Health Canada | Santé Canada

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number:	2015-0283
Application:	New Active Ingredient - Maximum Residue Limits (MRL) only
Product:	Fluensulfone Technical
Registration Number:	n/a
Active ingredients (a.i.):	fluensulfone
PMRA Document Number:	**2502994**

Background

Fluensulfone is nematicide proposed for use on the cucurbit and fruiting vegetable crop groups. Proposed registration of this active ingredient for domestic use is on-going in Canada but it has been granted in the U.S. and other jurisdictions.

Purpose of Application

The purpose of this application was to establish maximum residue limits for the cucurbit and fruiting vegetable crop groups that have been treated with fluensulfone and are being imported into Canada.

Chemistry Assessment

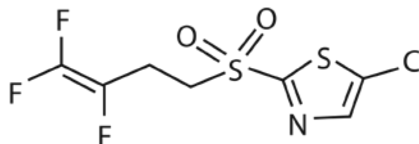
1.0 The Active Ingredient, Its Properties and Uses

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

Canada

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)
Ultraviolet (UV)-visible spectrum	Solution wavelength molar extinction coefficient (nm) (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

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 Methods for Residue Analysis

High performance liquid chromatography methods with tandem mass spectrometric detection (HPLC-MS/MS; Methods 1977W (equivalent to 2061W) and 11M03036-01-VMPL in plant matrices) were developed and proposed for data gathering 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 matrices. The proposed enforcement methods were successfully validated in plant matrices by an independent laboratory. Extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method.

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. Mechanistic studies were also provided to support a proposed mode of action (MOA) for lung tumours in mice, and to investigate a possible MOA leading to decreases in alanine aminotransferase (ALAT) activity in serum and liver homogenates in dogs. Acute and repeated-dose oral toxicity studies as well as genotoxicity studies were also conducted with certain metabolites of fluensulfone. 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.

Fluensulfone, radiolabelled on either the thiazole ring or the butene moiety, was rapidly and extensively absorbed following single oral low or high dose administration to rats. Approximately 60% to 80% of the administered dose was absorbed, with maximum plasma concentrations of radioactivity detected within 1 to 8 hours of dosing. Elimination of fluensulfone occurred primarily via the urine. No significant differences were observed between sexes, between single low or high dosing regimens, or between single and repeated low dosing regimens with respect to the extent of absorption or excretion profiles. However, the rate of elimination was much slower following administration of the high dose of fluensulfone radiolabelled on the thiazole ring when compared to that of the low dose of fluensulfone radiolabelled on the thiazole ring as well as both doses of fluensulfone radiolabelled at the butene position. Fluensulfone was slowly eliminated from whole blood.

The results of the toxicokinetics studies suggested that fluensulfone reacts with the free thiol moiety of the globin protein of hemoglobin to form a covalent linkage to the thiazole group, releasing derivatized hemoglobin and butene sulfinic acid. The slow removal of radiolabel from blood with derivatized hemoglobin seems to be dependent on the metabolic removal of red blood cells.

The tissue distribution of radioactivity was similar in rats given a single oral thiazole-radiolabelled dose when compared to that in rats dosed once with the thiazole-radiolabelled substance after 14 days of dosing with the unlabelled material. Levels of radioactive residues in tissues were very low but widely distributed in the rat, with highest levels detected in the gastrointestinal tract, liver, kidney, pancreas, lung and thyroid gland. The radioactivity was slowly eliminated from certain tissues (e.g. hair, skin, heart, lung), which may reflect metabolism of fluensulfone to 1- and 2-carbon fragments with reincorporation into natural products, such as protein and fatty acids, with long turnover rates.

The metabolism of fluensulfone in the rat was extensive as the parent compound was not detected in urine or feces following a single dose, and only low levels of parent were detected in feces following repeated oral administration of a low dose of fluensulfone radiolabelled on the thiazole ring. Metabolites identified in urine and feces differed based on the position of radiolabel. Following administration of a single dose of the fluensulfone radiolabelled on the thiazole ring, the metabolites identified in urine were thiazole mercapturate, thiazole glucuronide, and thiazole sulfonic acid (also known as M-3625), which was the only metabolite identified in feces. The metabolites identified in urine following administration of the fluensulfone radiolabelled at the butene position included butene sulfinic acid and butene sulfonic acid (also known as M-3627); no metabolites were identified in feces.

Following oral administration in rats, the proposed metabolic pathway for fluensulfone involves reaction with glutathione and the release of butene sulfinic acid, which is converted to butene sulfonic acid. The glutathione adduct of the thiazole ring is cleaved to the cysteine conjugate and ultimately is acetylated to the mercapturate. The glutathione adduct is also cleaved to thiazole thiol that is either oxidized to thiazole sulfonic acid or conjugated with glucuronic acid to give two thiazole glucuronides that are probably α- and β-isomers at anomeric C-1 of the glucuronic acid moiety.

In acute toxicity testing, fluensulfone was demonstrated to be of slight to moderate toxicity via the oral route in rats. In repeated-dose dietary studies, adaptive hepatic effects noted in rats, mice and dogs included hepatocellular hypertrophy accompanied by increased liver weight, as well as induction of phase II cytochrome P450 enzymes. Frank hepatoxicity was evident only in mice at the highest dose tested in the subchronic dietary studies, and consisted of cytoplasmic alteration, necrosis, degeneration, increased incidence of mitotic figures, and bile duct hyperplasia. Clinical chemistry alterations suggestive of perturbations in the metabolism of carbohydrate, lipids and proteins were observed and included increased cholesterol, increased or decreased triglycerides, increased phospholipids, increased or decreased bilirubin, decreased protein, decreased albumin and albumin/globulin ratio, and decreased glucose.

