	5.6 g a.i./ha	240 g a.i./ha	43	**Yes**
	Vegetative vigour	2.2 kg a.i./ha		109	**Yes**
Vascular plants – refined					
	Seedling emergence	5.6 g a.i./ha	240 × 6% drift = 14.4 g a.i./ha	2.6	**Yes**
	Vegetative vigour	2.2 kg a.i./ha		6.5	**Yes**

Table 5 Expanded risk assessment of fomesafen for birds based on the highest rate for ground application – various crops (240 g a.i./ha)

Study Type	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)										
Reproduction	4.00	Insectivore	19.54	**4.9**	1.17	0.3	13.49	**3.37**	0.81	0.20
	4.00	Granivore (grain and seeds)	3.02	0.8	0.18	0.0	1.44	0.36	0.09	0.02
	4.00	Frugivore (fruit)	6.05	**1.5**	0.36	0.1	2.88	0.72	0.17	0.04
Medium-sized Bird (0.1 kg)										
Reproduction	4.00	Insectivore	15.24	**3.8**	0.91	0.2	10.53	**2.63**	0.63	0.16
	4.00	Granivore (grain and seeds)	2.36	0.6	0.14	0.0	1.13	0.28	0.07	0.02
	4.00	Frugivore (fruit)	4.72	**1.2**	0.28	0.1	2.25	0.56	0.14	0.03
Large-sized birds (1 kg)										
Reproduction	4.00	Insectivore	4.45	**1.1**	0.27	0.1	3.07	0.77	0.18	0.05
	4.00	Granivore (grain and seeds)	0.69	0.2	0.04	0.0	3.07	0.77	0.02	0.00
	4.00	Frugivore (fruit)	1.38	0.3	0.08	0.0	0.66	0.16	0.04	0.01
	4.00	Herbivore (short grass)	9.85	**2.5**	0.59	0.1	3.50	0.87	0.21	0.05

Study Type	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
	4.00	Herbivore (long grass)	6.01	**1.5**	0.36	0.1	1.96	0.49	0.12	0.03
	4.00	Herbivore (Broadleaf plants)	9.11	**2.3**	0.55	0.1	3.01	0.75	0.18	0.05

Table 6 Expanded Risk Assessment of fomesafen for mammals based on the highest rate for ground application – various crops (240 g a.i/ha)

Study Type	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
Medium-sized Mammal (0.035 kg)										
Reproduction	12.5	Insectivore	9.85	0.79	0.59	0.05	6.80	0.54	0.41	0.03
	12.5	Granivore (grain and seeds)	1.52	0.12	0.09	0.01	0.73	0.06	0.04	0.00
	12.5	Frugivore (fruit)	3.05	0.24	0.18	0.01	1.45	0.12	0.09	0.01
	12.5	Herbivore (short grass)	21.79	**1.74**	1.31	0.10	7.74	0.62	0.46	0.04
	12.5	Herbivore (long grass)	13.31	**1.06**	0.80	0.06	4.34	0.35	0.26	0.02
	12.5	Herbivore (Broadleaf plants)	20.16	**1.61**	1.21	0.10	6.67	0.53	0.40	0.03

Values in bold exceed Level of Concern (≥1)

Table 7 Effects on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
Freshwater species					
Daphnia magna	48 h-Acute	Technical	EC_{50} = 330 mg a.i./L	Practically non-toxic	1258796
	Chronic - duration not reported	Formulated product, converted to active	NOEC = 50 mg a.i./L	Not Applicable	2821594
Rainbow trout	96h-Acute	Formulated product, converted to	LC_{50} = 170 mg a.i./L	Practically non-toxic	1258794

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
		active			
	Chronic	No data available			
Bluegill sunfish	96h-Acute	Formulated product, converted to active	LC_{50} = 1508 mg a.i./L	Practically non-toxic	1258795
	Chronic	No data available			
Amphibians (rainbow trout data used as a surrogate)	96h-Acute	Formulated product, converted to active	LC_{50} = 170 mg a.i./L	Practically non-toxic	1258794
Freshwater algae: Green algae (species not stated) Blue-green algae (species not reported) Mesocosm study, including freshwater phytoplankton	Acute (duration not stated)	Technical	EC_{50} biomass = 0.092 mg a.i./L LC_{50} = 71 mg a.i./L Short-term effects on abundance and biomass not anticipated for water concentrations < 0.06 mg/L (PMRA EECs for water were below this concentration)	Not applicable	2821594
Vascular plant – *Lemna gibba*	Duration not reported - Dissolved	Technical	EC_{50} dry weight = 0.210 mg a.i./L	Not applicable	2821594
Marine species					
Crustacean (Mysid shrimp)	Duration not reported- Acute	Formulated product, converted to active	LC_{50} = 25 mg a.i. /L	Slightly toxic	2821594
	Chronic - duration not reported		NOEC = 0.7 mg a.i./L, LOEC = 1.7 mg a.i./L (parental mortality)	Not applicable	
Sheepshead minnow	Duration not reported - Acute		LC_{50} > 163 mg a.i./L	Practically non-toxic	
	Chronic - duration not reported		NOEC = 12.2 mg a.i./L, LOEC = 20.1 mg a.i./L (reduced larval survival)	Not applicable	
Salt water diatom	Acute - duration		LC_{50} = 1.51		

