Proposed Registration Decision PRD2017-02

Fluensulfone

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

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Overview

Proposed Registration Decision for Fluensulfone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Fluensulfone Technical and Nimitz 480EC, containing the technical grade active ingredient fluensulfone, on cucurbit vegetables and fruiting vegetables, except small tomatoes, for the management of nematodes in soil.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Fluensulfone Technical and Nimitz 480EC.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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

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

Before making a final registration decision on fluensulfone, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on fluensulfone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Fluensulfone?

Fluensulfone is the active ingredient in the commercial product, Nimitz 480EC. The product is to be used for the management of nematodes found in the soil that impact production of fruiting vegetables and cucurbits. Fluensulfone represents a valuable addition to the limited options available to Canadian producers for nematode management.

Health Considerations

Can Approved Uses of Fluensulfone Affect Human Health?

Nimitz 480EC, containing fluensulfone, is unlikely to affect your health when used according to label directions.

Potential exposure to fluensulfone may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

In laboratory animals, the active ingredient fluensulfone was of slight to moderate acute toxicity by the oral route; consequently, the signal word and hazard statement "Warning–Poison" are required on the label. It was of low acute toxicity dermally and through inhalation exposure. Fluensulfone was non-irritating to the eyes and minimally irritating to the skin. It was demonstrated that fluensulfone has the potential to cause an allergic skin reaction; consequently, the hazard statement "Potential Skin Sensitizer" is required on the label.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product (EP) Nimitz 480EC, containing fluensulfone, was low via the oral, dermal and inhalation routes of exposure. It was mildly irritating to the skin and moderately irritating to the eyes; consequently, the signal word and hazard statement "Warning–Eye and Skin Irritant" are required on the label. It was demonstrated that Nimitz 480EC has the potential to cause an allergic skin reaction; consequently, the hazard statement "Potential Skin Sensitizer" is required on the label.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of fluensulfone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment included effects on the liver, kidney and lungs of adult animals and reduced survival of young animals. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and infants, the subpopulation which would ingest the most fluensulfone relative to body weight, are expected to be exposed to less than 21% and 58%, respectively, of the acceptable daily intake. Based on these estimates, the aggregate chronic dietary risk from fluensulfone is not of health concern for all population subgroups.

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than 51% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was infants less than one year old.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using fluensulfone on tomatoes, peppers (bell and non-bell), cucumbers, summer squash and cantaloupes (melons) are acceptable. For the MRLs for this active ingredient on crop commodities, please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management section of Health Canada's website.

Occupational Risks From Handling Nimitz 480EC

Occupational risks are not of concern when Nimitz 480EC is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Nimitz 480EC, as well as field workers re-entering recently treated fields, can come in direct contact with Nimitz 480EC residues on the skin. Therefore, the label specifies that anyone using Nimitz 480EC for chemigation must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes when mixing, loading, and during clean-up and repair, and wear goggles or faceshield during mixing and loading. The label also specifies that anyone using Nimitz 480EC for banded or broadcast applications must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes when mixing, loading, applying, and during clean-up and repair, and wear goggles or faceshield during mixing and loading. The label also requires that applications be incorporated into the soil and workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, risks to handlers are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Fluensulfone Is Introduced Into the Environment?

When used according to label directions, fluensulfone is not expected to pose risks of concern to the environment.

When fluensulfone is sprayed onto soil to protect fruiting vegetables (like tomatoes, peppers) and cucurbits (like cucumber, zucchini) from nematodes, it breaks down quickly and is not expected to move a great distance downward into soil and therefore not likely to reach groundwater. Some fluensulfone is expected to evaporate from the soil surface after it is sprayed. It is not likely to accumulate in plant or animal tissue.

Because it is possible that fluensulfone can enter ponds, streams and rivers after it is sprayed, it can affect aquatic life. Fluensulfone can also affect birds, small mammals and beneficial insects. Without precautions in place on how fluensulfone should be used, the organisms listed above may be affected. Therefore, precautions are required to reduce the environmental exposure to fluensulfone, thereby reducing the environmental risks. When fluensulfone is used in accordance with the label and the required precautions, the resulting environmental risk is considered to be acceptable.

Value Considerations

What Is the Value of Nimitz 480EC?

This product has demonstrated efficacy against agriculturally important nematode species that are harmful to various high value Canadian crops.

Nimitz 480EC will provide Canadian growers an additional valuable option that works against nematode pests in cucurbits and fruiting vegetables.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Nimitz 480EC to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is potential that users can come in direct contact with Nimitz 480EC on the skin, the label specifies that anyone using Nimitz 480EC for chemigation must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes when mixing, loading, and during clean-up and repair, and wear goggles or faceshield during mixing and loading. The label also specifies that anyone using Nimitz 480EC for banded or broadcast applications must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes when mixing, loading, applying, and during clean-up and repair, and wear goggles or faceshield during mixing and loading. In addition, the label requires that workers do not enter treated fields for 12 hours after application, and a standard label statement to protect against drift during application was added to the label.

Environment

Label statements and no-spray buffer zones to reduce the risk of spray drift to aquatic ecosystems are required. Label statements indicating the hazards to birds, small mammals and beneficial insects are required. Label statements indicating the potential for leaching through the soil profile are required. As aromatic petroleum distillates are present in the end-use product Nimitz 480EC, hazard statements are required on the label.

Next Steps

Before making a final registration decision on fluensulfone, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

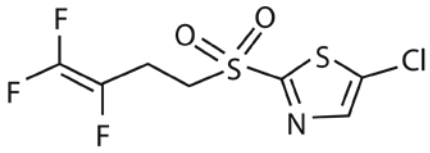
When the PMRA makes its registration decision, it will publish a Registration Decision on fluensulfone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Fluensulfone

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Fluensulfone
Function	Nematicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	5-chloro-2-(3,4,4-trifluorobut-3-en-1-ylsulfonyl)-1,3-thiazole
2. Chemical Abstracts Service (CAS)	5-chloro-2-[(3,4,4-trifluoro-3-buten-1-yl)sulfonyl]thiazole
CAS number	318290-98-1
Molecular formula	$C_7H_5ClF_3NO_2S_2$
Molecular weight	291.7
Structural formula	
Purity of the active ingredient	96.1

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

Technical Product—Fluensulfone Technical

Property	Result
Colour and physical state	Yellow resinous solid
Odour	Characteristic odour
Melting range	34.8°C
Boiling point or range	decomposes before boiling
Density	1.88 g/cm^3
Vapour pressure at 25°C	3.0×10^{-2} Pa (estimated)

Property	Result
Ultraviolet (UV)-visible spectrum	Solution / wavelength (nm) / molar extinction coefficient (l/mol × cm) Neutral / 224 / 3256 271 / 9467 Acidic / 223 / 2470 271 / 8770 Basic / 256 / 5118
Solubility in water at 20°C	5.45 mg/L
Solubility in organic solvents at 20°C	Solvent / Solubility (g/L) Methanol / 359 Xylene / 356 Ethyl Acetate / 351 Acetone / 350 Dichloromethane / 306 n-Octane / 90 n-Heptane / 19
n-Octanol-water partition coefficient (K_{ow})	1.96
Dissociation constant (pK_a)	does not dissociate in the environmental pH range
Stability (temperature, metal)	stable in air to 150°C

End-Use Product—Nimitz 480EC

Property	Result
Colour	Gold coloured or amber
Odour	Used oil
Physical state	Liquid
Formulation type	EC (emulsifiable concentrate)
Guarantee	480 g/L
Container material and description	1–200 L HDPE containers
Density	1.20 g/mL
pH of 1% dispersion in water	5.2
Oxidizing or reducing action	Not an oxidizing substance or reducing substance
Storage stability	Stable on storage for one year in commercial containers
Corrosion characteristics	Not corrosive to commercial packaging materials
Explodability	Not explosive

1.3 Directions for Use

Nimitz 480EC can be applied by broadcast or band spray applications followed by soil incorporation. It can also be applied by drip irrigation. The rate of application for the product is 4 to 8 L/ha applied once per cropping cycle at least seven days before transplanting.

1.4 Mode of Action

Studies have shown that the active ingredient fluensulfone impacts nematodes through a range of effects including direct nematicidal activity likely resulting from affected motility, feeding, reproduction, and development.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70-120%) were obtained in environmental media.

HPLC-MS/MS methods (Method 1977W, equivalent to 2061W, and Method 11M03036-01-VMPL in plant matrices, and Method 11M03036-01-VMAT in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70-120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Extraction solvents used in the methods were similar to those used in the metabolism studies, demonstrating the ability of the methods to efficiently extract bioincurred residues of fluensulfone and butene sulfonic acid (BSA; M-3627) from plant and animal commodities.

Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for fluensulfone was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to fluensulfone.

The results from the majority of the toxicological studies conducted with fluensulfone are summarized in the Evaluation Report for submission number 2015-0283,[5] prepared for the establishment of MRLs in/on imported commodities. The previous evaluation for the establishment of MRLs in/on imported commodities focused on toxicity studies conducted via the oral route. A short summary of the principal findings noted in oral toxicity studies conducted with fluensulfone follows. Detailed information relating to studies conducted via other routes of exposure (for example, dermal and inhalation) that were not discussed in the previous Evaluation Report is also included below.

In acute toxicity testing, fluensulfone was demonstrated to be of slight to moderate toxicity via the oral route and of low toxicity via the dermal and inhalation routes in rats. Fluensulfone was minimally irritating to skin and non-irritating to the eyes of rabbits, and elicited a positive dermal sensitization reaction in a local lymph node assay in mice.

In short- and long-term dietary studies with adult animals, the targets of toxicity were the liver, kidney, thyroid gland, and lung. Slight alterations in hematological parameters were also observed. There was no evidence of dysregulation of the immune system. In an acute neurotoxicity study in rats, potential neurotoxic effects were observed on the day of dosing. However, no signs of neurotoxicity were noted in any other study, including a repeated-dose dietary neurotoxicity study in rats in which the observed effects were attributed to systemic toxicity. Increased fluoride levels in bone and teeth as well as tooth discoloration, observed in several studies, were not considered to be adverse in the absence of structural signs of dental or skeletal fluorosis. In oral gavage developmental toxicity testing, there was no evidence of increased susceptibility of the young in rats or rabbits. In the rat two-generation dietary reproductive toxicity study, reduced postnatal viability, considered a serious endpoint, was observed in the presence of maternal toxicity.

Following repeated dermal or inhalation exposure to fluensulfone, systemic effects were similar in nature to those seen following repeated dietary exposure, such as increases in liver and kidney weight, reticulocytes, cholesterol and/or or triglycerides, and decreases in serum alanine aminotransferase (ALAT) levels. Effects at the site of first contact were also evident, including adaptive acanthosis/hyperkeratosis following dermal application, and squamous metaplasia, epithelial hyperplasia, and focal mononuclear cell infiltrates of the epiglottis as well as squamous

[5] http://pr-rp.hc-sc.gc.ca/pi-ip/adoc-ddoc-eng.php?p_app_id=2015-0283

epithelial hyperplasia of the nasal cavity following inhalation exposure. It is noteworthy that effects at the site of first contact were also noted in the subchronic dietary toxicity study in rats, in which hyperplasia of the forestomach was observed.

Overall, it was concluded that there was no evidence of genotoxicity for fluensulfone. There was no evidence of oncogenicity in rats exposed to fluensulfone via the diet for two years. Chronic dietary dosing with fluensulfone over 18 months resulted in lung tumours in female mice. While a treatment-related increase in lung tumours was not observed in male mice, preneoplasia, in the form of alveolar/bronchiolar hyperplasia (bronchiolization), was evident in both sexes, and a numerical increase in tumour response in males may have been masked by a slightly high incidence of lung tumours in control mice when compared to historical controls.

A proposed mode of action (MOA) for the formation of lung tumours in mice was provided. The involvement of mouse-specific metabolic activation in the lung, namely in the Club cells (formerly known as Clara cells) by mouse-specific CYP 2f2, was identified as a key event required for the tumorigenic response. Humans express another orthologue of this enzyme, CYP 2F1. An abundance of metabolic capacity makes Club cells susceptible to injury by a wide variety of chemicals, often due to covalent binding of reactive metabolites.

The key events in this proposed MOA included (1) extensive metabolism of fluensulfone by the mouse lung, predominantly by the mouse-specific cytochrome P450 isoform CYP 2f2 contained in Club cells, (2) early increased proliferation of Club cells, (3) alveolar/bronchiolar hyperplasia (bronchiolization), and (3) progression of alveolar/bronchiolar hyperplasia to adenomas and carcinomas.

At the time of the evaluation for the establishment of MRLs in/on imported commodities, two mechanistic studies were available to provide support for the proposed MOA. In the first mechanistic study, which included an evaluation of the proliferative cell response in the lung of CD-1 female mice using bromodeoxyuridine (BrdU) incorporation, increased cell proliferation was evident in the bronchiolar epithelium following dosing with fluensulfone in the diet for three days. An increase in cell proliferation was not observed after seven days of dosing. Only one dose of fluensulfone was used in this study, which was comparable to the highest dose tested in the 18-month oncogenicity study in mice. In the second mechanistic study, the in vitro metabolic conversion kinetics of fluensulfone were compared in mouse and human lung microsomes. The study was conducted to determine the contribution of the mouse-specific Cyp 2f2 enzyme, and the CYP 2E1 and CYP 2e1 isoforms, which are expressed in humans and mice, respectively, to the metabolism of fluensulfone. This was accomplished by co-incubation with and without selective inhibitors. No metabolic activity towards fluensulfone was detected after incubation with human lung microsomes. In contrast, fluensulfone was extensively metabolized by lung microsomes of female and male mice. Based on the results of this study, the mouse-specific isoenzyme CYP 2f2 appeared to play a major role in the degradation process.

Although the results of the mechanistic studies suggested that the proposed MOA was plausible in the mouse, the overall weight of evidence, at that time, was considered insufficient to support the proposed MOA due to limitations regarding dose concordance, specificity, and reversibility of key events. As such, human relevance of the lung tumors could not be discounted. Therefore, a unit cancer risk estimate (q1*) was derived for the cancer risk assessment.

Subsequently, three additional mechanistic studies addressing gaps in the proposed MOA for lung tumours were received by the Agency. The first study consisted of an evaluation of the proliferative cell response in the lung of CD-1 male mice after three and seven days of dosing with fluensulfone at one dose level using BrdU incorporation. In the second study, the proliferative cell response in the lung of CD-1 female mice, the strain of mice used in the carcinogenicity study, was examined after three days of dosing with fluensulfone. This study included three dose levels and included immunohistochemical staining of the lung against BrdU and the Ki67 antigen. The second study also included wildtype C57BL/6 female mice, the strain for which a CYP 2f2 knockout type is commercially available. Before testing in the CYP 2f2 knockout mouse model, the cell proliferation response was validated in the lungs of wildtype C57BL/6 mice. For the third study, the proliferative cell response in the lung of C57BL/6-CYP 2f2 knockout female mice was evaluated after three days of dosing with fluensulfone at one dose level using BrdU incorporation.

In these studies, a proliferative response in the bronchiolar epithelium comparable to that observed in CD-1 female mice was observed in CD-1 male mice and in female wildtype C57BL/6 mice. In addition, a dose response in the cell proliferation response was evident in the lungs of both female CD-1 and female C57BL/6 mice, and the proliferating cells in the lungs of CD-1 and C57BL/6 female mice were demonstrated to be Club cells through the use of anti-CC10 (anti-Club cell 10 kD) staining. Notably, there was no increase in bronchiolar epithelial cell proliferation following three days of dosing with fluensulfone in C57BL/6-derived CYP 2f2 knockout mice at a dose level that caused cell proliferation and lung tumours in wildtype mice. Overall, the mechanistic data were considered sufficient to support the proposed MOA that the induction of lung tumors in mice following exposure to fluensulfone likely results from extensive metabolism by the mouse-specific CYP 2f2 enzyme, suggesting that this tumor is not relevant for human health risk assessment.

As outlined in the Evaluation Report for submission number 2015-0283, the metabolites thiazole sulfonic acid (TSA; M-3625) and butene sulfonic acid (BSA; M-3627), which are found in rats, soil, aquatic systems, and crops, were both demonstrated to be of low acute toxicity via the oral route of exposure in rats. A third environmental metabolite that was not detected in the rat, methyl sulfone, was demonstrated to be of moderate acute toxicity via the oral route of exposure in rats. Overall, it was concluded that these three metabolites were not genotoxic. Repeated dietary dosing in rats with the metabolites thiazole sulfonic acid (M-3625) for up to 90 days and butene sulfonic acid (M-3627) for 28 days resulted in no adverse toxicological effects up to limit doses.