Hematological parameters were altered in rats, dogs and mice administered fluensulfone in the diet. While not always consistent with respect to species or duration of dosing, the effects on hematological parameters in subchronic dietary studies generally included increased white and red blood cell counts, hematocrit, mean cell volume, and reticulocytes; decreased mean corpuscular hemoglobin concentration; and either increased or decreased hemoglobin. After chronic dosing, mice exhibited decreases in red and white blood cell counts, while rats showed decreases in white blood cells counts and mean corpuscular hemoglobin, and increased red blood cell counts. These alterations may be related to the binding of the thiazole group of fluensulfone with the free thiol moiety of the globin protein within hemoglobin.

Evidence of renal toxicity was limited to rats administered high dietary doses of fluensulfone. Effects on the kidney were more prominent in male rats than in females, and were purported to be related to the accumulation of α-2μ-globulin, a protein specific to the male rat. Renal effects in males included tubular basophilia, degeneration, hyaline inclusion, necrosis, tubulosclerosis, and mononuclear cell infiltration. A treatment-related increase in the incidence of Schmorl-positive material in renal tubules was noted in male rats. In addition, immunohistochemical staining for α-2μ-globulin revealed a reaction that was stronger and more widely distributed throughout the renal cortex of males from the high dose group when compared to control males. These findings lend support to the assertion that the renal effects were related to the accumulation of the male rat-specific protein α-2μ-globulin and would thus not be relevant to humans. However, some effects were observed in female rats, consisting of increased severity of Schmorl-positive material in renal tubules and pigment deposits in kidney in the 90-day dietary study, and chronic renal nephropathy, tubular basophilia, and mononuclear cell foci in the two-year dietary study.

In repeated-dose dietary studies in rats and dogs, decreases in ALAT activity, both in plasma and liver tissue, were observed. Specific mode of action investigations performed in dogs suggested that this decrease was not caused by direct binding of fluensulfone or a metabolite of fluensulfone, or by a significant interaction with the co-factor pyridoxal 5'-phosphate. Overall, this finding was not considered to be adverse, due to the inconsistent and/or weak dose response seen in many studies, as well as the evidence of reversibility of the effect after the cessation of dosing with fluensulfone.

Effects on the thyroid gland were apparent in some studies, with reductions in serum thyroxine hormone levels observed at the highest dose tested in the 28-day dietary rat study, and elevations in thyroid stimulating hormone in the blood of dogs administered a high dose of fluensulfone in the diet for 28 or 90 days. The only pathology of the thyroid gland evident in the database was the finding of follicular cell hypertrophy in a few adult male rats of both generations at the high dose in the two-generation dietary reproductive toxicity study.

Dietary administration of fluensulfone resulted in effects on the lung only after long term dietary dosing. Chronic interstitial inflammation of the lungs was apparent in female rats after administration for two years. Bronchiolization (a type of hyperplasia) was observed in male and female mice in the 18-month oncogenicity study. Morphologically, the finding of bronchiolization consisted of a change from flattened epithelium to cuboidal epithelium, or hypertrophy of the epithelium (Clara cells), lining the terminal bronchioles. In the highest dose, this change extended to the adjacent alveolar walls. The diagnosis was confirmed by using

transmission electron microscopy analysis on slides from one control mouse/sex and one mouse/sex from the high dose, which revealed hypertrophy of the epithelium of the terminal bronchioles affecting mostly the non-ciliated Clara cells as well as the surrounding ciliated cells. These cells were arranged in a few layers giving rise to a pseudo-stratified epithelium extending occasionally to the respiratory bronchioles and alveolar ducts.

In a 28-day dietary immunotoxicity study conducted in mice, no evidence of disregulation of the immune system was apparent.

In an acute neurotoxicity study in rats, decreased locomotor activity in females, and decreased spontaneous activity, decreased rearing, and impaired righting response in both sexes were observed on the day of dosing at the lowest dose. No signs of neurotoxicity were noted in any other study, including a 90-day dietary neurotoxicity study in rats. In addition to reduced body weight and food consumption, high-dose males in the 90-day dietary neurotoxicity study exhibited lower motor activity, reduced grip strength, and a slight decrease in brain weight. The lower motor activity, reduced grip strength, and a slight decrease in brain weight observed in the 90-day neurotoxicity study were attributed to systemic toxicity and not considered to be indications of neurotoxicity. There was no treatment-related effect on neuropathology in either study.

Following in utero exposure where maternal animals received fluensulfone via gavage, developmental effects included decreased fetal weight in both rats and rabbits, and an apparent acceleration of fetal ossification in rats based on a decreased incidence of incomplete ossification of various bones including the parietal, interparietal and squamosal bones. In addition, an increased incidence of incomplete ossification of the fifth digit of the medial phalanx in both forelimbs was observed in rabbit fetuses. In the rat, a decrease in the number of viable fetuses was attributed to four dead fetuses in one litter and was considered to be secondary to maternal body weight effects. Developmental toxicity in both species occurred only at the highest dose tested and in the presence of decreased body weight in maternal animals. There was no evidence of teratogenicity in rats or rabbits.

In a two-generation dietary reproductive toxicity study in rats, there was no treatment-related effect on reproductive performance. Effects observed in parental animals were consistent with those reported in other repeated-dose dietary studies in rats and included reductions in body weight, as well as hepatotoxicity and renal effects. Pathology of the thyroid gland, which was not seen in other studies, was noted in parental male rats of both generations and was manifested as follicular cell hypertrophy. At the same dose level, offspring of both generations exhibited reduced body weights during the postnatal period as well as reductions in spleen and thymus weights. An increase in pup loss between postnatal days (PND) 1 and 4 was also observed at this dose level. This study demonstrated a serious endpoint (reduced viability) in the presence of maternal effects.