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]	PMRA#
	not reported		mg a.i./L NOEC = 0.94 mg a.i./L (biomass)		

a USEPA classification, where applicable

Table 8 Screening Level Risk Assessment of fomesafen for aquatic organisms following a single application at 240 g a.i./ha

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	EEC** (mg a.i./L)	RQ	LOC Exceeded
Freshwater organisms							
Invertebrate	Acute	Daphnia magna	96 hr EC_{50} = 330 mg a.i./L	165 mg a.i./L	0.03 mg a.i./L	0.0002	No
	Chronic	*Daphnia magna*	(duration not reported) NOEC = 50 mg a.i./L	50 mg a.i./L	0.03 mg a.i./L	0.0006	No
Fish	Acute	Rainbow trout	96 hr LC_{50} = 170 mg a.i./L	17 mg a.i./L	0.03 mg a.i./L	0.002	No
Amphibian	Acute	Rainbow trout surrogate	96 hr LC_{50} = 170 mg a.i./L	17 mg a.i./L	0.16 mg a.i./L	0.009	No
Aquatic vascular plants	Acute	*Lemna gibba*	EC_{50} = 0.210 mg a.i./L	0.105 mg a.i./L	0.03 mg a.i./L	0.3	No
Algae	Acute (duration unknown)	Green algae (species name not reported)	EC_{50} = 0.092 mg a.i./L	0.046 mg a.i./L	0.03 mg a.i./L	0.65	No
Marine/Estuarine organisms							
Invertebrate	Acute	Mysid shrimp (*Mysidopsis bahia*)	(Unreported time) LC_{50}: 25 mg a.i./L)	12.5 mg a.i./L	0.03 mg a.i./L	0.002	No
	Chronic	Mysid shrimp (*Mysidopsis bahia*)	(unreported time) NOEC parental mortality = 0.7 mg a.i./L	0.7 mg a.i./L	0.03 mg a.i./L	0.04	No
Fish	Acute	*Cyprinodon variegatus*	(unreported time) LC_{50} =	16.3 mg a.i./L	0.03 mg a.i./L	0.002	No

Organism	Exposure	Species	Endpoint reported (mg a.i./L)	Endpoint for RA* (mg a.i./L)	EEC** (mg a.i./L)	RQ	LOC Exceeded
			163 mg a.i./L				
	Chronic	*Cyprinodon variegatus*	(unreported time)-NOEC reduced larval survival = 12.2 mg a.i./L	12.2 mg a.i./L	0.03 mg a.i./L	0.002	No
Algae	Acute	Species not reported	(unreported time) LC_{50} = 1.51 mg a.i./L	0.76 mg a.i./L	0.03 mg a.i./L	0.04	No

* Endpoints used in the acute exposure risk assessment (RA) are derived by dividing the EC_{50} or LC_{50} from the appropriate laboratory study by a factor of two for aquatic invertebrates and plants, and by a factor of ten for fish and amphibians.
** EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms (see Section 2.9.2).
Values in bold exceed Level of concern (≥1)

Table 9 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria			
TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Fomesafen Are criteria met?**
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Yes: 773 days
	Water	Half-life ≥ 182 days	Yes: Stable
	Whole system (Water + Sediment)	Half-life ≥ 365 days	Yes: Stable
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilization is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<4\times10^{-3}$ mPa) and Henry's law constant (1.461×10^{-2} mmHg).
Bioaccumulation[4]	Log K_{ow} ≥ 5		No: -1.2
	BCF ≥ 5000		No: 0.2 to 5.2
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet all TSMP Track 1 criteria.**

Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria		
TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**	**Fomesafen Are criteria met?**
[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met). [2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases. [3]If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met. [4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).		

Appendix VII Water Modelling and Monitoring Data

Monitoring data and modelling estimates provide different types of information and are therefore not directly comparable. Pesticide concentrations in water are highly variable in time and location, and Canadian monitoring data usually are sparse. When it is possible, monitoring data from the United States are used together with the Canadian data to provide a more robust analysis. These two types of data are complementary and are considered in conjunction with each other when estimating the potential exposure of humans.

Water Modelling Estimates

Application Information and Model Inputs

Fomesafen is a herbicide proposed for use on various crops. Information on application rates and timing was provided by VRD (PMRA# 2412118). The use pattern modelled was one application of 240 g a.i./ha, applied every other year. Modelling used initial application dates between 11 May and 26 June based on the information provided by VRD. Application information and the main environmental fate parameters used in the Level 1 model are summarized in Table 10.

Table 1 Summary of Use Pattern Modelled for the Level 1 Assessment of fomesafen, based on information from VRD

Item	Value
Method of application	Ground
Yearly rate of application (g a.i./ha)	240
Rate per application (g a.i./ha), if multiple applications	240
Number of applications per year	1 application every other year
Typical dates of first application	11 May to 26 June

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

EECs of fomesafen in potential drinking water sources (groundwater and surface water) outside of British Columbia were generated using a computer simulation model. Modelling for surface water used a standard Level 1 scenario, a small reservoir adjacent to an agricultural field. EECs in groundwater were calculated by selecting the highest EEC from several selected scenarios representing different regions of Canada. All scenarios were run for 50 years.