Subsequent to the issuance of the Evaluation Report for submission number 2015-0283, a 90-day dietary study in rats conducted with butene sulfonic acid (M-3627) was submitted. Based on the results of these studies, it was concluded that these two metabolites are less toxic than fluensulfone.

During product development, the formulation of the end-use product, Nimitz 480EC, was modified slightly. Based on the results of acute toxicity studies conducted with the development formulation and/or the current formulation, Nimitz 480EC was demonstrated to be of low acute toxicity via the oral, dermal and inhalation routes of exposure in rats. It was mildly irritating to the skin and moderately irritating to the eyes of rabbits. Nimitz 480EC elicited a positive dermal sensitization reaction in a local lymph node assay in mice.

Results of the toxicology studies conducted on laboratory animals with fluensulfone and its metabolites are summarized in Table 1 of Appendix I of the Evaluation Report for submission number 2015-0283. Results of the additional toxicology studies, submitted subsequent to the 2015 evaluation, and those for critical studies relevant to the proposed MOA for lung tumours, are summarized in Appendix I, Table 2 of this document. Appendix I, Table 3 of this document summarizes the results of the acute toxicity studies for the associated end-use product, Nimitz 480EC. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4 of this document.

Incident Reports

Fluensulfone is a new active ingredient pending registration for use in Canada; as such, there have been no incident reports submitted to the PMRA involving fluensulfone. Once products containing fluensulfone are registered, the PMRA will monitor for incident reports.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies, including gavage developmental toxicity studies in rats and rabbits, and a two-generation dietary reproductive toxicity study in rats, was available.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses compared to parental animals in the developmental toxicity studies. Minor developmental effects (reduced fetal weight, accelerated or delayed ossification) were observed in the rat and rabbit developmental toxicity studies; however, these effects occurred in the presence of maternal toxicity as demonstrated by body weight reductions. In the rat, a decrease in the number of viable foetuses was attributed to four dead fetuses in one litter and was considered to be secondary to maternal body weight reductions. In the two-generation reproductive toxicity study, a serious endpoint (reduced pup viability) was observed in the presence of maternal toxicity (reduced body weights, increased liver and kidney weights, and hepatocellular hypertrophy).

Overall, the database is adequate for determining the sensitivity of the young and effects on the young are well-characterized. The *Pest Control Products Act* factor was reduced to 3-fold for exposure scenarios using the point of departure (POD) from the two-generation reproductive toxicity study, in which a serious endpoint was observed in the presence of maternal toxicity. For all other exposure scenarios, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

To estimate acute dietary risk, the two-generation reproductive toxicity study with a no observed adverse effect level (NOAEL) of 18 mg/kg bw/day was selected for risk assessment. At the lowest observed adverse effect level (LOAEL) of 149 mg/kg bw/day for parental females, increased postnatal loss from postnatal day (PND) 1 to 4 was observed in offspring in the presence of reduced body weights, increased liver and kidney weights, and hepatocellular hypertrophy in parental animals. The possibility that the postnatal loss could be the result of a single exposure could not be ruled out; this endpoint is, therefore, 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 *Pest Control Products Act* factor was reduced to 3-fold. The composite assessment factor (CAF) is, thus, 300.

The acute reference dose (ARfD) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{18 \text{ mg/kg bw}}{300} = 0.06 \text{ mg/kg bw of fluensulfone}$$

3.3 Determination of Acceptable Daily Intake

To estimate risk from repeated dietary exposure to fluensulfone, the results from the one-year dietary toxicity study in the dog and the two-year dietary combined chronic toxicity/oncogenicity study in the rat were considered as co-critical. The effect levels established in these studies were similar, and provided the lowest effect levels in the database. In the one-year dog study, the NOAEL of 1.5 mg/kg bw/day was established based on reduced body weight in females at the LOAEL of 3.3 mg/kg bw/day. In the two-year study in the rat, the NOAEL of 1.4/1.7 (males/females) mg/kg bw/day was established, based on effects at the LOAEL of 9.6/11 mg/kg bw/day which included reduced body weight in males and chronic interstitial inflammation of the lungs in females.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. The CAF is, thus, 100.

The acceptable daily intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.5 \text{ mg/kg bw/day}}{100} = 0.02 \text{ mg/kg bw/day of fluensulfone}$$

This ADI provides a margin of 900 to the NOAEL for the increased postnatal loss observed in the two-generation reproductive toxicity study in the rat.

Cancer Assessment

A treatment-related increase in the incidence of lung tumours was observed in female mice administered fluensulfone in the diet for 18 months. However, a proposed MOA for these tumours was supported by the available mechanistic data, demonstrating that the tumours observed in mice are not relevant to humans. Therefore, a cancer risk assessment is not required for fluensulfone.

3.4 Occupational Risk Assessment

Occupational exposures to Nimitz 480EC are characterized as short-term in duration and are predominantly by the dermal and inhalation routes.

3.4.1 Toxicological Endpoints

Short- to Intermediate-Term Dermal

For assessing risk from short- to intermediate-term exposure via the dermal route, the NOAEL of 18 mg/kg bw/day from the two-generation reproductive toxicity study in rats was selected. At the LOAEL of 149 mg/kg bw/day in parental females, increased postnatal loss from PND 1 to 4 was observed in offspring in the presence of reduced body weights, increased liver and kidney weights, and hepatocellular hypertrophy in parental animals. Worker populations could include women of reproductive age and therefore this endpoint was considered appropriate for the occupational risk assessment. Although the database contained a 28-day dermal toxicity study in rats, this study did not assess the relevant endpoints of concern (in other words, developmental effects in pups following pre-natal and/or postnatal exposure).

The target margin of exposure (MOE) is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The concerns outlined in the *Pest Control Products Act* Hazard Characterization section regarding this endpoint are also relevant to the worker population. For these reasons, an additional factor of three-fold was applied to these risk assessments to protect for sensitive subpopulations such as unborn children.

Short- to Intermediate-Term Inhalation

For assessing risk from short- to intermediate-term exposure via the inhalation route, the lowest observed adverse effect concentration (LOAEC) of 0.04 mg/L (equivalent to 11 mg/kg bw/day) from the 90-day inhalation toxicity study in the rat was selected. Effects at this concentration included reduced body weight in males, and respiratory tract lesions (squamous metaplasia, epithelial hyperplasia, and focal mononuclear cell infiltrates of the epiglottis as well as squamous epithelial hyperplasia of the nasal cavity) in both sexes. This study represented the appropriate route and duration of exposure.

The target MOE is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, and a three-fold factor for the use of a LOAEL. The selection of this POD and MOE is considered protective of sensitive subpopulations, such as women of reproductive age, pregnant women, and unborn children.

3.4.1.1 Dermal Absorption

Although in vitro and in vivo dermal absorption studies were submitted, fluensulfone does not meet the requirements of the draft NAFTA triple pack approach. Therefore, the rat in vivo study was chosen to determine a dermal absorption value.

The rat in vivo dermal absorption of fluensulfone was determined using an emulsifiable concentrate containing ^{14}C-labelled active ingredient which was applied to shaved areas on rats at two target dose levels reflecting the undiluted commercial product, and the typical concentration recommended for use in the field. Following an exposure period of 10 hours, representing a typical exposure period of a field worker, application sites were washed, and groups of rats were monitored for 24, 72, and 120 hours after the application, to assess the fate of skin-bound residues. At the termination of the monitoring periods, samples (*stratum corneum* tape strips, application site skin, non-treated skin, whole blood, GI tract, carcass, charcoal paper, 'O'-ring and cover tape) were collected from the rats and analyzed.

There is evidence to suggest that residues continue to be absorbed beyond the exposure period, therefore, all skin-bound residues were considered potentially absorbed. The lower application rate resulted in more absorption of the radiolabelled active ingredient; therefore, the dermal absorption estimate was taken from this dose. Taking into consideration the method and rates of application of the study, and distribution of residues over time, the dermal absorption value of 58% from the in vivo rat study was concluded to be appropriate for risk assessments of fluensulfone.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Nimitz 480EC during mixing, loading and application. Therefore, dermal and inhalation exposure estimates for workers were generated using the Pesticide Handlers Exposure Database (PHED, v.1.1, 2002) to identify appropriate unit-exposures for the mixer/loader and applicator scenarios for each method of application. The default area treated per day (ATPD) for foliar spraying of small area crops is 26 hectares per day and is used as a surrogate for soil surface spraying and chemigation by farmers and custom applicators because of the small size of cucurbit and fruiting vegetable farms.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted.

Exposure to workers mixing, loading, and applying Nimitz 480EC is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer, loaders, and applicators applying Nimitz 480EC to the soil surface using broadcast or banded field spraying, and chemigation. The exposure estimates are based on mixers/loaders and applicators (applicators are not considered necessary for chemigation) wearing a long-sleeved shirt, long pants, chemical-resistant gloves.

Dermal exposure was estimated by coupling the unit-exposure values with the amount of product handled per day and the 58% dermal absorption value. Inhalation exposure was estimated by coupling the unit-exposure values with the amount of product handled per day with 100% systemic absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints to obtain the MOE; the target MOE is 300 for dermal and inhalation exposures; however, they cannot be combined because of differing toxicological effects. An additional protective measure for the acute toxicological hazard is protective eyewear.

Table 3.4.2.1-1 Input Parameters for Mixer, Loader, and Applicator Risk Assessments

Scenario	PPE/engineering controls	Area Treated per Day (ha)	PHED Unit Exposure (µg/kg ai handled)	
			Dermal	Inhalation†
Liquid, Open Mixing/Loading; and Trickle Chemigation (M/L only)	long-sleeved shirt, long pants, chemical-resistant gloves	26	51.14	1.6
Open cab equipment; broadcast or banded application (groundboom) Farmer/Custom	long-sleeved shirt, long pants, and chemical-resistant gloves		32.98	0.96
		Total unit exposure	84.12	2.56

† Light inhalation rate

Table 3.4.2.1-2 Exposure and Risk Estimates for Mixer/Loaders and Applicators of Nimitz 480EC

Application Equipment	Mixer/Loader Scenario	Applicator Scenario	Dermal Exposure [a] (mg/kg bw/day)	Inhalation Exposure [a] (mg/kg bw/day)	Dermal MOE [b] Target= 300	Inhalation MOE [b] Target=300
Drip (trickle) Chemigation	Open mix-load; long-sleeved shirt, long pants, chemical-resistant gloves	Not Applicable	3.70E-02	2.00E-03	486	5509
Banded or Broadcast Spray	Open mix-load; long-sleeved shirt, long pants, and chemical-resistant gloves	open-cab groundboom; long-sleeved shirt, long pants, and chemical-resistant gloves	6.09E-02	3.19E-03	296	3443

Note: for example, E-02 = $\times 10^{-2}$

a. Exposure (mg/kg bw/day) = (AR * UE * ATPD * A * CF) / BW

Where: AR = maximum application rate of 3.84 kg ai/ha;
UE = unit-exposure (µg ai/kg ai handled), PHED scenarios dermal and inhalation routes, for PPE (Table 3.4.2.1-1);
ATPD = area treated per day (26 ha/day);
A = dermal absorption value is 58%; inhalation systemic absorption is considered to be 100%;
CF = conversion factor (0.001 mg/µg);
BW = body weight, adult of 80kg

b. MOE = NOAEL / Exposure [(M/L +A)], for dermal and for inhalation routes

Where: MOE = Margin of Exposure (target is 300 for both routes of exposure);
$NOAEL_{dermal}$ = NOAEL of 18 mg/kg bw/day, based on a reproduction study;
$LOAEL_{inhalation}$ = 11 mg/kg bw/day, based on a 90-day inhalation study

Mixer/loader risks are not of concern for farmers conducting chemigation when wearing a long-sleeved shirt, long pants, and chemical-resistant gloves. Custom applicators and farmers conducting broadcast or banded groundboom applications must wear a long-sleeved shirt, long pants, and chemical-resistant gloves for mixing/loading and application. The dermal margin of exposure for banded or broadcast spray does not meet the target of 300; however, given the conservative nature of the exposure inputs, risks to workers are not expected to be of concern. Also, considering the product was shown to be mildly irritating to the eyes, mixers/loaders will be required to wear goggles or faceshield in addition to the baseline PPE.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Nimitz 480EC, such as inspection of treated soil and transplanting crops. The duration of exposure is considered to be short-term, and the primary route of exposure for workers re-entering treated areas would be through the dermal route. Given the low-contact activities performed and incorporation of the

application into the soil, dermal contact with treated soil is expected to be minimal. Also, a label restricted entry interval (REI) statement requires that workers do not enter treated fields for 12 hours after application. Therefore, a quantitative risk assessment of postapplication exposure is not required.

3.4.3 Residential Exposure and Risk Assessment

There are no residential uses.

3.4.4 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural areas only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products is fluensulfone and the metabolite butene sulfonic acid (BSA; M-3627), expressed as parent equivalents. The residue definition for risk assessment in plant products is fluensulfone. The data gathering/enforcement analytical method is valid for the quantitation of residues of fluensulfone and M-3627 in crop matrices. The residues of fluensulfone and M-3627 are stable in tomatoes for up to 469 days and in peppers, cucumbers and cantaloupes (melons) for up to 488 days when stored in a freezer between -12°C and -20°C. Tomatoes were processed into purée, paste, juice, wet pomace and/or dry pomace according to simulated industrial practice. Residues of fluensulfone were all less than the limit of quantitation (LOQ) in the tomato raw agricultural commodity (RAC) and processed fractions (purée, paste, juice, wet pomace and dry pomace) while quantifiable residues of M-3627 were observed in the same tomato matrices. Processing factors for M-3627 in tomato processed fractions ranged from 0.66- to 6.57-fold. As the petitioned crops are not livestock feed items, no feeding studies were required. Crop field trials conducted throughout Canada and the United States, using an end-use product containing fluensulfone that was applied at approved rates to tomatoes, peppers (bell and non-bell), cucumbers, summer squash and cantaloupes (melons), are sufficient to support the use on cucurbit vegetables and fruiting vegetables, except small tomatoes.

3.5.2 Dietary Risk Assessment

Acute and chronic (non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates food consumption data from the National Health and Nutritional Examination Survey, What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005-2010 available through CDC’s National Center for Health Statistics (NCHS).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the chronic non-cancer analysis for fluensulfone: 100% crop treated, experimental processing factors (where available) and median residues of fluensulfone. The chronic dietary exposure from all supported fluensulfone food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 6.7-21% (0.001346-0.004198 mg/kg bw/day) of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to fluensulfone from food and drinking water is 21% (0.004082 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for infants at 58% (0.011524 mg/kg bw/day) of the ADI.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the acute analysis for fluensulfone: 100% crop treated, experimental processing factors (where available) and maximum fluensulfone residues in/on crops. The acute dietary exposure (food alone) for all supported fluensulfone registered commodities is estimated to be 13% (0.007816 mg/kg bw) of the ARfD for total population (95^{th} percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable: 20% of the ARfD for total population. Specifically, 13-50% of the ARfD was obtained for all population subgroups, with infants less than one year old as the highest exposed population subgroup.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for fluensulfone consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Please refer to the Maximum Residue Limit Database in the Pesticides and Pest Management section of Health Canada's website for the established MRLs for fluensulfone.

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

3.6 Exposure from Drinking Water

3.6.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of fluensulfone in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of fluensulfone in groundwater were calculated using the Pesticide Root Zone Model Groundwater (PRZM-GW) model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are based on the flux, or movement, of pesticide into shallow groundwater with time. EECs of fluensulfone in surface water were calculated using

the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in a vulnerable drinking water source, a small reservoir.

The Level 1 modelling was conducted on the combined residues for fluensulfone (fluensulfone + MS + deschloro-fluensulfone). EECs in surface water were calculated using the PRZM/EXAMS models on standard Level 1 scenarios, a small reservoir. EECs in groundwater were calculated using the PRZM-GW model. All scenarios were run using 50-year weather data.

Information on application rates and timing was considered for the uses of fluensulfone on cucumber, pepper, squash and tomato. The maximum yearly application rate of fluensulfone is 3.84 kg a.i./ha, applied once per year. The typical dates of first application for all uses generally ranged from April through early July, and the starting dates used in the models at Level 1 were chosen accordingly.

Level 1 EECs of the combined residues in potential drinking water sources are given in Table 3.6.1-1. The EECs resulting from this Level 1 assessment were calculated using conservative inputs with respect to application rate and timing, and geographic scenario.

Table 3.6.1-1 Level 1 Estimated Environmental Concentrations of the Combined Residues of Fluensulfone (Fluensulfone+MS+Deschloro-Fluensulfone) in Potential Sources of Drinking Water.