In several studies, increased fluoride levels in bone and teeth were observed down to the lowest dose tested. This effect was apparent in rats following short-term and chronic dietary exposure, and in dogs following one year of dietary exposure. The increased fluoride content of bones and teeth was observed in rats four weeks after the cessation of treatment in the 90-day dietary study. This finding was also evident in parental animals and 21-day old offspring in the rat two-

generation reproductive toxicity study, with offspring demonstrating a less marked effect than parental animals. In the 90-day dietary study conducted in rats, tooth discoloration, whereby teeth appeared paler in comparison to the normal yellow-brown appearance of teeth in rats, was observed. Tooth discoloration was not observed in any other study, including the chronic dietary toxicity study or the two-generation dietary reproductive toxicity study in rats, in which the fluoride content in bones and teeth was elevated in treated animals. Furthermore, no studies showed any histopathological effects on teeth or bones. The increased fluoride levels in bone and teeth observed following exposure to fluensulfone do not necessarily indicate exposure to free fluoride because the analytical method for measuring fluoride levels in these studies includes fluorine in fluensulfone and its metabolites. Metabolism studies in plants and animals did not show that metabolism of fluensulfone resulted in the release of free fluoride as a metabolite. However, these studies are not definitive in that not all radiolabelled material in the studies was identified. Regardless, in the absence of structural signs of dental or skeletal fluorosis, the findings of increased fluoride in bones and teeth and tooth discoloration are not considered adverse.

Fluensulfone tested negative for genotoxicity in several assays, including two bacterial reverse mutation assays, a forward mutation assay in mammalian cells, a chromosomal aberration assay, and an in vivo micronucleus assay. In one reverse mutation assay, fluensulfone elicited a weak positive response in one strain of *Salmonella typhimurium* (TA100) in the absence of metabolic activation. Overall, it was concluded that fluensulfone was not genotoxic.

In the 18-month dietary oncogenicity study conducted in mice, an increased incidence of alveolar/bronchiolar tumours at the two highest dose levels in females was determined to be treatment-related. A proposed MOA for the formation of these tumours was provided. 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 Cyp2f2 that produces metabolites that are presumptively reactive, (2) increased proliferation of Clara cells resulting in alveolar/bronchiolar hyperplasia (bronchiolization), and (3) progression of alveolar/bronchiolar hyperplasia to adenomas and carcinomas. The involvement of mouse-specific metabolic activation in the lung, namely in the Clara cells by mouse-specific Cyp2f2, was identified as a key event required for the tumorigenic response. Humans express another orthologue of this enzyme, CYP2F1. An abundance of metabolic capacity makes Clara cells susceptible to injury by a wide variety of chemicals, often due to covalent binding of reactive metabolites. Two special studies conducted to elucidate the proposed MOA were provided.

In an in vivo investigation using bromodeoxyuridine (BrdU) labelling, an increase in BrdU index (an indicator of cell proliferation) was evident in the bronchiolar epithelium of female mice 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 an in vitro study, the 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 Cyp2f2 enzyme, and the CYP2E1 and Cyp2e1 isoforms, which are expressed in humans and mice, respectively, to the metabolism of fluensulfone, by co-incubation with and without selective inhibitors. Two concentrations of fluensulfone were tested; however, the

highest concentration was found to be too high (only a small percentage was metabolized) and the results obtained were considered only as confirmatory. No metabolic activity towards fluensulfone was detectable after incubation with human lung microsomes. In contrast, fluensulfone was extensively metabolized by lung microsomes of female and male mice. The study investigators concluded that the mouse-specific isoenzyme Cyp2f2 appears to play a major role in the degradation process.

It was purported that the available data provided evidence that the lung hyperplasia/bronchiolization and tumors in the 18-month mouse oncogenicity study were of Clara cell origin, there was increased bronchiolar cell proliferation at three days of treatment that reverted to control levels by seven days, and that metabolic activation occurred with mouse microsomes but not with human microsomes. It was further argued that metabolic activation by fluensulfone is not likely in humans and as such, the increased Clara cell proliferation, alveolar/bronchiolar hyperplasia and adenoma are unlikely to occur in humans.

The proposed MOA was deemed plausible in the mouse; however, there were limitations regarding dose concordance, specificity, and reversibility of key events. In particular, there was no dose-response assessment for cell proliferation; as such, a threshold for this early key event could not be identified. Therefore, a linear low dose extrapolation approach (q_1*) to the cancer risk assessment was deemed appropriate.

The rat metabolites thiazole sulfonic acid and butene sulfonic acid, which are also environmental metabolites, 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. With one exception, genotoxicity testing conducted with these metabolites yielded negative results for reverse gene mutations in bacteria (thiazole sulfonic acid and butene sulfonic acid), chromosomal aberrations (thiazole sulfonic acid and butene sulfonic acid), and forward mutations in mammalian cells (methyl sulfone) in in vitro testing, as well as for unscheduled DNA synthesis (methyl sulfone) and the induction of micronuclei (all three metabolites) in vivo. Only methyl sulfone induced a weakly positive response in one strain of *Salmonella typhimurium* (TA100) in the absence of metabolic activation in a bacterial reverse mutation assay. 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.

Results of the toxicology studies conducted on laboratory animals with fluensulfone and its metabolites are summarized in Tables 1 and 2 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 3 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Fluensulfone is not yet registered 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 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* (PCPA) 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 database contains 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.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses compared to parental animals in the prenatal 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 indicated previously, the death of four fetuses from the same litter in the rat developmental toxicity study was considered to be a secondary effect of reduced maternal body weight. In the rat two-generation reproductive toxicity study, reduced pup viability was observed in the presence of maternal toxicity, as evidence by reduced body weight, increased liver and kidney weight, and hepatocellular hypertrophy.