EECs of fomesafen in potential drinking water sources are given in Table 11. The EECs resulting from this Level 1 assessment were calculated using conservative inputs with respect to application rate and timing, and geographic scenario. These EECs should therefore allow for future use expansion into other crops at this application rate and method.

Table 2 Level 1 Estimated Environmental Concentrations of Fomesafen in Potential Sources of Drinking Water

Crop/use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]
Single application of 240 g a.i./ha applied every other year	119	120	12	2.2

1 90th percentile of daily average concentrations
2 90th percentile of 365-day moving average concentrations
3 90th percentile of the peak concentrations from each year
4 90th percentile of yearly average concentrations

Monitoring Data

Monitoring data collected from the year 2000 onward were considered relevant for this assessment; older data were deemed unlikely to represent current Canadian use conditions. Water monitoring information was available for fomesafen from Quebec, Ontario, and the Atlantic region. A compilation of the raw data with analyses is provided in PMRA# 2794329.

For the purposes of the water assessment, information extracted from the available sources was summarized by water type. Groundwater, finished/treated water and ambient surface water bodies such as rivers, lakes and reservoirs are considered potential sources of drinking water and thus relevant for use in the dietary risk assessment for human health.

Summary of Water Monitoring Results

In general, sampling occurred in use areas and during the summer months when fomesafen would be applied. Based on available monitoring data, fomesafen is detected in water in Ontario and Quebec. Fomesafen was not detected in the few samples from the Atlantic region.

Groundwater and Treated water sources

There was no groundwater or treated water monitoring data available for fomesafen from Canadian or American sources at the time of the assessment.

Surface water sources relevant for the human health and aquatic risk assessment (PMRA# 1726638, 1739256, 1763866, 2681876)

A total of 193 ambient surface water samples were analyzed for fomesafen residues in Canada. Fomesafen was detected in 23 of these samples (11.91%). The maximum concentration of fomesafen residues detected was 0.8737µg/L from a sample taken in Ontario. There was no surface water monitoring data available from American sources at the time of assessment.

Discussion and Conclusion

Potential drinking water sources for humans

Based on available monitoring data, fomesafen is detected in water in Quebec and Ontario. The maximum concentration of fomesafen detected in potential drinking water sources was 0.8737 µg/L, from a surface water sample collected in Ontario. The small number of samples in Canada precludes the use of an EEC based on Canadian monitoring data for acute and chronic drinking water exposure.

Water monitoring data, particularly for surface water, may miss peak concentrations, as sampling is typically sporadic and peak concentrations can be flushed through a system in a short amount of time after a runoff event. Therefore, particularly for surface water, EECs generated through modelling are typically better suited for use in an acute dietary risk assessment as opposed to surface water monitoring values. Additionally, due to the small number of samples, a reliable chronic exposure estimate cannot be obtained using the Canadian monitoring data.

Surface water relevant for aquatic risk assessments

For aquatic risk assessment purposes, the highest concentration of fomesafen detected in water was 0.8737 µg/L, which is considerably lower than the EECs determined in 15 and 80 cm water depths (0.16 and 0.03 mg/L, respectively) after a direct overspray of fomesafen at the highest registered application rate of 240 g a.i./ha. Therefore, based on monitoring data from surface waters, the potential for acute exposure of aquatic organisms to fomesafen in surface water is expected to be limited. However, because of the low detection frequency of fomesafen in water 11.91%, and the low number of samples taken in Canada, it is difficult to estimate a long-term exposure concentration based on available water monitoring data; as such, a chronic aquatic exposure assessment based on monitoring data cannot be conducted.

Appendix VIII Label Amendments for Products Containing Fomesafen

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.

LABEL STATEMENTS TO PROTECT HUMAN HEALTH

LABEL AMENDMENTS FOR END-USE PRODUCTS

General Label Updates

The following label statements are proposed to be added to the PRECAUTIONS of all commercial end-use product labels, unless already present:

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

Label statements must be amended (or added) to include the following directions to the appropriate labels:

> "DO NOT APPLY BY AIR."
>
> "DO NOT APPLY IN GREENHOUSES."

Restricted-Entry Interval

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

> "DO NOT enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."

LABEL STATEMENTS TO PROTECT THE ENVIRONMENT

LABEL AMENDMENTS FOR TECHNICAL GRADE ACTIVE INGREDIENTS AND MANUFACTURING CONCENTRATES (Reg. No. 28828, 28133, 28827, and 28134)

Add the title "ENVIRONMENTAL PRECAUTIONS" and add the following:

> "Toxic to aquatic organisms"

Replace all wording under the DISPOSAL heading with the following:

"Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean-up of spills, contact the manufacturer or the provincial regulatory agency."

LABEL AMENDMENTS FOR END-USE PRODUCTS

- **END-USE PRODUCT CONTAINING ONLY FOMESAFEN (Reg. No. 24779)**

Under PRECAUTIONS, remove the following:

The entire paragraph starting with:

***"DO NOT** contaminate food and feed,…"*

The entire paragraph starting with:

"For tank mixes,…"

Under ENVIRONMENTAL PRECAUTIONS heading, remove all current information and add the following:

> "Toxic to aquatic organisms"
>
> "TOXIC to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Fomesafen is persistent and may carryover. It is recommended that any products containing fomesafen not be used in areas treated with this product during the previous season.