Crop	Groundwater (µg a.i./L)			Surface Water (µg a.i./L)		
Cucumber, pepper, squash and tomato (1 × 3.9 kg a.i./ha)	Daily[1]	Yearly[2]	Average[5]	Daily[3]	Yearly[4]	Average[6]
	107	101	84	36	3.9	1.8

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations
5 50-year simulation post breakthrough average
6 50-year simulation average

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate and behaviour of fluensulfone in the terrestrial and aquatic environment are summarized in Appendix I, Tables 7-10.

Fluensulfone is soluble in water but does not contain acidic or basic functional groups that will readily dissociate in water. The transformation products, thiazole sulfonic acid (TSA; M-3625), butene sulfonic acid (BSA; M-3627), deschloro-fluensulfone, thiazole methyl sulfone (MS; M-3626), and butene sulfinic acid exhibit very high solubilities in water. Based on its octanol-water partition coefficient, fluensulfone is not expected to bioaccumulate. TSA, BSA, deschloro-fluensulfone, MS and butene sulfinic acid exhibit log K_{ow} values indicating bioaccumulation is negligible for these compounds. The calculated Henry's Law Constant for fluensulfone indicates

it is slightly volatile from moist soil and water. This characteristic of slight volatility was evident in a laboratory study (phototransformation on soil) where a small fraction of the applied fluensulfone was captured in traps for volatile organics.

Fluensulfone is stable to hydrolysis under environmental conditions (pH 4, pH 7 and pH 9). On soil, phototransformation is not an important route in the transformation of fluensulfone. In water, however, phototransformation is an important route in the transformation of fluensulfone. Fluensulfone rapidly phototransforms in water to numerous polar compounds which further phototransform to three major polar fractions (unidentified). In air, phototransformation is an important route in the transformation of fluensulfone, hence, long-range atmospheric transport is not anticipated.

Under laboratory conditions, fluensulfone is non-persistent in aerobic soil. TSA is the major transformation product which is persistent in aerobic soil. BSA is also a major transformation product but is slightly persistent in aerobic soil. In anaerobic soil, fluensulfone is persistent with TSA and BSA being minor transformation products.

Results of the terrestrial field dissipation study confirm those of the aerobic soil studies. Fluensulfone was shown to be non-persistent in soil by readily transforming to the major transformation product, TSA, which was shown to be persistent in soil. In addition, BSA was shown to have slight persistence in soil under field conditions.

Under laboratory conditions, fluensulfone has medium mobility in soil and is classified as a borderline leacher. MS, TSA and BSA are classified as having high to very high mobility in soil. Under terrestrial field conditions, however, fluensulfone showed limited mobility as it did not leach below the top soil layer. TSA did leach through the soil profile, thereby confirming the results of laboratory studies. BSA and MS, however, being slightly persistent, dissipated to concentrations below the LOQ in the top soil layer and were not detected at greater soil depths.

In aerobic water/sediment systems, fluensulfone is moderately persistent. The major transformation products are TSA, BSA and deschloro-fluensulfone. With time, residues of fluensulfone will partition out of the aqueous phase and accumulate in sediment. Subsequently, residues become tightly bound to sediments over time. Extractable residues in sediment decreased over time with a corresponding increase in non-extractable residues.

In anaerobic water/sediment systems, fluensulfone is slightly persistent. The major transformation products are MS, deschloro-fluensulfone, butene sulfinic acid and BSA. TSA is a minor product detected only in the water layer. With time, residues of fluensulfone will partition out of the aqueous phase and accumulate in sediment. Subsequently, residues become tightly bound to sediments over time leading to an increase in non-extractable residues.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse ecological effects. This integration is achieved by comparing exposure concentrations (i.e. the estimated environmental concentration, EEC) with concentrations at which adverse effects occur (for example, toxicity endpoints such as

LC50, LD50, NOEC or NOEL). For characterizing acute risk, acute toxicity values (for example, LC50, LD50, and EC50) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (in other words, feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the NOEC or NOEL is used and an uncertainty factor is not applied.

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 RQ is then compared to the level of concern (LOC = 1 for most species, 0.4 for pollinators and 2 for beneficial arthropods (acute screening tests for predatory mite and parasitoid wasp)). 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 RQ is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

The environmental risk of fluensulfone and its related end-use product to non-target organisms was assessed based upon the maximum annual application rate to fruiting vegetables (like tomatoes, peppers) and cucurbits (like cucumber, zucchini).

4.2.1 Risks to Terrestrial Organisms

Appendix I, Table 12 summarizes the screening level risk assessment for terrestrial organisms other than birds and mammals resulting from the broadcast application of fluensulfone. Of these terrestrial organisms, the LOC is exceeded in the parasitic wasp, predatory mite and in vascular plants with RQ values of 247, 4.0 and 2.7, respectively.

Appendix I, Table 13 summarizes the refined risk assessment for those terrestrial species (other than birds and mammals) where the LOC was exceeded in the screening level risk assessment. The refined assessment considered the off-target spray drift at 1 m off-field when fluensulfone is used as a broadcast application using field sprayers. Here, the refined EEC of 240 g a.i./ha resulting from spray drift was used to assess the risk to terrestrial arthropods and non-target plants.

Earthworms
The screening level RQ for earthworms was determined to be <1, thereby indicating a negligible risk from acute and chronic exposure to fluensulfone.

Honeybee
The screening level RQ for honeybees was determined to be <1 on the basis of acute exposure to fluensulfone, indicating that the risk is negligible.

Beneficial arthropods
At the screening level, the LOC was exceeded in the parasitic wasp and the predatory mite with respective RQs of 247 and 4.0 from acute exposure to fluensulfone. Effects on reproduction were negligible (RQ<1) in the predatory mite as well as in the springtail and ground-active beetle. At the refined level of assessment, the parasitic wasp (*Aphidius rhopalosiphi*) was the only species tested where the LOC was exceeded (RQ = 14.8) from exposure to spray drift at 1 m off-field.

Terrestrial plants
A screening level RQ of 2.7 was determined for terrestrial plants indicating that the LOC was exceeded with exposure to fluensulfone at the maximum seasonal rate . At the refined level of assessment, the risk to terrestrial plants was negligible (RQ<1) through exposure from spray drift at 1 m off-field.

Birds and Mammals
Appendix I, Tables 14 and 15 summarize the risk to birds and mammals respectively, resulting from the broadcast application of fluensulfone. In birds, RQ values range from 0.10-5.2 for on-field exposure with exceedance in the LOC (RQ>1) occurring largely on a chronic reproductive basis. For off-field exposure in birds, the RQ values were <1 indicating a negligible risk. In small mammals, RQ values range from 0.45-20.18 for on-field exposure indicating an exceedance in the LOC. For off-field exposure in small mammals, the RQ values were <1 indicating a negligible risk. There were two exceptions in the off-field exposure where the LOC was exceeded (RQ>1) on a chronic reproductive basis.

4.2.2 Risks to Aquatic Organisms

Appendix I, Table 16 summarizes the screening level risk to aquatic organisms. Of the aquatic organisms, green algae was the most sensitive taxonomic group (RQ=66.7). Other groups where the LOC was exceeded include freshwater and marine invertebrates, fish and amphibians.

Appendix I, Table 17 summarizes the refined aquatic risk assessment for those species where the LOC was exceeded in the screening level risk assessment.The refined assessment considered the off-target spray drift at 1 m off-field when fluensulfone is used as a broadcast application using field sprayers. Here, the refined EEC of 0.03 mg a.i./L (0.80 m deep pond) resulting from spray drift is used to assess the risk to aquatic invertebrates, fish and algae whereas for amphibians, the risk is assessed using the EECs of 0.16 mg a.i./L (0.15 m deep pond). In addition, the refined assessment considered the surface runoff of fluensulfone entering aquatic habitats.

For aquatic invertebrates, fish and algae, the EEC (96-h) of 0.014 mg a.i./L (0.80 m deep pond) resulting from surface runoff is used to assess the acute risk, whereas for the chronic risk, the EEC (21-day) of 0.011 mg a.i./L is considered. For amphibians, the risk is assessed using the EEC (96-h) of 0.057 mg a.i./L (0.15 m deep pond).

Freshwater invertebrates
At the screening level, the LOC was exceeded in *Daphnia magna* on an acute and chronic basis as the RQs were determined to be 2.6 and 2.5, respectively. At the refined level of assessment, the risk to *Daphnia magna* on an acute and chronic basis was negligible (RQ<1) for exposure to spray drift and surface runoff.

Marine invertebrates
At the screening level, the LOC was exceeded in the saltwater mysid and Eastern oyster on an acute basis as the RQs were determined to be 4.2 and 12.8, respectively. At the refined level of assessment, the risk to saltwater mysid and Eastern oyster on an acute basis was negligible (RQ<1) for exposure to spray drift and surface runoff.

Freshwater fish
At the screening level, the LOC was exceeded in the bluegill sunfish on an acute basis as the RQ was determined to be 2.0. The LOC was not exceeded (RQ<1) in the fathead minnow. At the refined level of assessment, the risk to the bluegill sunfish on an acute basis was negligible (RQ<1) for exposure to spray drift and surface runoff.

Amphibians
At the screening level, the LOC was exceeded in amphibians on an acute basis as the RQ was determined to be 10.8. At the refined level of assessment, the risk to amphibians on an acute basis was negligible (RQ<1) for exposure to spray drift and surface runoff.

Freshwater Algae
At the screening level, the LOC was exceeded in algae on an acute basis as the RQ was determined to be 66.7. At the refined level of assessment, the LOC was exceeded (RQ=4.0) for exposure to spray drift and from exposure through surface runoff (RQ=1.9).

Freshwater Macrophytes
At the screening level, the acute risk to *Lemna gibba* was negligible as the RQ was determined to be <1.

Marine algae
At the screening level, the acute risk to the diatom, *Skeletonema costatum*, was negligible as the RQ was determined to be <1.

Of the aquatic organisms, green algae was the only taxonomic group where the LOC was exceeded from exposure to spray drift at 1 m off-field (RQ=4.0) and from exposure through surface runoff (RQ=1.9). In all other organisms, the risk from spray drift and surface runoff was negligible (RQ<1).

4.2.3 Risk Mitigation

Environmental risks are identified (LOC exceeded) in birds, small mammals, beneficial arthropods (parasitic wasp) and freshwater algae. In addition, there are concerns with the leaching potential of the transformation product TSA. To address these environmental concerns, the following mitigation measures, precautions and hazard warnings are required for Nimitz 480EC:

- Fluensulfone can enter aquatic habitats through spray drift. The observance of buffer zones can effectively mitigate the risk of spray drift to aquatic organisms. Pesticide spray drift from field sprayers (ground boom) is predicted using a model that is based on the data of Wolf and Caldwell (2001). Buffer zones are required for broadcast applications of fluensulfone to mitigate spray drift.
- The transformation products of fluensulfone can leach through the soil profile and have the potential to reach groundwater. Precautionary measures must be included on product labels to minimize leaching.
- Fluensulfone can pose a risk to birds, small mammals and beneficial arthropods. Hazard warnings must be included on product labels to minimize these risks.

4.2.4 Environmental Incident Reports

No incident reports were available. This is a new active ingredient and incident reports are not expected.

5.0 Value

5.1 Consideration of Benefits

Registration of fluensulfone and the end-use product Nimitz 480EC will offer Canadian growers a new soil treatment to reduce the impact of nematode pests on the production of cucurbits and fruiting vegetables. Current options for these uses are limited to a small number of restricted conventional fumigants (methyl bromide, chloropicrin, dazomet) or biological fumigants with claims of lower levels of efficacy. Due to the limited choice of options to manage nematodes in Canada and its novel mode of action, fluensulfone is a valuable alternative nematicide.

The use patterns being registered for fluensulfone are generally compatible with cultural and other non-chemical nematode management practices, which include selection of tolerant varieties, sanitation, and crop rotation.

5.2 Effectiveness Against Pests

Efficacy data from a total of 43 small scale efficacy trials conducted between 2008 and 2011 submitted to support the value of claims against root-knot nematodes and lesion nematodes in fruiting vegetables and various cucurbit vegetables. The trials were located either in Canada or the United States.

Efficacy against lesion nematodes was demonstrated through observations of significant reductions in nematode populations during the course of a growing season. In the case of root-knot nematodes, significant reductions in symptoms caused by this type of nematode were reported as a result of fluensulfone applications.

5.3 Non-Safety Adverse Effects

Phytotoxicity resulting from applications of fluensulfone was not reported in any of the available trial data. There is no indication that non-safety adverse effects would result from Nimitz 480EC use when applied in accordance with label directions and restrictions

5.4 Supported Uses

The use of Nimitz 480EC was supported for single seasonal applications at rates of 4 to 8 L/ha to manage root-knot and lesion nematodes on fruiting vegetables and cucurbit vegetables. The product is to be applied either through drip irrigation or as a soil-directed spray followed by incorporation.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, fluensulfone and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Fluensulfone does not meet any Track 1 criteria.
- Fluensulfone does not meet the Track 1 criterion for persistence because of the half-life values in soil (7-14 days) aquatic systems (56-59 days) and air (half-life = 0.94 days).
- One major transformation product, TSA, meets the Track 1 criterion for persistence because of its half-life in aerobic soil (315-561 days).
- Fluensulfone does not meet the Track 1 criterion for bioaccumulation, as its octanol-water partition coefficient (log K_{ow} = 2.2) is below the Track 1 criterion.
- The major transformation products, TSA, BSA, MS, deschloro-fluensulfone and butene sulfinic acid do not meet the Track 1 criterion for bioaccumulation, as the octanol-water partition coefficient values (log K_{ow} =-3.5 to 0.93) are below the Track 1 criterion.

[6] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical 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*.[7] The list is used as described in the PMRA Notice of Intent NOI2005-01[8] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[9], 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 Fluensulfone and the end-use product Nimitz 480EC do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*
- The end-use product, Nimitz 480EC, contains an aromatic petroleum distillate as a formulant, which is an environmental concern pertaining to toxicity to aquatic organisms. Hazard statements are required on the label.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for fluensulfone is adequate to define the majority of toxic effects that may result from exposure. In short- and long-term studies with adult animals, the targets of toxicity were the liver, kidney, thyroid gland, and lung. Slight alterations in hematological parameters were also observed. Increased fluoride levels in bones and teeth as well as tooth discoloration were observed in several studies; however, in the absence of structural signs of dental or skeletal fluorosis, these findings were not considered adverse. Irritation at the point of contact was observed in repeated-exposure dermal and inhalation toxicity studies. There was no evidence of disregulation of the immune system or overt neurotoxicity. There was no evidence of increased susceptibility of the young in rabbits. In the rat, reduced postnatal viability, considered a serious endpoint, was observed in the presence of maternal toxicity.

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7 *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*.

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

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

Chronic dosing with fluensulfone resulted in lung tumours in female mice that were deemed not relevant to human health risk assessment. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders, and applicators handling Nimitz 480EC, and workers re-entering treated fields are not expected to be exposed to levels of Nimitz 480EC that will result in an unacceptable risk when Nimitz 480EC is used according to label directions. The personal protective equipment and the restricted entry interval on the product label are adequate to protect workers. Bystander exposures are not expected to result in risks of concern.

The nature of the residues in plants is adequately understood. The residue definition for enforcement for primary and rotational crops is fluensulfone and the metabolite M-3627, expressed as fluensulfone equivalents. The proposed use of fluensulfone on fruiting vegetables and cucurbit vegetables does not represent a health concern, based on acute and chronic dietary exposures (food and drinking water), to all segments of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to support the use on cucurbit vegetables and fruiting vegetables, except small tomatoes. For the MRLs for this active ingredient on crop commodities, please refer to the Maximum Residue Limit Database in the Pesticides & Pest Management section of Health Canada's website.

7.2 Environmental Risk

Fluensulfone is soluble in water and is stable to hydrolysis under environmental conditions (pH 4, pH 7 and pH 9). Based on its Henry's Law Constant, fluensulfone is classified as slightly volatile which was also demonstrated under laboratory conditions. Fluensulfone has a low potential to bioaccumulate as indicated by its low octanol-water partition coefficient.

Fluensulfone is non-persistent in aerobic soil under terrestrial field conditions and in laboratory studies. Phototransformation on soil is not an important route in the transformation of fluensulfone. Fluensulfone is classified as moderately mobile under laboratory conditions and is not expected to leach below the top soil layer under field conditions. TSA is the major transformation product in aerobic soil and is classified as persistent. BSA is also a major transformation product in aerobic soil but is slightly persistent. Under anaerobic soil conditions, fluensulfone is persistent. TSA, BSA and MS, have high to very high mobility in soil and are expected to leach to groundwater.