Although the reduced pup viability in the two-generation reproductive toxicity study was considered a serious endpoint, concern for this finding was tempered by the fact that maternal toxicity was evident at the same dose level. Accordingly, the 10-fold PCPA factor was reduced to 3-fold for exposure scenarios using the toxicological endpoint from the two-generation reproductive toxicity study. For all other exposure scenarios, the PCPA factor was reduced to 1-fold.

3.2 Acute Reference Dose

To estimate acute dietary risk [Acute Reference Dose (ARfD)], the rat two-generation reproductive toxicity study with an offspring NOAEL of 18 mg/kg bw/day was selected for risk assessment. At the LOAEL of 149 mg/kg bw/day, reduced pup viability (PND 1 to 4) was observed 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 PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. The composite assessment factor (CAF) is thus 300.

The 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 Acceptable Daily Intake

To estimate risk from repeated dietary exposure to fluensulfone [Acceptable Daily Intake (ADI)], the results from both the one-year dietary study in the dog and the two-year combined chronic toxicity/oncogenicity study in the rat were considered as co-critical studies. 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 combined chronic toxicity/oncogenicity study in the rat, the NOAEL of 1.4/1.7 mg/kg bw/day was established in males/females, based on effects at the LOAEL of 9.6/11 mg/kg bw/day which included reduced body weight (males) and chronic interstitial inflammation of the lungs (females).

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, the PCPA factor was reduced to 1-fold. The composite assessment factor (CAF) is thus 100.

The 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

Lung tumours were observed in female mice administered fluensulfone in the diet for 18 months. Although the proposed MOA was deemed plausible in the mouse, it could not be fully supported on the basis of the mechanistic data provided, and therefore the human relevance of these tumours could not be discounted. There were limitations in the proposed MOA regarding dose concordance, specificity, and reversibility of key events. In particular, there was no dose-response assessment for cell proliferation; as such, a threshold for this early key event could not be identified. Therefore, a linear low-dose extrapolation approach for the cancer risk assessment was deemed appropriate. The cancer unit risk (q_1*) for the combined incidence of alveolar/bronchiolar adenomas and carcinomas for female mice is 8.14 x 10^{-2} (mg/kg bw/day)$^{-1}$.

3.4 Occupational and Residential Risk Assessment

As this was an import MRL application, no occupational or residential risk assessment was required.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant Foodstuffs

The residue definition for enforcement in plant products is fluensulfone and metabolite 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. The tomato raw agricultural commodities (RAC) were processed into purée, paste, juice, wet pomace and/or dry pomace according to simulated industrial practice. Residues of fluensulfone were all less than LOQ in the tomato RAC and processed fractions (purée, paste, juice, wet pomace and dry pomace) while quantifiable residues of M-3627 were measured in the same tomato matrices. Processing factors for M-3627 in tomato processed fractions ranged from 0.66- to 6.57-fold. Crop field trials conducted throughout Canada and the United States using end-use product containing fluensulfone at 1.3- to 1.5-fold the maximum US registered rates (US registered GAP = 2.80 kg ai/ha/season) in or on tomatoes, peppers (bell and non-bell), cucumbers, summer squash and cantaloupes (melons) are sufficient to support the proposed import MRLs.

3.5.2 Dietary Risk Assessment

Acute and chronic (non-cancer and cancer) dietary exposure 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 2003-2008 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 intermediate chronic non-cancer analysis for fluensulfone: 100% crop treated and imported to Canada, default and experimental processing factors (when available), and residues of fluensulfone in/on tomatoes, pepper (bell and non-bell), cantaloupes/melons, summer squash and cucumbers based on supervised trial median residue (STMdR) values. The intermediate chronic dietary exposure from all supported fluensulfone food uses (alone) for the total population, including infants and children, and all representative population subgroups is 0.1- 0.2% (0.000013-0.000037 mg/kg bw/day) of the ADI.

The intermediate chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment. The lifetime cancer risk from exposure to fluensulfone in food (alone) was estimated to be 1.32×10^{-6} for the general population, which is not of health concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the intermediate acute analysis for fluensulfone: 100% crop treated and imported to Canada, default and experimental processing factors (when available), residues of fluensulfone in/on tomatoes, pepper (bell and non-bell), cantaloupes/melons, summer squash and cucumbers based on maximum values. The intermediate acute dietary exposure (food alone) for all supported fluensulfone commodities is estimated to be 0.11% (0.000067 mg/kg bw/day) of the ARfD for the total population (95th percentile, deterministic) and is considered acceptable.

3.5.3 Maximum Residue Limits

The recommendation for MRLs for fluensulfone was based upon the submitted field trial data from Canada and US, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of fluensulfone and the metabolite M-3627, expressed as parent equivalents, in/on crops and processed commodities are proposed as shown in Table 3.5.1. Residues in processed commodities not listed in Table 3.5.1 are covered under the proposed MRLs for the RAC.

Table 3.5.1. Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs)

Commodity	Application Method/ Total Application Rate (kg ai/ha)	Preharvest Interval (days)	Total Residues of Fluensulfone and M-3627 (expressed as parent equivalents) (ppm)		Experimental Processing Factor
			Min	Max	
Tomato	Broadcast spray, 7 days pre-planting/2.80	78-150	<0.02	0.301	3.4-fold (paste)
	Drip irrigation, 7 days pre-planting/2.80	85-146	0.033	0.100	

Commodity	Application Method/ Total Application Rate (kg ai/ha)	Preharvest Interval (days)	Total Residues of Fluensulfone and M-3627 (expressed as parent equivalents) (ppm)		Experimental Processing Factor
Bell Pepper	Broadcast spray, 7 days pre-planting/2.80	50-108	0.038	0.266	N/A
	Drip irrigation, 7 days pre-planting/2.80	76-104	0.073	0.090	
Non-Bell Pepper	Broadcast spray, 7 days pre-planting/2.80	50-102	0.041	0.229	N/A
Cucumber	Broadcast spray, 7 days pre-planting/2.80	41-73	<0.02	0.232	N/A
	Drip irrigation, 7 days pre-planting/2.80	41-70	<0.02	0.386	
Summer Squash	Broadcast spray, 7 days pre-planting/2.80	36-71	<0.02	0.273	N/A
	Drip irrigation, 7 days pre-planting/2.80	45-49	0.038	0.076	
Cantaloupe (Melon)	Broadcast spray, 7 days pre-planting/2.80	66-133	<0.02	0.077	N/A

4.0 Environmental and Value Assessment

Environmental and value assessments were not required for this application.