This product demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of fomesafen in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination.

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."

Under the DIRECTIONS FOR USE heading, add the following:

> "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."

"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.

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 below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands).

Method of application	Crops	Buffer Zones (metres) Required for the Protection of Terrestrial Habitat:
Field sprayer	Soybean, dry edible beans, snap common beans, lima beans, otebo beans, cucumber, potato, strawberry	4

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."

Remove the heading "STORAGE CONDITIONS" and associated information.

Replace with a new "STORAGE" heading, and add the following:

"To prevent contamination store this product away from food or feed."

Under the DISPOSAL heading, remove the entire first paragraph starting with:

"For information on disposal…"

Remove the heading "CONTAINER DISPOSAL:".

Replace all the information under "FOR DISPOSAL OF PLASTIC JUGS" with the following:

"For disposal of non-recyclable, non-returnable or non-refillable containers:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.

2. Follow provincial instruction for any required additional cleaning of the container prior to its disposal.

3. Make the empty container unsuitable for further use.

4. Dispose of the container in accordance with provincial requirements.

5. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills."

- **CO-FORMULATED END-USE PRODUCTS (Reg. No. 29644 and 30412)**

Under the PRECAUTIONS heading, remove the following:

The entire paragraph starting with:

*"**DO NOT** contaminate food and feed,…"*

Under ENVIRONMENTAL PRECAUTIONS heading on pages 3 and 8 of Reg. No. 29644 or the ENVIRONMENTAL HAZARDS heading on page 4 of Reg. No. 30412, remove all current information and add the following:

"Toxic to aquatic organisms"

"TOXIC to non-target terrestrial plants. Observe buffer zones specified under DIRECTIONS FOR USE.

Fomesafen is persistent and may carryover. It is recommended that any products containing fomesafen not be used in areas treated with this product during the previous season.

This product demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of fomesafen in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination.

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."

Amend the heading "ENVIRONMENTAL HAZARDS" heading on page 4 of Reg. No. 30412 to ENVIRONMENTAL PRECAUTIONS

On pages 3 and 8 of Reg. No. 29644 and page 5 of Reg. No. 30412, remove the heading "STORAGE CONDITIONS" and associated information.

Replace with a new "STORAGE" heading, and add the following:

"To prevent contamination store this product away from food or feed."

On pages 4 and 9 of Reg. No. 29644 and page 5 of Reg. No. 30412, replace the "DECONTAMINATION AND DISPOSAL" heading with "DISPOSAL". Under the new DISPOSAL heading, remove the entire first paragraph starting with:

"*For information on disposal…*"

On pages 4 and 9 of Reg. No. 29644 and page 5 of Reg. No. 30412, remove the heading "CONTAINER DISPOSAL OR REFILLING:".

Replace all the information under "FOR DISPOSAL OF PLASTIC JUGS" with the following:

"For disposal of non-recyclable, non-returnable or non-refillable containers:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.

2. Follow provincial instruction for any required additional cleaning of the container prior to its disposal.

3. Make the empty container unsuitable for further use.

4. Dispose of the container in accordance with provincial requirements.

For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills."

Under the DIRECTIONS FOR USE heading on page 10 of Reg. No. 29644 or page 6 and 7 of Reg. No. 30412, remove the paragraphs starting with the following wording:

"Avoid contact with desirable vegetation…"

"Avoid drift or overspray…"

"Do not contaminate water sources…"

Add the following information under the same heading:

"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." (Reg. No. 29644 only)

Add to DIRECTIONS FOR USE:

> "Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.
>
> **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 below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands).

Method of application	Crops	Buffer Zones (metres) Required for the Protection of Terrestrial Habitat:
Field sprayer	Soybean, dry edible beans, snap common beans, lima beans, otebo beans, cucumber, potato, strawberry	4

> 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

Information Considered in the Chemistry Assessment

A. Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
1243491	2004, Description of Production Process - Confidential Cross Reference 3, DACO: 2.11.1,2.11.3
1243496	2004, Detailed Production Process Description - Note to the Reviewer, DACO: 2.11.3
1243492	2004, Manufacturing Process Description and Supporting Data for Fomesafen Technical and Material Safety Data Sheets, DACO: 0.9,0.9.1,2.11.2
1243484	2004, Analysis of Five Representative Batches of Fomesafen Technicale (Dry) (PP21C) for Registration, DACO: 2.13.3
2546619	2014, Fomesafen Technical (PP21). Validation of Analytical Method AG-1229/2. Final Report, DACO: 2.13.1
2546620	1998, Methodology/Validation. DACO: 2.13.1
2546621	2015, Impurities of Toxicological Concern. DACO: 2.13.4
2546622	2015, Impurities of Toxicological Concern. DACO: 2.13.4
1304967	2006, Fomesafen Technical DACO 2 Source Documents, DACO: 2.0,2.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.13.1,2.13.2,2.13.3,2.13.4,2.2,2.3,2.4, 2.5,2.6,2.7,2.8,2.9