In water, phototransformation within the photic zone is an important route in the transformation of fluensulfone, potentially forming three major (unidentified) transformation. Under aerobic aquatic conditions, fluensulfone is moderately persistent with TSA, BSA and deschloro-fluensulfone as the major transformation products. In anaerobic aquatic conditions, fluensulfone is slightly persistent with MS, deschloro-fluensulfone, butene sulfinic acid and BSA as the major transformation products. Over time, residues of fluensulfone are expected to accumulate in the sediment of aquatic systems.

On the basis of the TSMP assessment, fluensulfone and the major transformation products, TSA, BSA, deschloro-fluensulfone, MS and butene sulfinic acid do not meet all the criteria for a Track I substance**.**

Overall, the highest environmental risk was attributed to the end-use product, Nimitz 480EC, compared to the technical grade active ingredient (TGAI). Of the terrestrial arthropods, the parasitic wasp (*Aphidius rhopalosiphi*) is the only species tested where the LOC was exceeded from exposure to spray drift at 1 m off-field. In birds, the LOC was exceeded for on-field exposure, whereas, for off-field exposure, the risk was negligible. In mammals, the LOC was exceeded for on-field and off-field exposure. In terrestrial plants, the risk is negligible from exposure to spray drift at 1 m off-field. Of the aquatic organisms, green algae is the most sensitive taxonomic group where the LOC was exceeded from exposure to spray drift and surface runoff. In all other organisms, the risk from spray drift (at 1 m off-field) and surface runoff is negligible.

Environmental risks are identified (LOC exceeded) in birds, small mammals, beneficial arthropods (parasitic wasp) and freshwater algae. In addition, there are concerns with the leaching potential of the transformation product TSA, and with a formulant (aromatic petroleum distillate) in the end-use product. To address these environmental concerns, mitigation measures, precautions and hazard warnings are required for the end-use product, Nimitz 480EC.

7.3 Value

The value information submitted was sufficient to support the registration of nematicidal claims against root-knot and lesion nematodes in two vegetable crop groups; i.e. cucurbits and fruiting vegetables. Intended for pre-planting soil-directed applications, Nimitz 480EC will be valuable in the preparation of field sites to be used for the production of economically important horticultural crops in Canada. The new mode of action will be a valuable addition to a limited set of currently registered options for nematode management in Canada.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Fluensulfone Technical and Nimitz 480EC, containing the technical grade active ingredient fluensulfone, for the management of nematodes in soil that impact production of fruiting vegetables and cucurbit vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	microgram(s)
µM	micromolar
ADI	acceptable daily intake
a.i.	active ingredient
ALAT	alanine aminotransferase
AR	applied radioactivity
ARfD	acute reference dose
ASAT	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
BrdU	bromodeoxyuridine
BSA	butene sulfonic acid / 3,4,4-trifluoro-but-3-ene-1-sulfonic acid / M-3627
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CC10	Club cell 10 kD protein
CF	conversion factor
CG	crop group
cm	centimetre(s)
CYP	cytochrome P450 protein
DAP	day(s) after planting
DAT	day(s) after treatment
DEEM	Dietary Exposure Evaluation Model
DFOP	double first-order in parallel
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EC	emulsifiable concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
EH	epoxide hydrolase
EP	end-use product
ER_{50}	effective rate on 50% of the population
EROD	7-ethoxyresorufin deethylase
EXAMS	Exposure Analysis Modelling System
fc	food consumption
FCID	Food Commodity Intake Database
FDA	*Food and Drugs Act*
g	gram(s)
GI	gastrointestinal

GAP	good agricultural practice
GST	glutathione-S-transferase
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
IORE	indeterminate order rate equation model
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
Ki67	cellular marker for proliferation
K_{oc}	organic-carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LA12OH	lauric acid 12-hydroxylase activity
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LSC	liquid scintillation counting
LR_{50}	lethal rate 50%
M-3625	thiazole sulfonic acid (TSA)
M-3626	thiazole methyl sulfone (MS)
M-3627	butene sulfonic acid (BSA)
MAS	maximum average score for 24, 48 and 72 hours
MCH	mean corpuscular hemoglobin
MCW-2	fluensuflone
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	thiazole methyl sulfone / 5-chloro-2-methylsulfonyl thiazole / M-3626
MS/MS	tandem mass spectrometry
N/A	not applicable
NAFTA	North American Free Trade Agreement
NCHS	National Center for Health Statistics
NHANES/WWEIA	National Health & Nutritional Exam Survey/What We Eat in America
nm	nanometer(s)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand White

Pa	pascal(s)
PBI	plant-back interval
PES	postextraction solids
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POD	point of departure
PPE	personal protective equipment
PPI	pre-planting interval
ppm	parts per million
PRZM-GW	Pesticide Root Zone Model Groundwater
RAC	raw agricultural commodity
RDW	red blood cell distribution width
REI	restricted entry interval
rel.	relative
RQ	risk quotient
SDH	sorbitol dehydrogenase
SFO	single first-order rate model
TGAI	technical grade active ingredient
TLC	thin layer chromatography
TRR	total radioactive residue
TSA	thiazole sulfonic acid / 5-chloro-thiazole-2-sulfonic acid / M-3625
TSMP	Toxic Substances Management Policy
uv	ultraviolet
WBC	white blood cell
wc	water consumption
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	1977W (equivalent to 2061W)	Fluensulfone; M-3627	HPLC-MS/MS Data-gathering/ Enforcement	0.01 ppm per analyte	Tomato, pepper, cucumber, melon	PMRA# 2181331
	11-009	Fluensulfone; M-3627	HPLC-MS/MS ILV of 1977W	0.01 ppm per analyte	Tomato, cucumber	PMRA# 2181390
	11M03036-01-VMPL	Fluensulfone; M-3627	HPLC-MS/MS Data-gathering/ Enforcement	0.01 ppm per analyte	Orange flesh, wheat grain, peanut	PMRA# 2181370
	R-27478	Fluensulfone; M-3627	HPLC-MS/MS ILV of 11M03036-01-VMPL	0.01 ppm per analyte	Lemon, wheat grain, peanut	PMRA# 2181384
Animal	11M03036-01-VMAT	Fluensulfone; M-3627	HPLC-MS/MS Data-gathering/ Enforcement	0.01 ppm per analyte	Liver, kidney, meat, eggs, milk, fat	PMRA# 2181387
	R-29562	Fluensulfone; M-3627	HPLC-MS/MS ILV of 11M03036-01-VMAT	0.01 ppm per analyte	Milk, eggs, meat, liver, fat	PMRA# 2181389
Soil	2049W	fluensulfone (MCW-2)	HPLC-MS/MS 292 → 166 *m/z*	0.01 mg/kg		PMRA# 2181179 PMRA# 2181182
		M-3625	HPLC-MS/MS 198 → 82 *m/z*			
		M-3626	HPLC-MS/MS 198→ 135 *m/z*			
		M-3627	HPLC-MS/MS 189 → 81 *m/z*			
Water	1870W	fluensulfone (MCW-2)	HPLC-MS/MS 292 → 89 *m/z*	0.05 µg/L		PMRA# 2181183 PMRA# 2257040
		Des-chloro-MCW-2	HPLC-MS/MS 258 → 132 *m/z*			
		M-3625	HPLC-MS/MS 198→ 82 *m/z*			
		M-3626	HPLC-MS/MS 198 → 120 *m/z*			
		M-3627	HPLC-MS/MS 189 → 80 *m/z*			

Table 2 Summary of Selected Toxicity Studies for Technical Fluensulfone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.)

Study Type / Animal / PMRA #	Study Results
Acute dermal Rat (Wistar) PMRA 2181197	Low Toxicity LD_{50} > 2000 mg/kg bw
Acute inhalation Rat (Wistar) PMRA 2181198	Low Toxicity LC_{50} > 5.1 mg/L
Dermal irritation Rabbit (NZW) PMRA 2181199	Minimally Irritating MAS = 0.56 MIS = 1.0 (1 and 24 hours)
Eye irritation Rabbit (NZW) PMRA 2181200	Non-Irritating MAS = 0 MIS = 0
Dermal sensitization (Maximization) Guinea pig (Dunkin Hartley) PMRA 2181201	Potential Dermal Sensitizer
28-day dermal Rat (Wistar) PMRA 2181209	NOAEL = 400 mg/kg bw/day LOAEL = 2000 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↓ fc week 4, ↑ prothrombin time, ↑ rel. spleen wt (♂); ↓ fc week 1, ↑ RDW, ↑ reticulocytes, ↓ MCH, ↑ cholesterol, ↓ serum ALAT (♀). Treatment with vehicle alone or fluensulfone in the vehicle led to ↑ incidence and/or severity of acanthosis/hyperkeratosis in treated skin of ♂ at ≥ 400 and ♀ at 2000 mg/kg bw/day when compared to untreated sites of control animals. The presence of fluensulfone enhanced this finding.

Study Type / Animal / PMRA #	Study Results
14-day inhalation (range-finding) Rat (Wistar) PMRA 2257061	NOAEL and LOAEL not established (range-finding study) Effects at 0.35 mg/L (95 mg/kg bw/day): ↓ bw, ↓ fc; ↑ rel. kidney wt, ↓ spleen wt (♂). Effects at 3.5 mg/L (950 mg/kg bw/day): clinical signs (piloerection, soiled fur, blepharospasm, hunched posture, hypoactivity), ↑ wc, ↑ rel. lung wt, ↑ rel. liver wt, white discolouration at base of lower incisors; 1 ♀ killed moribund day 8, ↑ rel. kidney wt, ↓ spleen wt (♀).
90-day inhalation Rat (Wistar) PMRA 2257061	NOAEC not established as effects observed down to lowest concentration tested LOAEC = 0.04 mg/L (11 mg/kg bw/day) Effects at LOAEC: ↑ wc, squamous metaplasia of epiglottis; ↓ bw, ↓ bwg, ↓ fc, ↓ glucose, ↑ phosphate, ↓ thymus wt, epithelial hyperplasia of epiglottis, focal mononuclear cell infiltrate of epiglottis, squamous epithelial hyperplasia of nasal cavity (♂); pale lower incisors, ↑ prothrombin time (♀).
18-month oncogenicity (dietary) Mouse (CD-1) PMRA 2181218	NOAEL = 4/6 mg/kg bw/day (♂/♀) LOAEL = 27/39 mg/kg bw/day Effects at LOAEL: ↑ EH, ↑ SDH, ↑ incidence and severity of bronchiolization in lungs [hypertrophy of epithelium (Club cells) lining the terminal bronchioles (change from flattened cells to cuboidal cells)]; ↓ bw, ↓ bwg, ↓ prostate wt (♂); ↓ WBC, ↓ neutrophils, ↓ eosinophils, ↓ monocytes, ↑ serum ALAT, ↑ ASAT, lung nodules, ↑ hepatic P450 content, ↑ EROD, ↑ LA12OH, ↑ GST (♀). <u>Lung tumours in ♀</u> Alveolar/bronchiolar adenomas: 2, 4, 14**, 9* (4%, 8%, 28%, 18%) Alveolar/bronchiolar carcinomas: 2, 1, 1, 4 (4%, 2%, 2%, 8%) (trend*) Combined adenomas/carcinomas: 3, 5, 15**, 12* (trend*) * statistically significant ($p<0.05$) ** statistically significant ($p<0.01$) Evidence of oncogenicity, based on a treatment-related increase in alveolar/bronchiolar adenomas and carcinomas in ♀ mice. There was also a reduced latency to onset of adenomas and carcinomas in ♀ at 1200 ppm.

Study Type / Animal / PMRA #	Study Results
Special Study Comparative biotransformation in human and mice lung microsomes CD-1 mice, humans PMRA 2181219	2 µM: No metabolism of fluensulfone was detectable with human lung microsomes. In lung preparations from mice, only approximately 10% of the original fluensulfone remained after 120 minutes. The inhibition of mouse-specific Cyp2f2 (with 5-phenyl-1-pentyne) had a more pronounced effect on the degradation of fluensulfone than inhibition of Cyp2e1 in mice and CYP2E1 in humans (with 4-methyl pyrazole), although the metabolic activity towards fluensulfone was not abolished completely. 20 µM: Concentration of 20 µM fluensulfone was found to be too high and the turnover was limited, and therefore was not used for evaluation
Special Study 3- and 7-day dietary mechanistic lung toxicity study in mice Mouse (CD-1) PMRA 2181220	1200 ppm: ↑ BrdU positive cells in epithelium of bronchioles after 3 days of dosing. Severity and incidence similar to that observed with positive control. No difference in BrdU incorporation into the lung after 7 days of dosing.
3- and 7-day dietary mechanistic lung toxicity study in ♂ mice Mouse (CD-1) PMRA 2635356	1200 ppm: ↑ BrdU positive cells in epithelium of bronchioles after three days of dosing.
3-day dietary mechanistic lung toxicity study in ♀ mice Mouse (CD-1 and C57BL/6) PMRA 2635357	30 ppm: possible ↑ BrdU and Ki67 positive cells in C57BL/6 mice. ≥ 200 ppm: clear ↑ BrdU and Ki67 positive cells in epithelium of bronchioles in both strains of mice. 1200 ppm: moderate ↑ in bronchiolar cells with CC10 antibodies in both strains of mice.

Study Type / Animal / PMRA #	Study Results
3-day dietary mechanistic lung toxicity study in Cyp2f2 knock-out ♀ mice Mouse (C57BL/6-Cyp2f2^{tm1Ding}) PMRA 2635358	200 ppm: No significant ↑ BrdU or Ki67 positive cells in epithelium of bronchioles in Cyp2f2 knock-out mice.
90-day oral (dietary) Metabolite #3627 (butene sulfonic acid) Rat (Wistar) PMRA 2609867	NOAEL = 851/974 mg/kg bw/day No adverse treatment-related effects were observed.

Table 3 Toxicity Profile of Nimitz 480EC Containing Fluensulfone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral (Acute Toxic Class) – Development Formulation Rat (Wistar) PMRA 2181350	**Slight Toxicity** LD_{50} = 300-2000 mg/kg bw (cut-off 1000 mg/kg bw)
Acute oral (Acute Toxic Class) – Current Formulation Rat (Wistar) PMRA 2181380	**Low Toxicity** LD_{50} > 2000 mg/kg bw
Acute dermal – Development Formulation Rat (Wistar) PMRA 2181351	**Low Toxicity** LD_{50} > 2000 mg/kg bw

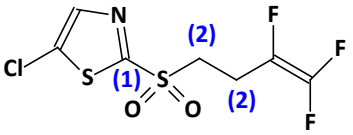
Study Type/Animal/PMRA #	Study Results
Acute inhalation – Development Formulation Rat (Wistar) PMRA 2181355	**Low Toxicity** LC_{50} > 6.0 mg/L
Dermal irritation - Development Formulation Rabbit (NZW) PMRA 2181353	**Moderately Irritating** MAS = 3.4 MIS = 3.7 (24 and 48 hours)
Dermal irritation – Current Formulation Rabbit (NZW) PMRA 2181381	**Mildly Irritating** MAS = 2.33 MIS = 3.33 (1 hour)
Eye irritation – Development Formulation Rabbit (NZW) PMRA 2181352	**Moderately Irritating** MAS = 17 MIS = 22 (24 hours)
Eye irritation – Current Formulation Rabbit (NZW) PMRA 2181382	**Moderately Irritating** MAS = 24 MIS = 31 (1 and 24 hours)
Dermal sensitization (Maximization) – Development Formulation Guinea pig (Dunkin Hartley) PMRA 2181354	**Dermal Sensitizer**

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

Exposure Scenario(s)	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary	Two-generation dietary reproductive toxicity study in the rat	NOAEL = 18 mg/kg bw/day, based on increased postnatal loss and reduced body weight in offspring, observed in the presence of reduced body weight and liver and kidney toxicity in parental animals	300 (3-fold *Pest Control Products Act* factor)
	ARfD = 0.06 mg/kg bw		
Chronic dietary	Co-critical studies: 2-year dietary chronic toxicity/oncogenicity study in the rat 1-year dietary toxicity study in the dog	NOAEL = 1.4 mg/kg bw/day, based on reduced body weight and body weight gain in males and chronic interstitial inflammation of the lungs in females NOAEL = 1.5 mg/kg bw/day, based on reduced body weight and body weight gain in females	100
	ADI = 0.02 mg/kg bw/day		
Short- to intermediate-term dermal[2]	Two-generation dietary reproductive toxicity study in the rat	NOAEL = 18 mg/kg bw/day, based on increased postnatal loss and reduced body weight in offspring, observed in the presence of reduced body weight and liver and kidney toxicity in parental animals	300 (3-fold factor for concerns relating to postnatal toxicity)
Short- to intermediate-term inhalation	90-day inhalation toxicity study in the rat	LOAEL = 0.04 mg/L (11 mg/kg bw/day), based on respiratory tract irritation in both sexes, decreased body weight and body weight gain in males	300 (3-fold factor for the use of a LOAEL)
Cancer	A treatment-related increase in the incidence of lung tumours was observed in female mice. Based on the results of mechanistic data, the tumours were determined not to be relevant to humans. Therefore, a cancer risk assessment is not required.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.
[2] Since an oral NOAEL was selected, a dermal absorption factor of 58% was used in a route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUES STUDIES	
	(1) ^{14}C-thiazole label (Th-label) (2) ^{14}C-butene label (Bu-label)

Study Design for Nature of the Residue in Laying Hens.						PMRA No. 2181244	
Group	**Species**	**Radiolabel Position**	**No. of Animals**	**Dosing Details**		**Sampling Details**	
				Dose per Day	**Duration (days)**	**Commodity**	**Collection Time**
Laying hens	*Gallus gallus domesticus*	Th-label: 99.8% purity 51.3 mCi/ mmol	10	9.8 mg/kg feed	7	Eggs	Twice daily
						Excreta	Once daily
		Bu-label: 99.0% purity 57.7 mCi/ mmol	10			Tissues	At sacrifice, 20-22 hours after last dose

Overall Radioactive Residues in Laying Hen Matrices.