5.0 Conclusion

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. There was no evidence of disregulation of the immune system. Neurotoxicity was evident after acute gavage dosing, but not after repeated dietary exposures. 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 developmental toxicity testing, there was no evidence of increased susceptibility of the young in rats or rabbits. In the rat reproductive toxicity study, reduced postnatal viability, considered a serious endpoint, was observed in the presence of maternal toxicity. Chronic dosing with fluensulfone resulted in lung tumours in female mice. Based on mechanistic data that were provided, a proposed MOA for lung tumours in mice was considered plausible but could not be fully supported due to limitations in the data; therefore the human relevance of these tumours could not be discounted. 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.

The nature of the residues in plants is adequately understood. The residue definition for enforcement is fluensulfone and metabolite M-3627, expressed as fluensulfone equivalents. The importation of fluensulfone-treated tomatoes, bell and non-bell peppers, cucumbers, summer squash and cantaloupes (melons) does not represent a health concern, based on chronic, acute and cancer dietary exposures (food alone), to all segments of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for total residues of fluensulfone.

Commodity	**Recommended MRL (ppm)**
Tomato paste	1
Cucurbit vegetables (CG 9)	0.6
Fruiting vegetables (CG 8-09; except small tomatoes)	0.5

MRLs are proposed for each commodity included in the listed crop groupings in accordance with the Residue Chemistry Crop Groups webpage in the Pesticides and Pest Management section of Health Canada’s website.

List of Abbreviations

♀	female
♂	male
°C	degree Celsius
6 ß-OHT	testosterone 6 ß hydroxylase
a/g	albumin/globulin
abs	absolute
AD	administered dose
ADI	acceptable daily intake
ALAT	alanine aminotransferase
ALD	aldrin epoxidase
ARfD	acute reference dose
AUC	area under the curve
BrdU	bromodeoxyuridine
bw	body weight
bwg	bodyweight gain
Ca	calcium
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control
CG	Crop Group
Cl	chloride
cm	centimetre
C_{max}	maximum concentration
DT_{90}	time from dose to 1/10 T_{max}
ECOD	7-ethoxycoumarin deethylase
EH	epoxide hydrolase
EROD	7-ethoxyresorufin deethylase
F1	first generation
F2	second generation
fc	food consumption
FOB	functional observational battery
g	gram(s)
GAP	Good Agricultural Practice
GD	gestation day
GLDH	glutamate dehydrogenase
GST	glutathione-S-transferase
HCT	hematocrit
HDW	hemoglobin concentration distribution width
HGB	hemoglobin
HPLC- MS/MS	High performance liquid chromatograph with Tandem Mass Spectrometry
IgM	immunoglobulin M
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*-Octanol-water partition coefficient

L	litre(s)
LA12OH	lauric acid 12-hydroxylase activity
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOAEL	Lowest Observed Adverse Effect Level
LOQ	Limit of Quantitation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mg	milligram(s)
MOA	mode of action
MOE	margin of exposure
Mol	mole
MRL	Maximum Residue Limits
mRNA	messenger ribonucleic acid
Na	sodium
NCHS	National Center for Health Statistics
N-Dem	N-demethylase
NHANES	National Health and Nutritional Examination Survey
nm	nanometre
NOAEL	no observed adverse effect level
NOAEL	No Observed Adverse Effect Level
NZW	New Zealand White
O-Dem	O-demethylase
OECD	Organisation for Economic Co-operation and Development
P	parental generation
Pa	Pascals
PCE	polychromatic erythrocyte
PCPA	*Pest Control Product Act*
pK_a	Dissociation constanT
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PTT	partial thromboplastin time
q_1*	cancer potency factor
RAC	raw agricultural commodities
RBC	red blood cell
RDW	red blood cell distribution width
rel	relative
SDH	sorbitol dehydrogenase
SRBC	sheep red blood cell
STMdR	supervised trial median residue
$T_{1/2}$	time to decline to 50% C_{max}
T_{max}	time to maximum concentration
TSH	thyroid stimulating hormone
UDPGT	uridine diphosphoglucuronosyl-transferase
US	United States
UV	ultraviolet
WBC	white blood cell

wc	water consumption
wt	weight
WWEIA	What We Eat in America
μM	micromolar
μg	microgram