Information Considered in the Toxicology Assessment

A. Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
1199899 1258633	1984, An examination of PP021 for potential carcinogenicity using two in vitro assays (CTL/P/596), DACO: 4.5.4
1199900 1258634	1981, PP021: Dominant lethal study in the mouse (CTL/P/609), DACO: 4.5.4
1199901 1258636	1981, PP021: A cytogenetic study in the rat (CTL/P/623), DACO: 4.5.4
1199936 1258631	1980, PP021: 4-week feeding study in male rats with a 6-week recovery period (CTL/P/541), DACO: 4.3.1
1222978 1258898	1984, Capacity of fomesafen to induce unscheduled DNA synthesis in cultured HeLa cells (M690), DACO: 4.5.4
1222989 1258902	1985, Fomesafen: covalent interaction with mouse liver macromolecules in vivo (CTL/P/1230), DACO: 4.5.4

PMRA Document Number	Reference
1249210	1981, PP021: acute oral toxicity, skin irritation and eye irritation (CTL/P/562), DACO: 4.2.1, 4.2.4, 4.2.5
1249211	1981, PP021: acute toxicity and local irritation (CTL/P/506), DACO: 4.2.1, 4.2.2
1249212	1982, Fomesafen (acid form and sodium salt): skin sensitization studies (CTL/P/601), DACO: 4.2.6
1249214 1249222	90-day feeding study in rats, DACO: 4.3.1
1258899	1984, In vitro study of chromosome aberration induced by fomesafen in cultured human lymphocytes (M689), DACO: 4.5.4
1258312 1258313	1984, Fomesafen: 2-year feeding study in rats (CTL/P/863). DACO: 4.4.1
1258315 1258324	1984, Report on fomesafen 2-generation reproduction study in the rat (CTL/P/869), DACO: 4.5.1
1258318	1981, Report on PP021: Teratogenicity study in the rabbit (CTL/P/578), DACO: 4.5.2
1258319	1981, Report on PP021: Teratogenicity study in the rat (CTL/P/576), DACO: 4.5.2
1258320	1982, Report on PP021: Teratogenicity study in the rat (CTL/P/656), DACO: 4.5.2
1258321	1984, Fomesafen: covalent interaction with rat liver macromolecules in vivo (CTL/R/745), DACO 4.4.2
1258322	Fomesafen: a repeat cytogenetic study in the rat, DACO 4.5.4
1258327 1258328 1258737 1258897	1983, Fomesafen: 2-year feeding study in mice (final report) (CTL/C/1207), DACO 4.4.1
1258626	1983, Fomesafen: subacute dermal toxicity study in rabbits (CTL/P/555), DACO 4.3.4
1258627	1981, The effects of fomesafen on marmoset liver (CTL/P/554), DACO 4.3.8
1258630	1981, PP021: 26 week oral dosing study in dogs (CTL/P/591), DACO 4.3.1
1258744	1982, Fomesafen: absorption, excretion and tissue retention of a single oral low dose in the rat (5 mg/kg) (CTL/C/1101), DACO: 6.4
1258745	1982, Fomesafen: absorption, excretion and tissue retention of a single oral dose in the rat (500 mg/kg) (CTL/C/1103), DACO: 6.4
1258746	1982, Fomesafen: excretion and tissue retention, intravenous dose, in the rat (5 mg/kg) (CTL/C/1100), DACO: 6.4
1258747	1982, Fomesafen: tissue retention, repeated oral administration in the rat (5 mg/kg) (CTL/C/1102), DACO: 6.4
1258748	1982, Fomesafen: disposition and excretion in the normal and bile duct cannulated rat (CTL/P/636), DACO: 6.4
1258752	1983, Fomesafen: biotransformation in the rat (CTL/P/797), DACO: 6.4

PMRA Document Number	Reference
1258753	1983, Fomesafen: absorption, excretion and tissue retention of a single oral dose (5 mg/kg) in the dog (CTL/P/637), DACO: 6.4
1258754	1983, Fomesafen: excretion and tissue retention of a single oral dose (5 mg/kg) in the mouse (CTL/P/883), DACO: 6.4
1258756	1984, Fomesafen: pharmacokinetic study in the marmoset (CTL/P/712), DACO: 6.4
2324789	2006, Fomesafen technical (147A) Acute dermal toxicity study in rats. Final report (T0001484-06), DACO: 4.2.2
2324791	2006, Fomesafen technical (147A) 4-hour acute inhalation limit toxicity study in the rat. Final report (T0001674-06), DACO: 4.2.3
2324794	2006, Fomesafen technical (147A) Primary eye irritation study in rabbits. Final report (T0001485-06), DACO: 4.2.4
2324795	2006, Fomesafen technical (147A) Primary skin irritation study in rabbits. Final report (T0001486-06), DACO: 4.2.5
2324797	2006, Fomesafen technical (147A) Local lymph node assay. Final report (T0001710-06), DACO: 4.2.6
2324799	2012, Fomesafen technical – Acute oral (gavage) neurotoxicity study in rats. (D41528), DACO 4.5.12
2324803	2013, Fomesafen technical – 13-week dietary combined toxicity and neurotoxicity study in the Wistar rat. Final report. Amendment 1. (D41541), DACO 4.5.13
2413803	2006, Fomesafen technical (147A) Acute oral toxicity up and down procedure in rats final report (T0001483-06), DACO 4.2.1
2413804	Fomesafen – A 28 day immunotoxicity study of fomesafen by oral (dietary) administration in mice using sheep red blood cells as the antigen. Final report (32287), DACO 4.8