Matrix	Th-label		Bu-label	
	(ppm)	% of dose	(ppm)	% of dose
Liver	0.643	0.3	1.368	0.7
Eggs (Day 1-7)	0.286	0.15	4.064	1.71
Omental Fat	0.044	0	0.311	0.1
Subcutaneous Fat	0.075	0	0.311	0
Thigh Muscle	0.043	0	0.127	0.1
Breast Muscle	0.043	0	0.117	0.1
Excreta	N/A	79.4	N/A	75.8
Gastrointestinal Tract	N/A	0.2	N/A	0.5
Total Recovery	N/A	80.1	N/A	79.0

Predominant Residues (> 10% of the TRR) Identified in Laying Hen Matrices.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Omental Fat	Fluensulfone	N/A	20.9	0.009
Subcutaneous Fat	Fluensulfone	Fluensulfone	11.4-54.7	0.037-0.041

Minor Residues (< 10% of the TRR) Identified in Laying Hen Matrices.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Omental Fat	N/A	Fluensulfone	5.1	0.016
Liver	M-3625	N/A	2.7	0.016

Study Design for Nature of the Residue in Lactating Goats.						PMRA No. 2181245	
Group	Species	Radiolabel Position	No. of Animals	Dosing Details		Sampling Details	
				Dose per Day	Duration (days)	Commodity	Collection Time
Lactating goat	*Capra hircus*, crossbreed	Th-label: 99.8% purity 58.2 mCi/ mmol	1	10.5 mg/kg feed	5	Milk	Twice daily
						Urine and feces	Once daily
		Bu-label: 98.7% purity 58.7 mCi/ mmol	1			Tissues	At sacrifice, 20-22 hours after last dose

Overall Radioactive Residues in Lactating Goat Matrices.

Matrix	Th-label		Bu-label	
	(ppm)	% of dose	(ppm)	% of dose
Liver	2.623	1.67	0.975	0.87
Kidney	1.402	0.20	0.671	0.10
Skim Milk	0.512	1.40	0.297	0.94
Milk Fat	1.977	0.31	0.531	0.12
Flank Muscle	0.217	4.2	0.054	0.93
Loin Muscle	0.239		0.040	
Subcutaneous Fat	0.131	0.01	0.071	0.02
Omental Fat	0.071	0.04	0.070	0.03
Renal Fat	0.083	0.06	0.043	0.02
Bile	1.412	0.02	0.082	0
Blood	0.948	2.76	0.146	0.47
Feces	N/A	15.66	N/A	12.05
Gastrointestinal Tract	N/A	2.93	N/A	2.08
Urine	N/A	37.49	N/A	69.66
Cage Wash	N/A	0.04	N/A	0.10
Total Recovery	N/A	66.85	N/A	87.39

Predominant Residues (> 10% of the TRR) Identified in Lactating Goat Matrices.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Kidney	Glucose	Glucose	13.4-16.8	0.090-0.236
Skim Milk	Lactose	Lactose	45.7-63.1	0.164-0.187

Minor Residues (< 10% of the TRR) Identified in Lactating Goat Matrices.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Liver	Glucose, lactose	Glucose, lactose	3.7-8.8	0.036-0.232

Nature of the Residue in Tomato.						**PMRA No. 2181241**
Group	**Radiolabel Position**	**Formulated Product**	**Type of Treatment**	**Application Details**		
				Rate (kg a.i./ha)	**#**	**Sampling**
Tomato (*Solanum lycopersicum* cv Early Girl)	Th-label: 99.2% purity 56.7 mCi/mmol	48% EC	Soil; preplanting, < 24 h before transplant of seedlings	4.07	1	87 DAT (mature tomato fruits)
	Bu-label: 99.0% purity 57.7 mCi/mmol	48% EC		4.07	1	

Overall Radioactive Residues in Tomato Fruit Following Pre-Planting Soil Treatment.		
Matrix	**Total Radioactive Residues (ppm)**	
	Th-label	**Bu-label**
Mature Tomato Fruit (87 DAT)	0.256	0.517

Predominant Residues (> 10% of the TRR) Identified in Tomato Fruit Following Pre-Planting Soil Treatment.				
Matrix	**Radiolabel Position**		**TRR**	
	Th-label	**Bu-label**	**(%)**	**(ppm)**
Mature Tomato Fruit (87 DAT)	M-3625	M-3627	41.6-45.4	0.116-0.215

Nature of the Residue in Potato.						**PMRA No. 2181243**
Group	**Radiolabel Position**	**Formulated Product**	**Type of Treatment**	**Application Details**		
				Rate (kg a.i./ha)	**#**	**Sampling**
Potato (*Solanum tuberosum* cv Red La Soda)	Th-label: 99.8% purity 51.3 mCi/mmol	48% EC	Soil; postplanting, < 24 h after sowing	4.04	1	70 DAT (immature potato tubers) 106 DAT (mature potato tubers)
	Bu-label: 99.0% purity 57.7 mCi/mmol	48% EC		4.13	1	

Overall Radioactive Residues in Potato Tubers Following Post-Planting Soil Treatment.		
Matrix	**Total Radioactive Residues (ppm)**	
	Th-label	**Bu-label**
Immature potato tubers (70 DAT)	0.335	0.225
Mature potato tubers (106 DAT)	0.467	0.163

Predominant Residues (> 10% of the TRR) Identified in Potato Tubers Following Post-Planting Soil Treatment.				
Matrix	**Radiolabel Position**		**TRR**	
	Th-label	**Bu-label**	**(%)**	**(ppm)**
Immature potato tubers (70 DAT)	M-3625	M-3627	30.7-63.0	0.069-0.211
Mature potato tubers (106 DAT)	M-3625	M-3627	25.8-65.3	0.042-0.305

Minor Residues (< 10% of the TRR) Identified in Potato Tubers Following Post-Planting Soil Treatment.				
Matrix	**Radiolabel Position**		**TRR**	
	Th-label	**Bu-label**	**(%)**	**(ppm)**
Mature potato tubers (106 DAT)	Fluensulfone	Fluensulfone	1.1-3.1	0.005

Nature of the Residue in Lettuce.						PMRA No. 2181242
Group	**Radiolabel Position**	**Formulated Product**	**Type of Treatment**	**Application Details**		
				Rate (kg a.i./ha)	**#**	**Sampling**
Lettuce (*Lactuca sativa* cv Salad Bowl)	Th-label: 99.8% purity 51.3 mCi/mmol	48% EC	Soil; postplanting < 24 h after sowing	4.08	1	49 DAT (immature lettuce plants without roots) 69 DAT (mature lettuce plants without roots)
	Bu-label: 99.0% purity 57.7 mCi/mmol	48% EC		4.19	1	

Overall Radioactive Residues in Lettuce Following Post-Planting Soil Treatment.

Matrix	Total Radioactive Residues (ppm)	
	Th-label	Bu-label
Immature lettuce (49 DAT)	5.302	2.071
Mature lettuce (69 DAT)	6.145	1.290

Predominant Residues (> 10% of the TRR) Identified in Lettuce Following Post-Planting Soil Treatment.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Immature lettuce (49 DAT)	M-3625	M-3627	23.8-67.5	0.492-3.572
Mature lettuce (69 DAT)	M-3625	M-3627	37.6-70.6	0.485-4.34

Minor Residues (< 10% of the TRR) Identified in Lettuce Following Post-Planting Soil Treatment.

Matrix	Radiolabel Position		TRR	
	Th-label	Bu-label	(%)	(ppm)
Immature lettuce (49 DAT)	Fluensulfone	Fluensulfone	0.2-0.4	0.008-0.009

Nature of the Residues in Confined Rotational Crop Study.		PMRA No. 2181372
Crops	**Radiolabel Position**	**Application Details**
		Rate (kg a.i./ha)
Radish (*Raphanus sativus* cv Crimson Giant)	Th-label: 99.8% purity, 58.2 mCi/mmol	3.97; applied onto bare soil outdoors
Lettuce (*Lactuca sativa* cv Salad Bowl)	Bu-label: 98.7% purity, 58.7 mCi/mmol	4.36; applied onto bare soil outdoors
Wheat (*Triticum aestivum* cv Pronto)		

Study Soil Characteristics: Sandy loam; pH (7.5); organic matter (1.2%); sand (71%); silt (16%); clay (13%); moisture holding capacity at 1/3 bar (10.7); CEC (9.7 meq/100 g). Samples of wheat (forage, hay, straw and grain), radish (roots, foliage) and lettuce were harvested from plants sown after plant-back intervals (PBI) of 30, 120, 360 and 390 (lettuce only) days.

Overall Radioactive Residues in Confined Rotational Crops.

Matrix	Total Radioactive Residues in Food Items (ppm)							
	Th-label				Bu-label			
PBI (days)	Immature Lettuce	Mature Lettuce	Radish Roots	Wheat Grain	Immature Lettuce	Mature Lettuce	Radish Roots	Wheat Grain
30	0.647	0.565	0.793	0.359	0.311	0.204	0.146	0.173
120	0.710	0.331	0.437	0.296	0.045	0.045	0.125	0.059
360	N/A	N/A	0.379	0.364	N/A	N/A	0.012	0.038
390	0.133	0.339	N/A	N/A	0.050	0.017	N/A	N/A

Predominant Residues (> 10% of the TRR) Identified in Food Items of Rotational Crops.									
Matrix	**Analytes**	**(% TRR)**				**(ppm)**			
		30 PBI	**120 PBI**	**360 PBI**	**390 PBI**	**30 PBI**	**120 PBI**	**360 PBI**	**390 PBI**
Immature lettuce	M-3625	28.3	56.5	N/A	64.7	0.183	0.401	N/A	0.086
Mature lettuce	M-3625	41.9	55.6	N/A	82.3	0.237	0.184	N/A	0.279
Radish roots	M-3625	86.6	81.2	90.0	N/A	0.687	0.355	0.341	N/A
	M-3627	40.0	39.4	—	N/A	0.058	0.041	—	N/A
Wheat grain	M-3625	33.4	57.8	57.0	N/A	0.120	0.171	0.195	N/A

Matrix	**Total Radioactive Residues in Feed Items (ppm)**							
	Th-label				**Bu-label**			
PBI (days)	**Radish Foliage**	**Wheat Forage**	**Wheat Hay**	**Wheat Straw**	**Radish Foliage**	**Wheat Forage**	**Wheat Hay**	**Wheat Straw**
30	5.263	16.579	34.549	20.918	0.479	2.530	6.719	2.480
120	1.756	2.963	11.400	3.942	0.467	0.775	0.501	0.386
360	2.860	3.326	13.231	7.124	0.038	0.060	0.155	0.208

Predominant Residues (> 10% of the TRR) Identified in Feed Items of Rotational Crops.							
Matrix	**Analytes**	**(% TRR)**			**(ppm)**		
		30 PBI	**120 PBI**	**360 PBI**	**30 PBI**	**120 PBI**	**360 PBI**
Radish foliage	M-3625	89.8	92.5	89.4	4.726	1.624	2.558
	M-3627	65.8	70.2	—	0.315	0.328	—
Wheat forage	M-3625	73.8	76.0	82.3	12.241	2.254	2.737
	M-3627	54.4	59.9	—	1.377	0.427	—
Wheat hay	M-3625	57.7	66.2	53.3	15.571	6.221	5.771
	M-3627	27.2	25.5	—	1.223	0.095	—
Wheat straw	M-3625	57.7	62.4	76.3	10.712	2.196	5.060
	M-3627	14.1	10.2	—	0.272	0.031	—

Study Design for Accelerated Hydrolysis of ^{14}C-Fluensulfone **PMRA No. 2181174**

The accelerated hydrolysis of [^{14}C-thiazole]-fluensulfone, at a concentration of 10 µg/mL, was investigated in 0.05 M sterile aqueous buffered solutions at pH of 4, 7 and 9 maintained at 50°C for 5 days. Duplicate samples were taken at time zero and after 5 days and were analysed by LSC, HPLC and/or TLC. Fluensulfone was found stable over the 5-day period in the three buffered solutions. It did not degrade into thiazole sulfonic acid (M-3625) or thiazole methyl sulfone (M-3626). Unknowns were found in all samples and accounted for less than 5% of the initial dose. Mean recoveries of the initial dose ranged from 99.9-100.3%.

pH	**Time (days)**	**% of Dose (Mean Values)**				
		MCW-2	**M-3625**	**M-3626**	**Others**	**Total Recovery**
4	0	99.3	0	0	0.8	100.0
	5	98.4	0	0	1.9	100.3
7	0	99.1	0	0	1.0	100.0
	5	97.3	0	0	2.6	99.9
9	0	98.6	0	0	1.4	100.0
	5	95.8	0	0	4.2	99.9

Overall Assessment of the Nature of the Residue Studies.

The nature of fluensulfone residues in commodities of animal origin was investigated in lactating goats and laying hens dosed with the ^{14}C-thiazole (labeled in the thiazole ring) and ^{14}C-butene (labeled in the trifluorobutene side chain) labeled fluensulfone. The lactating goats and laying hens were orally dosed for five and seven consecutive days, respectively at feeding levels of 10.5 and 9.8 mg/kg feed/day, respectively. The majority of the administered dose was excreta-related. Low levels of radioactivity were observed in milk, eggs and edible tissues. Among all animal tissues analysed, the liver contained the highest TRR levels in both lactating goats and laying hens. No fluensulfone was detected in any goat matrices, but was a predominant residue in omental (thiazole label only) and subcutaneous fat (both labels) of poultry. Glucose was identified as a predominant residue in goat kidney

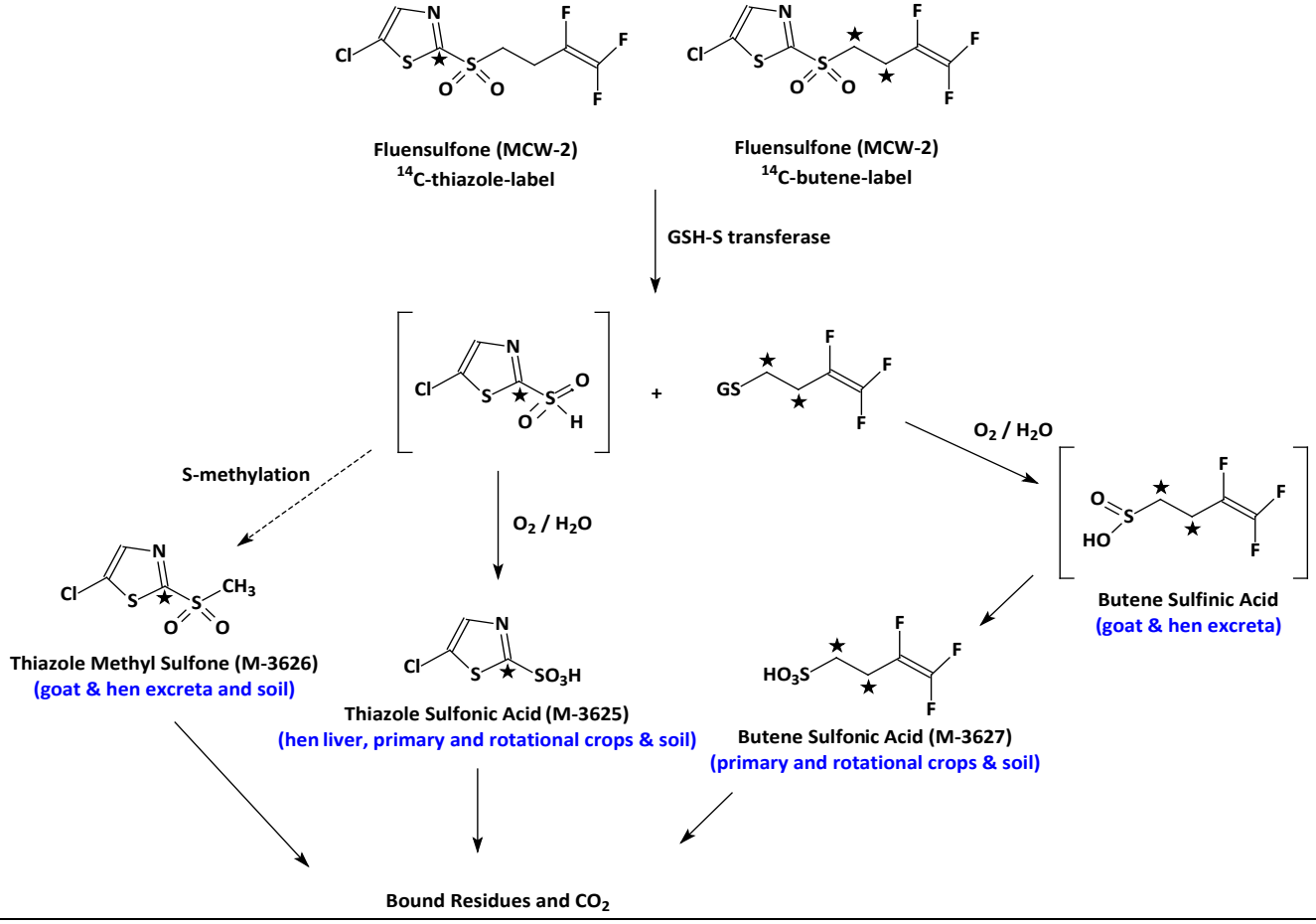
yet as a minor residue in goat liver. Similarly, lactose was identified as a major residue in skim milk yet a minor residue in liver. Thiazole sulfonic acid (M-3625) was detected at low levels in poultry liver.