Appendix I

Table 1 **Toxicity Profile of 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. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type / Animal / PMRA #	Study Results
Metabolism and excretion following single oral dose (low and high) Rat (Wistar) PMRA 2181184	Excretion: 63-78% of AD excreted in urine, 5-13% of AD excreted in feces, 7-14% of AD detected in cage wash, <4% of AD exhaled as $^{14}CO_2$. No significant differences between sexes, dose levels or label positions. Metabolism - thiazole label: Primary metabolites in urine identified as thiazole mercapturate (38-53% of AD), thiazole glucuronide I (12-19% of AD), thiazole glucuronide II (7-10% of AD), and thiazole sulfonic acid (1-5% of AD). The only metabolite identified in feces was thiazole sulfonic acid (0.1-0.5% of AD; no other peak >5% so not characterized). No significant differences were observed between sexes or dose levels. Metabolism – butene label: Primary metabolites in urine identified as butene sulfinic acid (32-35% of AD at low dose, 53-56% of AD at high dose) and butene sulfonic acid (4-5% of AD). No metabolites identified in feces (no peak >5% so not characterized). No significant differences were observed between sexes.
Pharmacokinetics following single oral dose (low and high) Rat (Wistar) PMRA 2181185	Absorption: Rapid absorption, with plasma T_{max} of 1-8 hours. Comparison of AUC for low and high dose groups indicated 67-70-fold and 45-47-fold difference in AUC between the low and high dose group for the thiazole and butene labels, respectively. Elimination: $T_{1/2}$ from plasma was 14-15 hours for the low dose thiazole label, 20 hours for the low dose butene label, and 24-26 hours for the high dose butene label, and much slower for the high dose thiazole label at 58-67 hours. The amount of radiolabel associated with whole blood increased relative to plasma with time (about 20-fold for the thiazole label but only 2-fold for the butene label). The results of the toxicokinetics studies suggested that fluensulfone reacts with the free thiol moiety of the globin protein of hemoglobin to form a covalent linkage to the thiazole group, releasing derivatized hemoglobin and butene sulfinic acid. The slow removal of radiolabel from blood with derivatized hemoglobin seems to be dependent on the metabolic removal of red blood cells.

Study Type / Animal / PMRA #	Study Results
Tissue distribution following single oral dose (low and high) Rat (Wistar) PMRA 2181186	Tissue distribution: For both labels and both dose levels, the gastrointestinal tract, liver and kidney contained the highest radioactivity levels at C_{max} for both sexes. Other tissues with high levels of radioactivity at C_{max} included the pancreas (♂ low dose thiazole label, ♀ high dose thiazole label, both sexes low dose butene label), the lung (♀ high dose thiazole label, both sexes low dose butene label), and the thyroid gland (both sexes high dose thiazole label). At DT_{90}, the levels of radioactivity remaining in the tissues accounted for ≤3% of the administered dose. Radioactivity from the thiazole label was slowly eliminated from red blood cells and organs associated with their formation/storage (bone, bone marrow, spleen), consistent with the derivatization of the hemoglobin cysteine thiol. Radioactivity from both labels was slowly eliminated from other tissues (e.g. hair and skin, heart, lung), which may reflect metabolism to 1- and 2- carbon fragments with reincorporation in natural products (e.g. protein, fatty acids) with long turnover rates as previously found for goats and hens.
Metabolism, excretion and tissue distribution following repeated oral dose (low) Rat (Wistar) PMRA 2181187	Excretion: 71-83% of AD excreted in urine, 9-11% of AD excreted in feces, 6-16% of AD detected in cage wash. No significant differences between sexes. Metabolism: Primary metabolites in urine identified as thiazole mercapturate (39-45% of AD), thiazole glucuronide I (20-23% of AD), thiazole glucuronide II (6-8% of AD), and thiazole sulfonic acid (2-3% of AD). Parent was detected at low levels in feces (0.1-0.2% of AD). No significant differences were observed between sexes. Tissue distribution: One day after dosing with [^{14}C]fluensulfone, the highest residues were in the gastrointestinal tract, liver, kidney, lung, thyroid, spleen and heart. The radiolabel residue in bone, brain, fat and muscle were 9 to 20-fold lower than in liver. The levels of residues were comparable in both sexes, although generally slightly higher in males. Seven days after dosing with [^{14}C]fluensulfone, radiolabel residues were 2 to10-folds lower compared to those measured one day after dosing.
Acute oral (Acute Toxic Class) Rat (Wistar) PMRA 2181195	Slight Toxicity LD_{50} = 300-2000 mg/kg bw (corresponding to LD_{50} cut-off of >1000 mg/kg bw)
Acute oral (Acute Toxic Class) Rat (Wistar) PMRA 2181196	Moderate Toxicity LD_{50} = 671 mg/kg bw