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
2817365	2003, USEPA (U.S. Environmental Protection Agency), Proposed OPPTS Science Policy: PPARα-mediated hepatocarcinogesis in rodents and relevance to human health risk assessments. https://archive.epa.gov/scipoly/sap/meetings/web/pdf/peroxisomeproliferatorsciencepolicypaper.pdf
2817366	2003, Klaunig J E, et al. PPARα agonist-induced rodent tumors: modes of action and human relevance Critical Reviews in Toxicology. Vol 33 (6): 655-780. http://www.tandfonline.com/doi/abs/10.1080/713608372
2817364	2005, Fomesafen: Second report of the cancer assessment review committee. US EPA Memorandum. PC Code: 123802, TXR No. 0053835, November 3, 2005. Docket: EPA-HQ-OPP-2010-0122; Document EPA-HQ-OPP-2010-0122-0013.

2817362	2006, Fomesafen sodium: Human health risk assessment for a proposal to amend use on soybeans, and proposals to add uses on cotton, dry beans, and snap beans. US EPA Memorandum. PC Code: 123802. February 28, 2006. Docket: EPA-HQ-OPP-2006-0239; Document EPA-HQ-OPP-2006-0239-0005
2817363	2013, Fomesafen sodium: Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments for the Section 3 registration action on cantaloupe, cucumber, pea (succulent), pumpkin, summer squash, winter squash, watermelon, soybean (succulent) and lima bean (succulent). PC Code: 123803; 123802. July 18, 2013. Docket: EPA-HQ-OPP-2012-0589; Document EPA-HQ-OPP-2012-0589-00104

ii) Unpublished Information

PMRA Document Number	Reference
2413809	2011, Fomesafen data. Sodium salt of fomesafen. US EPA Memorandum. PC Code 123802, July 21, 2011, DACO 12.5
2413811	2012, Fomesafen: Immunotoxicity study in mice. US EPA Memorandum. PC Code: 123803, TXR No. 0056285, April 9, 2012, DACO 12.5

Information Considered in the Dietary Assessment

A. Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
1165184	1996, Fomesafen: Determination of Fomesafen in Green Bean and Other Crops by Gas Chromatography (WRC-95-137;WINO 20319;TMR0626B)(Flex)
1169618	1989, Reflex (Fomesafen:) Magnitude-of-the-Residue Study on Soybeans. P.D. Francis, May 29, 1989. (021-MR88-01;021-MR88-02;RR89-039B;REF.13).(Flex)
1195903	2000, Residue Data Submitted in Support of Minor Use of 1998-0569, Reflex to Control Weeds on Lima Beans, FUNGI-014 – Fomesafen in Lima Beans by GC With Electron Capture Detection, Analytical Methods – Trace Organics and Pesticide Section, University of Guelph,
1199904	1985, Storage Stability of Residues in Deep Frozen Crop Samples
1207905	1986, Soybeans (M4336B)
1215403	1987, Residues in Snap Beans From Trials in Canada During 1986 (M4565B)
1245386	1981, Determination of Residues of PP021 in Soybeans – High Performance Liquid Chromatographic Method
1245388	1981, Flex on Soybeans – Crop Residue Data
1245389	1982, Fomesafen on Soya – Residues #1
1245390	1982, Fomesafen on Soya – Residues #2
1245391	1982, Fomesafen on Soya – Residues #3
1245392	1982, Fomesafen on Soya – Residues #4