The same two radiolabels were used in the plant metabolism and confined accumulation in rotational crops studies: ^{14}C-thiazole and ^{14}C-butene. In the plant metabolism studies, the test substances were applied once to the soil, pre- and post-planting of seeds of tomato, lettuce and potato (within ± 24 hours of application) at rates of 4.04-4.19 kg a.i./ha (GAP). Fluensulfone was only observed as a minor residue in immature lettuce (49 DAT) and mature potato tubers (106 DAT). The predominant residues in all plants were thiazole sulfonic acid (M-3625) and butene sulfonic acid (M-3627).

In the confined accumulation in rotational crops study, the test substances were applied to bare soil in test plot boxes located outdoors at rates of 3.97-4.36 kg a.i./ha (GAP). Rotational crops (i.e. radish, lettuce and wheat) were planted at plant-back intervals of 30, 120, 360 and/or 390 days (lettuce only) after treatment. TRR levels in food items (i.e. radish roots and foliage, lettuce and wheat grain) ranged from 0.012-0.793 ppm at all PBIs. Metabolite M-3625 (thiazole sulfonic acid) was the predominant residue in all food items at all PBIs and Metabolite M-3627 (butene sulfonic acid) was a predominant residue in radish roots only at PBIs of 30 and 120 days. TRR levels in feed items (i.e. radish foliage, wheat forage, wheat hay and wheat straw) ranged from 0.038-34.549 ppm at all PBIs. Metabolites M-3625 and M-3627 were the predominant residues in all matrices at all PBIs with the exception of metabolite M-3627 which was not observed in radish foliage, wheat hay and wheat straw at a 360-day PBI.

Proposed Metabolic Profile in Plant and Animal Matrices.

The metabolic degradation of fluensulfone was similar in primary plants and rotational crops. The degradation of the parent compound after soil treatment could have occurred either in the plants (i.e. tomato, lettuce or potato – primary plants) or in the soil prior to plant uptake, since M-3625 and M-3627 were also predominant components in soil metabolism. Fluensulfone is postulated to undergo (1) cleavage of the sulfonyl moiety by the GSH-S-transferase which is potentially present in the soil (2) followed by oxidation leading to metabolites M-3625 and M-3627. Another minor metabolite, M-3626, is formed by S-methylation. In livestock, a similar pathway was observed where fluensulfone also underwent cleavage followed by oxidation to metabolite M-3627 which was subsequently incorporated into the carbon pool.



Residue Definition (RD) for Enforcement and Risk Assessment Purposes.

Fluensulfone was found to degrade relatively rapidly in plants, rotational crops and in livestock.

Primary Crops: Metabolism studies showed that fluensulfone degraded to metabolites M-3625 and M-3627, which were the predominant residues in tomato fruit, lettuce and potato tubers. However, as the metabolite M-3625 is very persistent in soil and as the highest TRRs were observed at the longest PBIs of 360/390, as demonstrated in the confined accumulation in rotational crops study, the metabolite M-3625 is inappropriate for consideration as a marker compound for enforcement purposes. Therefore, the recommended residue definition in plants, for enforcement purposes, is the sum of fluensulfone and metabolite M-3627 expressed in parent equivalents. As both metabolites M-3625 and M-3627 were determined to be less toxic than the parent, the recommended residue definition for risk assessment purposes in plants is fluensulfone.

Rotational Crops: Fluensulfone was only found as a minor residue in rotational crops (i.e. radish (roots, foliage), lettuce and wheat (forage, hay, straw and grain)) at the earlier PBIs of 30 and 120 days. Fluensulfone was not observed at the longer PBIs. The predominant residue in all food items at all PBIs was the metabolite M-3625 with metabolite M-3627 present mostly in the feed items at the two earlier PBIs. These findings were supported by the field accumulation in rotational crops study. Therefore, the residue definitions for enforcement and risk assessment purposes for rotational crops are recommended to be the same as those for primary crops.

Livestock: In the livestock metabolism studies, fluensulfone was found to degrade rapidly. The radioactive residues were found to be mostly incorporated into natural products such as proteins, fatty acids and natural sugars (i.e. glucose and lactose). Fluensulfone was only identified as a minor residue in hen omental fat. In the absence of livestock feeding studies, no residue definitions for enforcement and risk assessment purposes can be recommended.

Storage Stability in Plants and Plant Products.	**PMRA No. 2181365, 2181366, 2181368**

The storage stability of fluensulfone and the metabolite M-3627 was investigated in tomatoes, peppers, cucumbers and cantaloupes/melons (all high-water content matrices) and in processed tomato commodities. Control representative crop samples were fortified at 0.10 ppm with each fluensulfone and M-3627. Samples were stored at -20°C and analysed concurrently with freshly spiked samples at storage intervals of 0, 3, 8-8.5 and 15-16 months.

Summary of Fluensulfone and M-3627 Stability in High Water Content Matrices and Processed Commodities During Freezer Storage at -20°C.

Matrix Type	Representative Commodity	Analytes	Demonstrated Storage Interval (months)
High-water content	Tomato	Fluensulfone; M-3627	15
	Pepper, cucumber, cantaloupe/melon		16
Processed commodities	Tomato paste, tomato puree	Fluensulfone; M-3627	6

Residues of fluensulfone and M-3627 were determined to be stable for up to 16 months in tomato and 15 months in pepper, cucumber and cantaloupe/melon under frozen conditions. The storage stability of residues of fluensulfone and M-3627 was demonstrated for up to 6 months in tomato purée and paste. The intervals of demonstrated storage stability cover the storage intervals of samples from the primary crop field trials and processing studies.

Crop Field Trials

The applicant submitted crop field trial data from field trials conducted in Canada and U.S.A. using Nimitz 480EC. Treatments were conducted either by broadcast spray or drip irrigation at pre-planting intervals (PPIs) of 7 days. Additional trials were also conducted by chemigation via drip irrigation at PPIs of 3 days. All trials were conducted at approximately the maximum supported GAP of 3.84 kg a.i./ha. All field trial samples were analysed using enforcement method 1977W. Samples were stored for intervals that were within the demonstrated storage intervals for fluensulfone and M-3627. In general, the number and geographic distribution of field trials were in accordance with OCSPP harmonized test guidelines 860.1500 and Health Canada's DIR2010-05.

Tomato			**PMRA No. 2181365, 2181368**
Application Types	Broadcast spray	Drip irrigation	Chemigation via drip irrigation
Crop	Tomato (RAC)	Tomato (RAC)	Tomato (RAC)
EP	Nimitz 480EC	Nimitz 480EC	Nimitz 480EC
No. of Applications	1 appl. 7-day pre-planting	1 appl. 7-day pre-planting	1 appl. 3-day pre-planting
Total Rate (kg a.i./ha)	3.64-4.12	4.00	3.99-4.01
PHI (days)	78-150	85-146	73-122
Statistic	Total residues of fluensulfone and M-3627, expressed in fluensulfone equivalents (mg/kg)		
n	40	4	6
Min	0.025	0.047	0.025
Max	0.432	0.143	0.078
HAFT	0.428	0.130	0.078
Median	0.100	0.088	0.036
Mean	0.148	0.092	0.045
SD	0.135	0.046	0.027

Bell and Non-bell Pepper				**PMRA No. 2181365, 2181368**
Application Types	Broadcast spray		Drip irrigation	Chemigation via drip irrigation
Crop	Bell pepper (RAC)	Non-bell pepper (RAC)	Bell pepper (RAC)	Bell pepper (RAC)
EP	Nimitz 480EC	Nimitz 480EC	Nimitz 480EC	Nimitz 480EC
No. of Applications	1 appl. 7-day pre-planting	1 appl. 7-day pre-planting	1 appl. 7-day pre-planting	1 appl. 3-day pre-planting
Total Rate (kg a.i./ha)	3.82-4.10	3.90-4.07	4.00-4.01	4.00-4.02
PHI (days)	50-108	50-102	76-104	53-102
Statistic	Total residues of fluensulfone and M-3627, expressed in fluensulfone equivalents (mg/kg)			
n	14	8	4	6
Min	0.051	0.058	0.105	0.025
Max	0.377	0.318	0.128	0.039
HAFT	0.366	0.292	0.121	0.038
Median	0.106	0.147	0.118	0.020
Mean	0.137	0.163	0.117	0.026
SD	0.100	0.103	0.010	0.010

The approved use pattern for Nimitz 480EC is one pre-plant application at a rate of 3.84 kg a.i./ha, seven days prior to planting by broadcast/band spray & incorporated or drip irrigation. Overall, the data support the registration of Nimitz 480EC on fruiting vegetables (CG 8-09).

Cucumber			**PMRA No. 2181366, 2181369**
Application Types	Broadcast spray	Drip irrigation	Chemigation via drip irrigation
Crop	Cucumber (RAC)	Cucumber (RAC)	Cucumber (RAC)
EP	Nimitz 480EC	Nimitz 480EC	Nimitz 480EC
No. of Applications	1 appl. 7-day pre-planting	1 appl. 7-day pre-planting	1 appl. 3-day pre-planting
Total Rate (kg a.i./ha)	3.71-4.11	4.00	4.00-4.01
PHI (days)	41-73	41-70	46-78
Statistic	Total residues of fluensulfone and M-3627, expressed in fluensulfone equivalents (mg/kg)		
n	14	4	6
Min	0.025	0.025	0.025
Max	0.340	0.552	0.119
HAFT	0.271	0.345	0.101
Median	0.094	0.079	0.034
Mean	0.114	0.183	0.052
SD	0.109	0.252	0.041

Summer Squash		**PMRA No. 2181369**
Application Types	Broadcast spray	Drip irrigation
Crop	Summer squash (RAC)	Summer squash (RAC)
EP	Nimitz 480EC	Nimitz 480EC
No. of Applications	1 appl. 7-day pre-planting	1 appl. 7-day pre-planting
Total Rate (kg a.i./ha)	3.80-4.14	4.00
PHI (days)	36-71	45-49
Statistic	Total residues of fluensulfone and M-3627, expressed in fluensulfone equivalents (mg/kg)	
n	16	4
Min	0.025	0.054
Max	0.403	0.105
HAFT	0.388	0.102
Median	0.203	0.101
Mean	0.201	0.090
SD	0.145	0.024

Cantaloupe\Melon		**PMRA No. 2181366, 2181369**
Application Types	Broadcast spray	Chemigation via drip irrigation
Crop	Cantaloupe/melon (RAC)	Cantaloupe/melon (RAC)
EP	Nimitz 480EC	Nimitz 480EC
No. of Applications	1 appl. 7-day pre-planting	1 appl. 3-day pre-planting
Total Rate (kg a.i./ha)	3.85-4.11	4.0
PHI (days)	66-133	70-77
Statistic	Total residues of fluensulfone and M-3627, expressed in fluensulfone equivalents (mg/kg)	
n	16	4
Min	0.025	0.025
Max	0.110	0.150
HAFT	0.107	0.148
Median	0.046	0.083
Mean	0.050	0.084
SD	0.032	0.074
The approved use pattern for Nimitz 480EC is one pre-plant application at a rate of 3.84 kg a.i./ha, seven days prior to planting by broadcast/band spray & incorporated or drip irrigation. Overall, the data support the registration of Nimitz 480EC on field cucurbit vegetables (CG 9).		

Study Design for Melon Greenhouse Trials		**PMRA No. 2181367**
One melon study was conducted in greenhouses in Europe to determine the distribution of residues of fluensulfone and metabolites M-3625 and M-3627 in/on melon peel and pulp fractions.		
Application Types	Drip Irrigation	
Crop	Melon (RAC)	
EP	MCW-2 480 EC	
No. of Applications	1	
Total Rate (kg a.i./ha)	3.94	
PHI (days)	62-84	
Analyte	Fluensulfone	M-3627
Residues in peel (mg/kg)	< 0.01	< 0.01-0.25
Residues in pulp (mg/kg)	< 0.01	< 0.01-0.17
Ratio of peel to pulp	N/A	1.00-3.00
The melon greenhouse trial demonstrated that higher residues of M-3627were found in the melon peel in comparison to the melon pulp indicating limited translocation of the residues.		

Field Accumulation in Rotational Crops (Leaf Lettuce, Winter, Wheat, Radish)	PMRA No. 2609866
A total of 87 field trials radish, green beans and wheat as rotational crops, were conducted in Canada and/or the United States encompassing North American Free Trade Agreement (NAFTA) Growing Regions. Forty-four wheat trials were conducted in Zone 2 and 10 (GA and CA), while 43 trials on lettuce, radish and green beans were conducted in Zone 3 and 10 (FL and GA) during the 2011-2014 growing seasons. Additional trials were conducted in France and Spain with lettuce, radish, tomato and wheat.	
At each trial location, one untreated control plot and one treated plot were established, each with six subplots for each of the six target plant-back intervals (PBIs) of 30, 60, 120, 180, 270, and 365 days. At each treated plot, a single pre-plant incorporation application of fluensulfone at a target rate of 4.0 kg ai/ha was made to bare soil and incorporated to a depth of ~8 inches (~20 cm). No adjuvants were included in the spray mixtures. Lettuce leaves, radish leaves and radish roots were collected at commercial maturity at a growth stage between BBCH 45 – 49. Samples of green bean pods were collected at commercial maturity. Wheat forage and hay were collected at the early flower to soft dough stage between BBCH 39-59, and wheat grain and straw were harvested at commercial maturity between BBCH 89 – 99. The collection of samples at commercial harvest for winter wheat, leaf lettuce, radish roots and tops, and green bean pods were 108 – 239, 37 – 116, 29 – 116, and 56 – 88 days after planting (DAP), respectively. Wheat hay was dried in the field to 10-20% moisture content; drying intervals were not reported. For the European trials, neither the analytical methods, the freezer storage stability duration, the regions (North or South), the varieties, the application rates nor the DAPs were reported. Therefore, these trials were considered as supplemental information only. All samples were maintained frozen at the testing facility, shipped and stored frozen until analysis. The maximum storage duration for samples between harvest and analysis was 21.9 months for green beans, 10.0 months for lettuce leaves, 11.4 months for radish roots and tops, 9.3 months for wheat forage, 32.6 months for wheat grain and wheat straw, and 34.4 months for wheat hay. Samples were analyzed using validated LC-MS/MS methods for determination of residues of fluensulfone and M-3627. The limit of quantitation (LOQ) was 0.01 ppm per analyte for all matrices. The results from the North American trials show that, in general, residues of fluensulfone were <LOQ (<0.01 ppm) in all matrices (exception of one sample of lettuce at a PBI of 30 days). Residues of M-3627 were <LOQ at PBIs ≥ 270 days for radish, ≥ 180 days for lettuce and ≥ 365 for green beans and wheat grain. Quantifiable residues of M-3627 were observed in wheat forage, hay, and straw at the 365-day PBI. Trials conducted in France and Spain showed residues of M-3627 at the 365-day PBI for all matrices except lettuce, for which residues of M-3627 were <LOQ by the 120-day PBI.	
Processed Food (Tomatoes)	**PMRA No. 2181368; 2402078**
In the first study, following treatment at approximately 2-fold the maximum approved seasonal GAP, residues of fluensulfone and M-3627 in/on tomato RAC, paste, purée and juice were all less than LOQ. In the second study, following treatment at approximately 5-fold the maximum approved seasonal GAP, residues of fluensulfone in/on tomato RAC, paste, purée, juice, wet pomace and dry pomace were all less than LOQ while residues of M-3627 were quantifiable and ranged from 2.19-11.3 ppm. The total anticipated residues of fluensulfone and M-3627, for enforcement purposes, in all tomato processed commodities, except tomato paste and dry pomace, are all covered by the established MRL for fruiting vegetables (CG 8-09; except small tomatoes) of 0.5 ppm. A separate MRL of 1 ppm was specified for total residues of fluensulfone and M-3627, expressed as parent equivalents, in tomato paste. No MRL was established for tomato dry pomace as it is not considered a human food item.	