Study Type / Animal / PMRA #	Study Results
28-day oral (dietary) Mouse (CD-1) PMRA 2181204	NOAEL = 30/41 mg/kg bw/day (♂/♀) LOAEL = 101/155 mg/kg bw/day Effects at the LOAEL: ↓ fc; ↓ platelets, ↓ abs heart wt (♂); ↑ rel liver wt (♀).
90-day oral (dietary) Mouse (CD-1) PMRA 2181205	NOAEL = 11/18 mg/kg bw/day (♂/♀) LOAEL = 51/68 mg/kg bw/day Effects at LOAEL: ↑ bilirubin; ↑ WBC, ↑ RBC, ↑ HGB, ↑ HCT, ↓ platelets (♂); ↓ fc, hepatocellular hypertrophy (♀).
28-day oral (dietary) Rat (Wistar) PMRA 2181203	NOAEL = 10/12 mg/kg bw/day (♂/♀) LOAEL = 42/37 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↓ HGB, ↓ serum ALAT, ↓ EROD, ↓ ALD, ↑ EH, ↑ GST; ↓ bw, ↓ GLDH, ↑ cholesterol, ↓ triglycerides, ↑ UDPGT, ↓ CD8 positive cells, surface changes of kidney, ↑ severity of basophilic tubules of kidney, degeneration and hyaline inclusions in proximal tubules of kidney (♂); ↓ fc, ↑ leukocytes, ↑ lymphocytes, ↓ ECOD (♀).
90-day oral (dietary) Rat (Wistar) PMRA 2181206	NOAEL = 8.3/11.7 mg/kg bw/day (♂/♀) LOAEL = 35/53 mg/kg bw/day Effects at LOAEL: ↓ serum ALAT, ↓ N-Dem, basal cell hyperplasia of forestomach; ↓ bw, ↓ bwg, ↑ wc, ↑ severity of hyaline deposits in proximal tubules, mononuclear cell infiltrates in pharynx (♂); ↑ cholesterol, ↑ triglycerides, ↓ O-Dem (♀).
90-day oral (dietary) Dog (Beagle) PMRA 2181207	NOAEL = 1.6/1.8 mg/kg bw/day (♂/♀) LOAEL = 17/18 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↓ MCHC, ↑ reticulocytes, ↓ bilirubin, ↓ albumin, ↓ a/g ratio, ↑ TSH, ↓ serum ALAT, ↓ hepatic ALAT, ↑ liver wt, pigmented Kupffer cells, ↑ EH; ↓ HGB, ↓ protein (♂); ↓ bw, ↓ fc, ↓ glucose, ↓ thymus wt, slight diffuse hepatocellular hypertrophy (1/4), ↑ 6 ß-OHT activity (♀).
One-year oral (dietary) Dog (Beagle) PMRA 2181208	NOAEL (♀) = 1.5 mg/kg bw/day LOAEL (♀) = 3.3 mg/kg bw/day Effects at LOAEL: ↓ bw, ↓ bwg, ↓ bilirubin, ↑ rel liver wt, ↓ abs thymus wt, ↑ rel kidney wt. NOAEL (♂) = 3.1 mg/kg bw/day LOAEL (♂) = 16 mg/kg bw/day Effects at LOAEL:↓ bw, ↓ bwg, ↓ HGB, ↓ MCHC, ↑ RDW, ↑ HDW, ↑ reticulocytes, ↓ serum ALAT, ↑ platelets, ↓ protein, ↓ albumin, ↓ a/g ratio, ↓ hepatic ALAT, hepatocellular hypertrophy, brownish pigment in liver, ↑ GST, ↑ EH, ↓ MCH, ↓ PTT, ↑ rel liver wt, ↑ kidney wt, ↑ rel adrenal wt.

Study Type / Animal / PMRA #	Study Results
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 (Clara 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 (♀). Evidence of oncogenicity, based on a treatment-related increase in alveolar/bronchiolar adenomas and carcinomas in female mice.
Two-year chronic toxicity/oncogenicity (dietary) Rat (Wistar) PMRA 2181217	NOAEL = 1.4/1.7 mg/kg bw/day (♂/♀) LOAEL = 9.6/11 mg/kg bw/day Effects at LOAEL: ↓ MCHC, ↑ Na, ↑ Ca, ↑ Cl, ↑ protein, ↑ EH, hyperkaratosis of the esophagus; ↓ bw, ↓ bwg, ↓ prothrombin time, ↑ globulin, ↑ phosphorous, foci in prostate (at gross exam) (♂); ↓ HDW, ↓ lymphocytes, ↓ neutrophils, ↓ WBC, ↓ serum ALAT, ↑ GST, ↑ UDPGT, chronic interstitial inflammation of the lung (♀). No evidence of oncogenicity.
Two-generation reproduction (dietary) Rat (Wistar) PMRA 2181222	Parental NOAEL = 18/20 mg/kg bw/day (♂/♀) Parental LOAEL = 137/149 mg/kg bw/day Effects at LOAEL: ↓ bw pre-mating P & F1, ↓ bwg pre-mating P, ↓ fc pre-mating week 1 P, ↑ kidney wt P, ↓ glycogen deposits in liver P, centrilobular hepatocellular hypertrophy F1; ↑ liver wt P, ↑ kidney wt F1, ↑ liver wt F1, ↑ rel testes wt F1, ↑ rel epididymal wt F1, centrilobular hepatocellular hypertrophy P, hyaline droplets in kidneys P & F1, renal tubular basophilia P & F1, mononuclear cell infiltration of kidneys P & F1, renal tubular casts P & F1, thyroid gland follicular hypertrophy P & F1, ↓ glycogen deposits in liver F1 (♂); ↓ bw gestation & lactation P & F1, ↑ bwg lactation P, ↓ bwg gestation F1, ↑ rel liver wt P & F1, ↓ adrenal wt P, ↑ rel kidney wt F1 (♀). Reproductive NOAEL = 137/149 mg/kg bw/day (♂/♀) No effects on reproductive performance. Offspring NOAEL = 18/20 mg/kg bw/day (♂/♀) Offspring LOAEL = 137/149 mg/kg bw/day Effects at LOAEL: ↑ postnatal loss PND 0-4 F1 & F2 (most on PND 2), ↓ bw F1 & F2, ↓ spleen wt F1 & F2, ↓ abs thymus wt F1 & F2, ↓ rel (to brain wt) thymus wt F1 & F2, ↓ severity of glycogen deposits in liver F2; ↓ incidence of glycogen deposits in liver F2 (♀). Serious endpoint (reduced viability) in the presence of maternal toxicity.