PMRA Document Number	Reference
1245393	1984, Fomesafen: Residues in Soybean – Canada Trials 1982
1245395	1984, Fomesafen: Residues in Snap Beans, Kidney Beans & White Beans from Canadian Trials - 1982
1258738	1981, Metabolism in Excised Soya Leaves & in Intact Plants
1258739	1981, Metabolism of 14C-Fomesafen in Excised Soya Bean Leaves
1258740	1982, Characterisation of Metabolites in Soya Beans Following Root Treatment
1258741	1982, Characterisation of Metabolites in Soya Beans Following Root Treatment
1258758	1982, Fomesafen: Residues in Eggs & Tissues of Domestic Fowl Following Repeated Oral Dosing with 14C Fomesafen
1258759	1982, Fomesafen: Metabolites in Eggs, Tissues & Excreta of Domestic Fowl
1258771	1982, Fomesafen: Radioactive Residues in a Goat
1258781	1982, Quantification of Radioactive Residues in Rotational Crops Following Soil Treatment with 14C-Nitrophenyl Labelled Fomesafen
1258782	1983, Fomesafen: Metabolism in a Goat
1258783	1982, Characterization of Residues in Rotational Crops
1258784	1982, Fomesafen Crop Rotation Field Residue Study
1258786	1982, Determination of Residues of Fomesafen in Rotational Crops
1258804	1979, An Investigation of the Fate & Mode of Action of the Herbicide PP021 in Susceptible & Non-Susceptible Species – Preliminary Studies
1258808	1981, Fate of 14C-Nitrophenyl Labelled PP021 in Soya Plants Grown Under Field Conditions and Quantification of the Radioactive Residue in Soya Beans at Harvest
1258809	1982, Characterisation of Radioactive Residues in Soya Beans
2205825	1986, The determination of PP021 in Soybeans - A High Performance Liquid Chromatographic Method
2205826	2010, Fomesafen: Magnitude of the Residue on Cucumber
2208871	1998. Fomesafen - Fate in cotton (*Gossypium hirsutum*)
2208872	2008, 14C-Fomesafen - Nature of residue in tomatoes
2208873	2000, Fomesafen: Metabolism in soybeans
2217821	1998, Fomesafen: Determination of fomesafen in soybeans by gas chromatography with nitrogen/phosphorus detection (WRC-98-146) (WINO 45189)
2217822	1999, Fomesafen: Determination of fomesafen in soybean oil by gas chromatography with nitrogen/phosphorus detection (WRC-99-045) (WINO 45190)
2217823	2006, USEPA DER. Residue Analytical Method - Soybean commodities
2217824	2009, GRM045.01A Analytical method for the determination of residues of fomesafen in crop commodities by LC-MS/MS
2217825	1998, Independent laboratory validation of TMR0800B - Fomesafen: determination of fomesafen in cottonseed and gin trash by gas chromatography
2217826	2009, Validation of analytical method GRM045.01A for the determination of residues of fomesafen in crop commodities by LC-MS/MS
2217827	2008, Fomesafen MRMT PAM test on soybean seed and forage Final Report.

PMRA Document Number	Reference
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2217829	2007, S-metolachlor/fomesafen/glyphosate - Residue levels on soybeans (forage, hay and seed)from trials conducted in Canada during 2006
2245347	2008, Fomesafen - Magnitude of the residue on potato
2245348	2010, Fomesafen - Uptake and metabolism in confined rotational crops
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2245351	2010, Fomesafen - Uptake and metabolism in confined rotational crops
2245352	2010, Fomesafen - Uptake and metabolism in confined rotational crops
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2287199	2009, USEPA DER. 14C-Fomesafen - Nature of the Residue in Tomatoes: Final Report
2294677	2005, USEPA DER. Fomesafen--Fate in Cotton (*Gossypium hirsutum*)
2294678	2005, USEPA DER. Fomesafen: Metabolism in Soybeans
2324071	2009, USEPA DER. Residue Analytical Method - Crops
2324074	2006, USEPA DER. Crop Field Trial - Soybean
2324805	2009, Fomesafen - Magnitude of the residue on pepper (bell and non-bell)
2324807	2009, Fomesafen - Magnitude of residues in or on peanut
2324808	2010, Fomesafen - Magnitude of the residue on cantaloupe
2324809	2010, Fomesafen - Magnitude of the residue on squash
2324811	1998, Fomesafen - Residue levels in cotton from trials conducted in the USA
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2552353	2013, Fomesafen: Magnitude of the Residue on Pea (Dry)
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2552597	2010, Fomesafen: Magnitude of the Residue on Pea (Succulent)

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
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Information Considered in the Occupational and Residential Assessment

A. List of Studies/Information Submitted by the Registrant/Provided by Task Force

i) Studies/Information Submitted by the Registrant

PMRA Document Number	Reference
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ii) Studies/Information Provided by Task Force

PMRA Document Number	Reference
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B. Additional Information Considered

i) Published Information

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Information Considered in the Environmental Assessment

A. Studies/Information Submitted by the Registrant

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1207909	The effect of the dietary inclusion of fomesafen on reproduction in the mallard duck (ICI 338/82134) Published by: Imperial Chemical Industries PLC., Plant Protection Division. Authors: Nicholas l. Roberts; Dennis o. Chanter; R.H. Almond of Huntingdon research centre, Huntingdon, Cambridgeshire. Study finalized: August 20, 1982, DACO: 9.6.3.1
1207910	The effect of the dietary inclusion of fomesafen on reproduction in the bobwhite quail (337/82259). Authors: Nicholas l. Roberts; Dennis O. Chanter; Richard H. Almond of Huntingdon Research Centre, Huntingdon, Cambridgesire. Study finalized: December 8, 1982., DACO: 9.6.3.1
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1207913	Fomesafen: Laboratory testing of the acute oral and contact toxicity to honey bees (RJ0224b). Authors: J.M. Bull; W. Wilkinson. Authorized by: D. Riley. Study finalized: October 20, 1981. Published by; Plant Protection Division., DACO: 9.2.4.1
1207914	Fomesafen: Effect on earthworms (lumbricidae) (RJ0238b). Authors: P.J. Edwards; S.M. Brown. Authorised by: D. Riley. Study finalized: January 26, 1982. Published by: Plant Protection Division., DACO: 9.3.1
1212586	Fomesafen - Degradation in soil under flooded conditions in the lab (rj0269b). Author: D.W. Bewick; C.K.J. Zinner; R.D. White. Authorized: D. Riley. Study finalized: January 11, 1983. Published by; Plant Protection Division, Jealotts Hill Research Station, Bracknell, Bershire., DACO: 8.2.3.1
1215404	Dissipation of residues from soil at Rodney and St. Davids, Ontario, Canada (RJ0566b). Authors: J. Pay; K.J. Harradine; N.C. Atreya. Authorized: R.J. Hemingway. Study finalized: July 28, 1987. Published by: Plant Protection Division, Jealott's Hill Research Station, Bracknell, Berkshire., DACO: 8.3.2.3