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

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (tomato, lettuce, potato)** **Rotational crops (radish, lettuce, wheat)**		Sum of fluensulfone and metabolite M-3627, expressed as fluensulfone equivalents	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (tomato, lettuce, potato)** **Rotational crops (radish, lettuce, wheat)**		Fluensulfone	
METABOLIC PROFILE IN DIVERSE CROPS		The profile in three diverse crops was similar.	
ANIMAL STUDIES			
ANIMALS		**Ruminant**	
RESIDUE DEFINITION FOR ENFORCEMENT		None at this time.	
RESIDUE DEFINITION FOR RISK ASSESSMENT		None at this time.	
METABOLIC PROFILE IN ANIMALS **(goat, hen)**		The profile is similar in the two investigated animals.	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK** **% of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
Refined acute dietary exposure analysis, 95th percentile **ARfD = 0.06 mg/kg bw** **Estimated acute drinking water concentration (Level 1) = 107 µg ai/L**	**All infants < 1 year**	**33.4**	**50.2**
	Children 1–2 years	**27.2**	**34.5**
	Children 3–5 years	**23.4**	**29.7**
	Children 6–12 years	**15.2**	**20.0**
	Youth 13–19 years	**8.7**	**13.3**
	Adults 20–49 years	**11.7**	**17.5**
	Adults 50+ years	**12.2**	**17.9**
	Females 13-49 years	**11.9**	**17.9**
	Total population	**13.0**	**19.6**
	POPULATION	**ESTIMATED RISK** **% of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary exposure analysis **ADI = 0.02 mg/kg bw** **Estimated chronic drinking water concentration (Level 1) = 101 µg ai/L**	**All infants < 1 year**	**19.5**	**57.6**
	Children 1–2 years	**21.0**	**35.0**
	Children 3–5 years	**16.1**	**27.5**
	Children 6–12 years	**10.6**	**19.1**
	Youth 13–19 years	**6.7**	**13.9**
	Adults 20–49 years	**9.0**	**19.1**
	Adults 50+ years	**10.6**	**20.5**
	Females 13-49 years	**9.2**	**19.2**
	Total population	**10.2**	**20.4**

Table 7 Fate and Behaviour of Fluensulfone in the Terrestrial Environment.

Study	Value / Results	Interpretation	PMRA Study No.
Physical and Chemical Properties			
Vapour pressure at 25°C (Pa)	3.0×10^{-2} Pa	Volatile under field conditions	2181167
Henry's law constant at 25°C	K = 1.61×10^{-2} Pa.m^3/mole K = 1.58×10^{-7} atm.m^3/mole 1/H = 1.54×10^{5}	Slightly volatile from moist soil and water based on 1/H value	NA
Ultraviolet (UV) / visible spectrum	Unadjusted methanol: λ max = 224 nm, ε = 3256 λ max = 271 nm, ε = 9467 Acidified methanol: λ max = 223 nm, ε = 2470 λ max = 271 nm, ε = 8770 Basified methanol: λ max = 256 nm, ε = 5118	Not expected to undergo phototransformation under environmental conditions	2181170
Solubility in water at pH 7 and 20°C (mg/L)	545.3	Soluble in water	2181171
n-Octanol/water partition coefficient (log K_{ow})	2.2	Not expected to bioaccumulate	2181173
Dissociation constant (pK_a)	The chemical structure of fluensulfone indicates there are no acidic or basic functional groups, or other substituents in the molecule, that will readily dissociate in water.	Not expected to dissociate under environmental conditions	2181176
Abiotic Transformation			
Hydrolysis	Stable	Hydrolysis is not an important route of transformation	2181174
Phototransformation on soil	Half-life = 38.5 days	Phototransformation on soil is not an important route of transformation	2181249
Soil Biotransformation			
Aerobic soil Fislis silt loam; France	DT_{50} = 9.6 days (IORE) DT_{90} = 50 days (IORE)	Non-persistent	2181247
Hagenthal silt loam; France	DT_{50} = 7.3 days (IORE) DT_{90} = 31.7 days (IORE)	Non-persistent	2181247
Horn loam; Switzerland	DT_{50} = 8.1 days (SFO) DT_{90} = 26.8 days (SFO)	Non-persistent	2181247
Montesquieu clay loam; France	DT_{50} = 11.9 days (SFO) DT_{90} = 39.4 days (SFO)	Non-persistent	2181247
Senozan loam; France	DT_{50} = 14 days (IORE) DT_{90} = 84.4 days (IORE)	Non-persistent	2181247
Sevelen sandy loam; Switzerland	DT_{50} = 7.0 days (IORE) DT_{90} = 30.3 days (IORE)	Non-persistent	2181247
Anaerobic soil	DT_{50} = 397 days (SFO)		2181248
Field Dissipation			
Terrestrial field dissipation (Ontario)	DT_{50} = 7.4 days (IORE) DT_{90} = 73 days (IORE)	Non-persistent	2181252

Study	Value / Results	Interpretation	PMRA Study No.
Mobility			
Adsorption/desorption			
sandy clay loam (N. Dakota)	K_{oc} = 203	Medium mobility	2181254
sandy loam (Ontario)	K_{oc} = 154	Medium mobility	2181254
loamy sand (California)	K_{oc} = 172	Medium mobility	2181254
sand (Texas)	K_{oc} = 157	Medium mobility	2181254
loamy sand (Florida)	K_{oc} = 275	Medium mobility	2181254

Table 8 Fate and Behaviour of the Transformation Products of Fluensulfone in the Terrestrial Environment.

Study	Value / Results	Interpretation	PMRA Study No.
Physical Chemical Properties			
Solubility in water (mg/L)	**MS:** 7644.6 (20°C at pH 2.9)	Very soluble in water	2402074
	TSA: 446200 (20°C at pH 4.2)	Very soluble in water	2402071
	BSA: 580,900 (20°C at pH 3)	Very soluble in water	2402069
	Deschloro-fluensulfone: 3473	Very soluble in water	2402068
	Butene sulfinic acid: 435100	Very soluble in water	2402068
Octanol-water partition (log K_{ow})	**MS:** 0.7 (22°C)	Not expected to bioaccumulate	2402070
	TSA: -3.5 (22°C)	Not expected to bioaccumulate	0402075
	BSA: -2.5(22°C)	Not expected to bioaccumulate	2402073
	Deschloro-fluensulfone: 0.93	Not expected to bioaccumulate	2402068
	Butene sulfinic acid: -1.02	Not expected to bioaccumulate	2402068
Soil Biotransformation of MS			
Aerobic soil (Fislis silt loam; France)	DT_{50} = 41.3 days (SFO) DT_{90} = 137 days (SFO)	Slightly persistent	2181250
Aerobic soil (Horn loam; Switzerland)	DT_{50} = 24.1 days (IORE) DT_{90} = 113 days (IORE)	Slightly persistent	2181250
Aerobic soil (Sevelen sandy loam; Switzerland)	DT_{50} = 23.1 days (IORE) DT_{90} = 146 days (IORE)	Slightly persistent	2181250
Soil Biotransformation of TSA			
Aerobic soil (Fislis silt loam; France)	DT_{50} = 561 days (SFO) DT_{90} = 1862 days (SFO)	Persistent	2181251
Aerobic soil (Horn loam; Switzerland)	DT_{50} = 448 days (SFO) DT_{90} = 1489 days (SFO)	Persistent	2181251
Aerobic soil (Sevelen sandy loam; Switzerland)	DT_{50} = 315 days (DFOP) DT_{90} = 1509 days (DFOP)	Persistent	2181251
Mobility of TSA			
Adsorption/desorption			
Fislis silt loam; France	K_{oc} = 7.1	Very high mobility	2181257
Sevelen sandy loam; Switzerland	K_{oc} = 9.7	Very high mobility	2181257
/Horn loam; Switzerland	K_{oc} = 8.0	Very high mobility	2181257
Speyer 2.2	K_{oc} = 8.4	Very high mobility	2181257
Speyer 6S	K_{oc} = 5.8	Very high mobility	2181257
Mobility of MS			
Fislis silt loam; France	K_{oc} = 14.3	Very high mobility	2181256
Sevelen sandy loam; Switzerland	K_{oc} = 17.5	Very high mobility	2181256

Study	Value / Results	Interpretation	PMRA Study No.
Horn loam; Switzerland	K_{oc} = 27.5	Very high mobility	2181256
Speyer 2.2	K_{oc} = 26.3	Very high mobility	2181256
Speyer 6S	K_{oc} = 50.5	High mobility	2181256
Mobility of BSA			
Fislis silt loam; France	K_{oc} not determined	-	
Sevelen sandy loam; Switzerland	K_{oc} = 5.3	Very high mobility	2181258
Horn loam; Switzerland	K_{oc} = 3.5	Very high mobility	2181258
Speyer 2.2	K_{oc} = 10.5	Very high mobility	2181258
Speyer 6S	K_{oc} = 5.0	Very high mobility	2181258

Table 9 Fate and Behaviour of Fluensulfone in the Aquatic Environment.

Study	Value / Results	Interpretation	PMRA Study No.
Physical and Chemical Properties			
Vapour pressure at 25°C (Pa)	3.0×10^{-2} Pa	Volatile under field conditions	2181167
Henry's law constant at 25°C	K = 1.61×10^{-2} Pa.m^3/mole K = 1.58×10^{-7} atm.m^3/mole 1/H = 1.54×10^{5}	Slightly volatile from water based on 1/H value; (Non-volatile from water based on K values)	N/A
Ultraviolet (UV) / visible spectrum	Unadjusted methanol: λ max = 224 nm, ε = 3256 λ max = 271 nm, ε = 9467 Acidified methanol: λ max = 223 nm, ε = 2470 λ max = 271 nm, ε = 8770 Basified methanol: λ max = 256 nm, ε = 5118	Not expected to undergo phototrans-formation in water under environmental conditions	2181170
Solubility in water at pH 7 and 20°C (mg/L)	545.3	Soluble in water	2181171
n-Octanol/water partition coefficient (log K_{ow})	2.2	Not expected to bioaccumulate to an appreciable extent	2181173
Dissociation constant (pK_a)	The chemical structure of fluensulfone indicates there are no acidic or basic functional groups, or other substituents in the molecule, that will readily dissociate in water.	Not expected to dissociate under environmental conditions	2181176
Abiotic Transformation			
Hydrolysis	Stable	Hydrolysis is not an important route of transformation	2181174
Phototransformation in water	Half-life = 0.68 days (sterile buffer) Half-life = 0.58 days (sterilized natural water)	Phototransformation in water is an important route of transformation	2181175

Study	Value / Results	Interpretation	PMRA Study No.
Aquatic Biotransformation			
Aerobic			
Golden Lake (loamy sand sediment)	DT_{50} = 58.7 days (IORE) DT_{90} = 130 days (IORE)	Moderately persistent	2181260
Goose river (loam sediment)	DT_{50} = 55.9 days (IORE) DT_{90} = 141 days (IORE)	Moderately persistent	2181260
Anaerobic			
Golden Lake (loamy sand sediment)	DT_{50} = 25.5 days (SFO) DT_{90} = 84.7days (SFO)	Slightly persistent	2181247
Goose river (loam sediment)	DT_{50} = 23.4 days (IORE) DT_{90} = 129 days (IORE)	Slightly persistent	2181247

Table 10 Fate and Behaviour of the Major Transformation Products of Fluensulfone in the Aquatic Environment.

Study	Value / Results	Interpretation	PMRA Study No.
Physical Chemical Properties			
Solubility in water (mg/L)	**MS:** 7644.6 (20°C at pH 2.9)	Very soluble in water	2402074
	TSA: 446200 (20°C at pH 4.2)	Very soluble in water	2402071
	BSA: 580,900 (20°C at pH 3)	Very soluble in water	2402069
	Deschloro-fluensulfone: 3473	Very soluble in water	2402068
	Butene sulfinic acid: 435100	Very soluble in water	2402068
Octanol-water partition (log K_{ow})	**MS:** 0.7 (22°C)	Not expected to bioaccumulate	2402070
	TSA: -3.5 (22°C)	Not expected to bioaccumulate	0402075
	BSA: -2.5(22°C)	Not expected to bioaccumulate	2402073
	Deschloro-fluensulfone: 0.93	Not expected to bioaccumulate	2402068
	Butene sulfinic acid: -1.02	Not expected to bioaccumulate	2402068

Table 11 Endpoints considered in the risk assessment.

Organism	Test substance	Exposure	Endpoint	Value	Uncertainty factor applied
Terrestrial Organisms					
Earthworms (*Eisenia fetida*)	Nimitz 480EC	Acute	14-d LC_{50}	57.4 mg a.i./kg soil d.w.	1
	Nimitz 480EC	Chronic	56-d NOEC	10.5 mg a.i./kg soil d.w.	1
Honeybee (*Apis mellifera* L.)	Nimitz 480EC	Acute oral	LD_{50}	83.7 µg a.i./bee	1
Parasitic wasp (*Aphidius rhopalosiphi*)	Nimitz 480EC	Acute (glass plate)	48-h LR_{50}	16.2 g a.i./ha	1
Predatory mite (*Typhlodromus pyri*)	Nimitz 480EC	Acute (glass plate)	7-d LR_{50}	1000 g a.i./ha	1
Predatory mite (*Hypoaspis aculeifer*)	Nimitz 480EC	Acute	14-d EC_{50} NOEC	82.5 mg a.i./kg soil (reproduction) 52.9 mg a.i./kg soil (reproduction)	1
Ground-active beetle (*Aleochara bilineata*)	Nimitz 480EC		28-d ER_{50}	6.8 mg a.i./kg soil (reproduction)	1

Organism	Test substance	Exposure	Endpoint	Value	Uncertainty factor applied
Springtail (*Folsomia candida*)	Nimitz 480EC		28-d EC_{50} NOEC	20.9 mg a.i./kg soil (mortality) 15.5 mg a.i./kg soil (reproduction)	1
Bobwhite quail (*Colinus virginianus*)	Nimitz 480EC	Acute oral	14-d LD_{50}	99.8 mg ai/kg-bw.	0.10
Bobwhite quail (*Colinus virginianus*)	Fluensulfone	Dietary	5-d LC_{50}	>116.3 mg ai/kg bw/day	0.10
Mallard duck (*Anas platyrhynchos*)	Fluensulfone	One generation	NOAEC	38.7 mg ai/kg-bw/day	1
Rat	Fluensulfone	Acute oral	LD_{50}	30.0 mg a.i./kg bw	0.10
Rat	Fluensulfone	2-generation reprod.	Parental NOAEL Offspring NOAEL	18 mg a.i./kg bw/day 18 mg a.i./kg bw/day	1 1
Terrestrial plants	Nimitz 480EC	Vegetative vigour	EC_{25}	1.5 kg a.i./ha	1
Aquatic Organisms					
Daphnia magna	Nimitz 480EC	Acute	48-h EC_{50}	0.38 mg a.i./L	0.5
	Fluensulfone	Life-cycle	NOAEC	0.20 mg a.i./L	1
Saltwater mysid (*Americamysis bahia*)	Nimitz 480EC	Acute	96-h LC_{50}	0.24 mg a.i./L	0.5
Eastern Oyster (*Crassostrea virginica*)	Nimitz 480EC	Acute	96-h EC_{50}	0.077 mg a.i./L	0.5
Bluegill sunfish (*Lepomis macrochirus*)	Nimitz 480EC	Acute	96-h LC_{50}	2.5 mg a.i./L	0.10
Fathead minnow (*Pimephales promelas*)	Fluensulfone	Early-life stage (ELS)	NOAEC	0.63 mg a.i./L	1
Lemna gibba G3)	Fluensulfone	Acute	7-d EC_{50}	2.7 mg a.i./L	0.5
Green alga (*Pseudokirchneriella subcapitata*)	Nimitz 480EC	Acute	96-h LC_{50}	0.015 mg a.i./L	0.5
Marine Diatom (*Skeletonema costatum*)	Fluensulfone	Acute	96-h EC_{50}	2.6 mg a.i./L	0.5

Table 12 Screening risk assessment for terrestrial organisms other than birds and mammals.