1215436	Determination of toxicity of a 25% w/v formulation to the green algae *Selenastrum capricornutum* (bl/b/3076). Authors: D.V. Smyth; J.F. Tapp. Approved by: B.R.H. Williams. Study finalized: July 1987., DACO: 9.8.2
1218640	Adsorption and desorption equilibria in soils (rj0223b). Authors: S.E. Newby; B.G. White. Author: D. Riley. Study finalized: December 9, 1981. Published by: Plant Protection Division., DACO: 8.2.4.1
1218641	Degradation in soil under aerobic conditions in the laboratory. Authors: D.W. Bewick; C.K.J. Zinner; R.D. White. Authorized: D. Riley. Study finalized; December 22, 1982. Published by: the Plant Protection Division, Jealotte Hill Research Station, Bracknell, Berkshire., DACO: 8.2.3.1
1249210	Acute Oral Tox, Skin Irritation & Eye Irritation, DACO: 4.2.1,4.2.4,4.2.5
1249211	Acute Tox & Local Irritation, DACO: 4.2.1,4.2.2
1258315	Fomesafen: 2-Generation Reproduction Study In The Rat (Contd On Roll 212), DACO: 4.5.1
1258763	Hydrolysis under acidic & basic conditions. Authors: J.D. Evans; B.D. Cavell. Study finalized: April 24, 1980. Published by: Plant Protection Division., DACO: 8.2.1
1258765	Photodegradation on a soil surface. Authors: E.A. Curl; J.P. Leahey. Authorized: R.J. Hemingway. Study finalized: December 24, 1981. Published by: Plant Protection Division., DACO: 8.2.1
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1258769	Mobility of fomesafen & its degradation products in soil columns. Authors: M.S. Weissler; N.J. Poole. Authorized by: D. Riley. Report finalized: February 16, 1982. Published by: Plant Protection Division., DACO: 8.2.4.1
1258772	Residue data report - soil (473/pp021b004) Canada. Author: H. Swaine. Experimental scientists: P. Francis; D. Rippington. Study finalized: February 12, 1981., DACO: 8.3.2.3
1258773	Residue data report - soil (473/pp021b001) - Canada. Author: H. Swaine. Experimental scientists: P. Francis; D. Rippington., DACO: 8.3.2.3
1258774	Residue data report - soil (pp021b022) - Canada. Author: J.P. Leahey. Experimental scientists: D.J. Sanderson; W.M.D. Collis. Published by: Imperial Chemical Industries Limited, Plant Division. Study finalized: January 5, 1983., DACO: 8.3.2.3

1258775	Residues in soil - published by: ICI Americas Inc., Agricultural Chemicals Division Research And Development Department. Author: H. Swaine. Experimental scientist: P. Francis; D. Rippington. Published by: Imperial Chemical Industries Limited, Plant Protection Division. Study finalized: February 12, 1981., DACO: 8.3.2.3
1258776	Residues in soil from soybean field trials - Reporter: J.P. Ussary. Approved by: J.P. Ussary. Report finalized: May 6, 1982. (Report series: tmu0803/b revised). Published by: ICI Americas Inc., Agricultural Chemicals Division Research And Development Department., DACO: 8.3.2.3
1258789	Acute Oral Tox - LD50 - Mallard Duck, DACO: 9.6.2.1
1258790	Subacute Dietary Tox - Mallard Duck, DACO: 9.6.2.4
1258791	Subacute Dietary Tox - Bobwhite Quail, DACO: 9.6.2.4
1258794	Acute Tox - 25% W/V Formulation - Rainbow Trout, DACO: 9.5.2.1
1258795	Acute Tox - 25% W/V Formulation - Bluegill Sunfish, DACO: 9.5.2.1
1258796	Tox Of Tech Material And Formulation To First Instar Daphnia Magna, DACO: 9.5.2.1
2821594	Environmental Fate, Ecological Risk And Endangered Species Assessment In Support Of The Registration Of Fomesafen Sodium (PCP123802)

B. Additional Information Considered

i) Published Information

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	De Snoo, G.R. and R. Luttik, 2004, Availability of pesticide-treated seed on arable fields. Pest Management Science 60:501-506.
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ii) **Unpublished Information**

PMRA Document Number	**Reference**
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1763866	Environment Canada, Unpublished Pesticide Science Fund water monitoring data from the Atlantic Region (complete raw dataset from 2003-2008), DACO: 8.6
2681876	Environment Canada's Water Quality Monitoring and Surveillance Division, 2016, Unpublished monitoring data for neonicotinoid insecticides, fungicides (strobins and conazoles), acid herbicides, neutral herbicides, op insecticides, sulfonyls herbicides and carbamate pesticides in Ontario surface water in 2015. DACO: 8.6