Organism	Test substance	Exposure	Endpoint value	EEC	RQ	Risk
Terrestrial organisms						
Earthworms (*Eisenia fetida*)	Nimitz 480EC	Acute	57.4 mg a.i./kg soil	1.78 mg a.i./kg soil	<1	Negligible
	Nimitz 480EC	Chronic	10.5 mg a.i./kg soil	1.78 mg a.i./kg soil	<1	Negligible
Honeybee (*Apis mellifera* L.)	Nimitz 480EC	Acute oral	83.7 µg a.i./bee (93.7 kg a.i./ha)	3.9 kg a.i./ha	<1	Negligible
Parasitic wasp (*Aphidius rhopalosiphi*)	Nimitz 480EC	Acute (glass plate)	16.2 g a.i./ha	3.9 kg a.i./ha	247	LOC exceeded
Predatory mite (*Typhlodromus pyri*)	Nimitz 480EC	Acute (glass plate)	1000 g a.i./ha	3.9 kg a.i./ha	4.0	LOC exceeded
Predatory mite (*Hypoaspis aculeifer*)	Nimitz 480EC	Acute	82.5 mg a.i./kg soil (reproduction) 52.9 mg a.i./kg soil (reproduction)	1.78 mg a.i./kg soil	<1 <1	Negligible Negligible
Ground-active beetle (*Aleochara bilineata*)	Nimitz 480EC	-	6.8 mg a.i./kg soil (reproduction)	1.78 mg a.i./kg soil	<1	Negligible
Springtail (*Folsomia candida*)	Nimitz 480EC	-	20.9 mg a.i./kg soil (mortality) 15.5 mg a.i./kg soil (reproduction)	1.78 mg a.i./kg soil 1.78 mg a.i./kg soil	<1 <1	Negligible Negligible
Terrestrial plants	Nimitz 480EC	Vegetative vigour	1.5 kg a.i./ha	3.9 kg a.i./ha	2.7	LOC exceeded

Table 13 Refined risk assessment for terrestrial organisms other than birds and mammals.

Organism	Test substance	Exposure	Endpoint value (g a.i./ha)	EEC – 6% drift (g a.i./ha)	RQ	Risk
Parasitic wasp (*Aphidius rhopalosiphi*)	Nimitz 480EC	Acute (glass plate)	16.2	240	14.8	LOC exceeded
Predatory mite (*Typhlodromus pyri*)	Nimitz 480EC	Acute (glass plate)	1000	240	<1	Negligible
Terrestrial plants	Nimitz 480EC	Vegetative vigour	1300	240	<1	Negligible

Table 14 Risk assessment for birds.

			Maximum nomogram residues			
			On-field		Off Field	
	Toxicity (mg ai/ kg bw/d)	Food Guild (food item)	EDE (mg ai/ kg bw)	RQ	EDE (mg ai/ kg bw)	RQ
Small Bird (0.02 kg)						
Acute	99.80	Insectivore (small insects)	201.55	2.02	12.09	0.12
	99.80	Granivore (grain and seeds)	50.39	0.50	3.02	0.03
	99.80	Frugivore (fruit)	100.78	1.01	6.05	0.06
Dietary	116.30	Insectivore (small insects)	201.55	1.73	12.09	0.10
	116.30	Granivore (grain and seeds)	50.39	0.43	3.02	0.03
	116.30	Frugivore (fruit)	100.78	0.87	6.05	0.05
Reproduction	38.70	Insectivore (small insects)	201.55	5.21	12.09	0.31
	38.70	Granivore (grain and seeds)	50.39	1.30	3.02	0.08
	38.70	Frugivore (fruit)	100.78	2.60	6.05	0.16
Medium Sized Bird (0.1 kg)						
Acute	99.80	Insectivore (small insects)	157.29	1.58	9.44	0.09
	99.80	Insectivore (large insects)	39.32	0.39	2.36	0.02
	99.80	Granivore (grain and seeds)	39.32	0.39	2.36	0.02
	99.80	Frugivore (fruit)	78.65	0.79	4.72	0.05
Dietary	116.30	Insectivore (small insects)	157.29	1.35	9.44	0.08
	116.30	Insectivore (large insects)	39.32	0.34	2.36	0.02
	116.30	Granivore (grain and seeds)	39.32	0.34	2.36	0.02
	116.30	Frugivore (fruit)	78.65	0.68	4.72	0.04
Reproduction	38.70	Insectivore (small insects)	157.29	4.06	9.44	0.24
	38.70	Insectivore (large insects)	39.32	1.02	2.36	0.06
	38.70	Granivore (grain and seeds)	39.32	1.02	2.36	0.06
	38.70	Frugivore (fruit)	78.65	2.03	4.72	0.12
Large Sized Bird (1 kg)						
Acute	99.80	Insectivore (small insects)	45.92	0.46	2.76	0.03
	99.80	Insectivore (large insects)	11.48	0.12	0.69	0.01
	99.80	Granivore (grain and seeds)	11.48	0.12	0.69	0.01
	99.80	Frugivore (fruit)	22.96	0.23	1.38	0.01
	99.80	Herbivore (short grass)	164.12	1.64	9.85	0.10
	99.80	Herbivore (long grass)	100.21	1.00	6.01	0.06
	99.80	Herbivore (forage crops)	151.85	1.52	9.11	0.09
Dietary	116.30	Insectivore (small insects)	45.92	0.39	2.76	0.02
	116.30	Insectivore (large insects)	11.48	0.10	0.69	0.01
	116.30	Granivore (grain and seeds)	11.48	0.10	0.69	0.01
	116.30	Frugivore (fruit)	22.96	0.20	1.38	0.01
	116.30	Herbivore (short grass)	164.12	1.41	9.85	0.08
	116.30	Herbivore (long grass)	100.21	0.86	6.01	0.05
	116.30	Herbivore (forage crops)	151.85	1.31	9.11	0.08
Reproduction	38.70	Insectivore (small insects)	45.92	1.19	2.76	0.07
	38.70	Insectivore (large insects)	11.48	0.30	0.69	0.02
	38.70	Granivore (grain and seeds)	11.48	0.30	0.69	0.02
	38.70	Frugivore (fruit)	22.96	0.59	1.38	0.04
	38.70	Herbivore (short grass)	164.12	4.24	9.85	0.25
	38.70	Herbivore (long grass)	100.21	2.59	6.01	0.16
	38.70	Herbivore (forage crops)	151.85	3.92	9.11	0.24

Table 15 Risk assessment for mammals.

			Maximum nomogram residues			
			On-field		Off Field	
	Toxicity (mg ai/ kg bw/d)	Food Guild (food item)	EDE (mg ai/ kg bw)	RQ	EDE (mg ai/ kg bw)	RQ
Small Mammal (0.015 kg)						
Acute	30.00	Insectivore (small insects)	115.93	3.86	6.96	0.23
	30.00	Granivore (grain and seeds)	28.98	0.97	1.74	0.06
	30.00	Frugivore (fruit)	57.96	1.93	3.48	0.12
Reproduction	18.00	Insectivore (small insects)	115.93	6.44	6.96	0.39
	18.00	Granivore (grain and seeds)	28.98	1.61	1.74	0.10
	18.00	Frugivore (fruit)	57.96	3.22	3.48	0.19
Medium Sized Mammal (0.035 kg)						
Acute	30.00	Insectivore (small insects)	101.62	3.39	6.10	0.20
	30.00	Insectivore (large insects)	25.41	0.85	1.52	0.05
	30.00	Granivore (grain and seeds)	25.41	0.85	1.52	0.05
	30.00	Frugivore (fruit)	50.81	1.69	3.05	0.10
	30.00	Herbivore (short grass)	363.20	12.11	21.79	0.73
	30.00	Herbivore (long grass)	221.76	7.39	13.31	0.44
	30.00	Herbivore (forage crops)	336.03	11.20	20.16	0.67
Reproduction	18.00	Insectivore (small insects)	101.62	5.65	6.10	0.34
	18.00	Insectivore (large insects)	25.41	1.41	1.52	0.08
	18.00	Granivore (grain and seeds)	25.41	1.41	1.52	0.08
	18.00	Frugivore (fruit)	50.81	2.82	3.05	0.17
	18.00	Herbivore (short grass)	363.20	20.18	21.79	1.21
	18.00	Herbivore (long grass)	221.76	12.32	13.31	0.74
	18.00	Herbivore (forage crops)	336.03	18.67	20.16	1.12
Large Sized Mammal (1 kg)						
Acute	30.00	Insectivore (small insects)	54.30	1.81	3.26	0.11
	30.00	Insectivore (large insects)	13.58	0.45	0.81	0.03
	30.00	Granivore (grain and seeds)	13.58	0.45	0.81	0.03
	30.00	Frugivore (fruit)	27.15	0.91	1.63	0.05
	30.00	Herbivore (short grass)	194.07	6.47	11.64	0.39
	30.00	Herbivore (long grass)	118.49	3.95	7.11	0.24
	30.00	Herbivore (forage crops)	179.55	5.99	10.77	0.36
Reproduction	18.00	Insectivore (small insects)	54.30	3.02	3.26	0.18
	18.00	Insectivore (large insects)	13.58	0.75	0.81	0.05
	18.00	Granivore (grain and seeds)	13.58	0.75	0.81	0.05
	18.00	Frugivore (fruit)	27.15	1.51	1.63	0.09
	18.00	Herbivore (short grass)	194.07	10.78	11.64	0.65
	18.00	Herbivore (long grass)	118.49	6.58	7.11	0.39
	18.00	Herbivore (forage crops)	179.55	9.98	10.77	0.60

Table 16 Screening risk assessment for aquatic organisms.

Aquatic organisms						
Organism	**Test substance**	**Exposure**	**Endpoint value**	**EEC in water (mg a.i./L)**	**RQ**	**Risk**
Daphnia magna	Nimitz 480EC	Acute	0.19 mg a.i./L	0.50 mg a.i./L	2.6	LOC exceeded
	Fluensulfone	Life-cycle	0.20 mg a.i./L	0.50 mg a.i./L	2.5	LOC exceeded
Saltwater mysid (*Americamysis bahia*)	Nimitz 480EC	Acute	0.12 mg a.i./L	0.50 mg a.i./L	4.2	LOC exceeded
Eastern Oyster (*Crassostrea virginica*)	Nimitz 480EC	Acute	0.039 mg a.i./L	0.50 mg a.i./L	12.8	LOC exceeded
Amphibians	Nimitz 480EC	Acute	0.25 mg a.i./L	2.7 mg a.i./L	10.8	LOC exceeded
Bluegill sunfish (*Lepomis macrochirus*)	Nimitz 480EC	Acute	0.25 mg a.i./L	0.50 mg a.i./L	2.0	LOC exceeded
Fathead minnow (*Pimephales promelas*)	Fluensulfone	Early-life stage (ELS)	0.63 mg a.i./L	0.50 mg a.i./L	<1	Negligible
Lemna gibba G3	Fluensulfone	Acute	1.35 mg a.i./L	0.50 mg a.i./L	<1	Negligible
Green alga (*Pseudokirchneriella subcapitata*)	Nimitz 480EC	Acute	0.0075 mg a.i./L	0.50 mg a.i./L	66.7	LOC exceeded
Marine Diatom (*Skeletonema costatum*)	Fluensulfone	Acute	1.3 mg a.i./L	0.50 mg a.i./L	<1	Negligible

Table 17 Refined risk assessment for aquatic organisms.

Organism	**Test substance**	**Exposure**	**Endpoint value**	**EEC in water (mg a.i./L)**		**RQ**		**Risk**
				Drift	**Runoff**	**Drift**	**Runoff**	
Daphnia magna	Nimitz 480EC	Acute	0.19 mg a.i./L	0.03	0.014	<1	<1	Drift – Negligible Runoff - Negligible
	Fluensulfone	Life-cycle	0.20 mg a.i./L	0.03	0.011	<1	<1	Drift – Negligible Runoff - Negligible
Saltwater mysid (*Americamysis bahia*)	Nimitz 480EC	Acute	0.12 mg a.i./L	0.03	0.014	<1	<1	Drift – Negligible Runoff - Negligible
Eastern Oyster (*Crassostrea virginica*)	Nimitz 480EC	Acute	0.039 mg a.i./L	0.03	0.014	<1	<1	Drift – Negligible Runoff - Negligible
Amphibians	Nimitz 480EC	Acute	0.25 mg a.i./L	0.16	0.057	<1	<1	Drift – Negligible Runoff - Negligible
Bluegill sunfish (*Lepomis macrochirus*)	Nimitz 480EC	Acute	0.25 mg a.i./L	0.03	0.014	<1	<1	Drift – Negligible Runoff - Negligible
Green alga (*Pseudokirchneriella subcapitata*)	Nimitz 480EC	Acute	0.0075 mg a.i./L	0.03	0.014	4.0	1.9	Drift – LOC Exceeded Runoff – LOC Exceeded

Table 18 List of Supported Uses.

Product Name	Nimitz 480EC
Treatment	Broadcast/band spray & incorporated, or drip irrigation
Host or Crop Group	Fruiting vegetables (Crop Group 8) and cucurbit vegetables (Crop Group 9)
Pest	Root knot nematodes (*Meloidogyne* spp.) and root lesion nematodes (*Pratylenchus* spp.)
Application Rate	4 to 8 L/ha
Number of Applications	1 per crop
Timing of Application or Application Interval	Can be applied in any season when soil conditions permit; minimum of seven days before transplanting.
Additional use directions	No more than 8 L of product per hectare, per year

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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2181171	2008, MCW 2 Determination of Water Solubility, DACO: 2.14.7,IIA 2.6
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2181161	2011, MCW-2 Determination of Explosive Properties - Authentication of Amendment to Final Report, DACO: 2.16,IIA 2.13
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2181328	2010, MCW-2 480 EC: Accelerated Storage Stability - First Amendment to Report, DACO: 3.5.1,3.5.10,3.5.2,3.5.3,3.5.7,8.2.3.6,IIIA 2.1,IIIA 2.4.2,IIIA 2.7.1,IIIA 2.8.2,IIIA 2.8.7.1
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2181134	2012, Identity, Physical and Chemical Properties, Data on Application, and Further Information, DACO: 12.7,Document M

2.0 Human and Animal Health

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2635356	2014, MCW-2 TECH: 3- and 7-Day Oral (Feeding) Mechanistic Lung Toxicity Study in Male CD-1 Mice, DACO: 4.8
2635357	2015, Dietary Mechanistic Lung Toxicity Study in Female CD-1 and C57 BL/6 Mice with MCW-2 tech., DACO: 4.8
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2181380	2011, MCW-2 480 EC: Acute Oral Toxicity Study in Rats, DACO: 4.6.1,IIIA 7.1.1
2181351	2009, MCW-2 480 EC Acute Dermal Toxicity Study in Rats, DACO: 4.6.2,IIIA 7.1.2
2181355	2009, MCW-2 480 EC 4-Hour Acute Inhalation Toxicity Study in the Wistar Rat, DACO: 4.6.3,IIIA 7.1.3
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2181200	2009, MCW-2 Tech Primary Eye Irritation Study in Rabbits, DACO: 4.2.4,IIA 5.2.5
2181201	2009, MCW-2 Tech Contact Hypersensitivity in Albino Guinea Pigs, Maximization-Test, DACO: 4.2.6,IIA 5.2.6
2181209	2011, MCW-2 TECH: 4-Week Dermal Toxicity Study in Rats. Harlan Laboratories Ltd., DACO: 4.3.5,IIA 5.3.7
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2181332	2011, MCW-2 Study on the Dermal Penetration of 14C-MCW-2 Formulated as MCW-2 480 EC in Rats, DACO: 5.8,IIIA 7.6.1
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2181331	2010, Method Validation of an Analytical Method for the Determination of MCW-2 and its Metabolites in Plant Matrices, DACO: 7.2.1,IIA 4.3
2181365	2011, Magnitude of the residue of MCW-2 on fruiting vegetables (2009 trials)., DACO: 7.3,7.4.1,7.4.2,IIA 6.1.1,IIA 6.3.1
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2181370	2011, Validation of an Analytical Method for the Determination of Residues of MCW-2 and three Metabolites in Plant Commodities (acidic, dry and fatty), DACO: 7.2.1,IIA 4.3
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3.0 Environment

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B. Additional Information Considered

i) Published Information

1.0 Environment

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