Study Type / Animal / PMRA #	Study Results
Developmental toxicity (gavage) Rat (Wistar) PMRA 2181223	Maternal NOAEL = 50 mg/kg bw/day Maternal LOAEL = 300 mg/kg bw/day Effects at LOAEL: ↓ bw GD 10-20, ↓ corrected bwg, ↓ fc GD 6-12, ↑ rel kidney wt, ↑ rel liver wt. Developmental NOAEL = 50 mg/kg bw/day Developmental LOAEL = 300 mg/kg bw/day Effects at LOAEL: ↓ viable fetuses (4 dead fetuses in one litter, secondary to maternal bw effects), "more progressed" ossification (i.e., reduced incidence of incomplete ossification of parietal bone, interparietal bone, and squamosal bone and enlarged sagittal suture, anterior fontanelle, posterior fontanelle and squamosal suture on fetal and litter basis); ↓ fetal bw (♀). No evidence of sensitivity of the young.
Developmental toxicity (gavage) Rabbit PMRA 2181224	Maternal NOAEL = 10 mg/kg bw/day Maternal LOAEL = 40 mg/kg bw/day Effects at LOAEL: ↓ fc GD 18-24, bw loss GD 6-9, ↓ bwg GD 6-28, ↓ corrected bwg. Developmental NOAEL = 10 mg/kg bw/day Developmental LOAEL = 40 mg/kg bw/day Effects at LOAEL: ↓ fetal bw, incomplete ossification of digit 5 of medial phalanx in both forelimbs. No evidence of sensitivity of the young.
Acute oral neurotoxicity (gavage) Rat (Wistar) PMRA 2181226	NOAEL not established as adverse effects were noted at the lowest dose tested. LOAEL = 100 mg/kg bw Effects at LOAEL: ↓ spontaneous activity, ↓ rearing, impaired righting response; piloerection (♂); ↓ locomotor activity (♀). All clinical signs, FOB and locomotor activity effects were noted on day of dosing.
90-day oral neurotoxicity (dietary) Rat (Wistar) PMRA 2181227	NOAEL = 31/34 mg/kg bw/day (♂/♀) LOAEL = 153/162 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↓ fc; ↓ bw, ↓ grip strength week 13, ↓ locomotor activity week 5, ↓ abs brain wt (♂).
28-day immunotoxicity (dietary) Mouse (CD-1) PMRA 2181189	NOAEL = 86 mg/kg bw/day LOAEL = 204 mg/kg bw/day Effects at LOAEL: death of one animal day 8, clinical signs in surviving animals day 8 (light coloured feces in all animals, ruffled fur in 2 animals, hunched posture in 1 animal), ↓ bw week 1, ↓ fc week 1, ↓ wc week 1. No treatment-related effect on anti-SRBC IgM levels.

Study Type / Animal / PMRA #	Study Results
Bacterial reverse mutation PMRA 2181211	Positive (weakly): Fluensulfone elicited a weak positive response in *S. typhimurium* strain TA100 in the absence of metabolic activation in both experiments (increases were less than 2-fold the vehicle control values). Negative in *S. typhimurium* strains TA98, TA102, TA1535, and TA1537 in the absence and presence of metabolic activation, and in *S. typhimurium* strain TA100 in the presence of metabolic activation.
Bacterial reverse mutation PMRA 2181212	Negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and in E. Coli strain WP2 uvrA, in the presence and absence of metabolic activation.
Bacterial reverse mutation PMRA 2181213	Negative in S. typhimurium strains TA98, TA100, TA1535, and TA1537, and in E. Coli strain WP2 uvrA, in the presence and absence of metabolic activation.
In vitro forward mutation assay in mammalian cells PMRA 2181215	Negative in Chinese hamster V79 lung cells.
In vitro chromosomal aberration assay PMRA 2181214	Negative in human peripheral lymphocytes. Significant increase in aberrations but only at cytotoxic concentration (1000 µg/mL)
In vivo micronucleus assay PMRA 2181216	Negative in the mouse (Hsd/Win:NMRI strain). ≥75 mg/kg bw: apathy, roughened fur, bw loss, spasm, difficulty breathing, slitted eyes, closed eyes.
Special Study 2 week oral (dietary) – effect on ALAT Dog (Beagle) PMRA 2181190	Effects at 21 mg/kg bw/day included ↓ plasma ALAT, ↓ plasma pyridoxal 5'-phosphate, ↑ hepatic pyridoxal 5'-phosphate, ↓ hepatic ALAT, ↑ hepatic ALAT mRNA levels. No effect of treatment was observed on hepatic ALAT protein expression. The reduction of the ALAT activity by fluensulfone is not mediated by a decrease in hepatic pyridoxal 5'-phosphate, or by a reduction of ALAT-protein or -mRNA expression. Other mechanisms, such as alteration of post-translational modification or a specific effect on the expression of other ALAT isoforms, might be the cause for the transiently decreased activity of ALAT.
Special Study In vitro study – ALAT in dog liver homogenate Dog (Beagle) PMRA 2181191	No inhibition of ALAT activity observed following incubation of dog liver homogenates with up to 19.1 µM fluensulfone for up to 1 hour. Results demonstrated effective metabolism of fluensulfone.

Study Type / Animal / PMRA #	Study Results
Special Study Inhibition of ALAT – serum and liver cytosol from dogs Dog (Beagle) PMRA 2181192	Decreased ALAT cannot be explained by an inhibition by fluensulfone or its metabolites. A decrease in the expression of ALAT protein is considered unlikely based on results, but cannot be fully excluded. Specificity of the immunoblotting antibody has not been tested against dog ALAT; levels of fluensulfone or metabolites in serum and liver not known.
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.

Table 2 Toxicity Profile of Metabolites of 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. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type / Animal / PMRA #	Study Results
Thiazole sulfonic acid (Metabolite #3625)	
Acute oral (Acute Toxic Class) Rat (Wistar) PMRA 2181232	Low Toxicity LD_{50} >2000 mg/kg bw
28-day oral (dietary) Rat (Wistar) PMRA 2402076	NOAEL not established (range-finding study) No treatment-related effects were observed up to 1194/1779 mg/kg bw/day in ♂/♀.
90-day oral (dietary) Rat (Wistar) PMRA 2424406	NOAEL = 975/1369 mg/kg bw/day in ♂/♀ No treatment-related effects were observed up to 975/1369 mg/kg bw/day in ♂/♀.
Bacterial reverse mutation PMRA 2181238	Negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and in E. Coli strain WP2 uvrA, in the presence and absence of metabolic activation.
In vitro chromosome aberration PMRA 2181229	Negative in Chinese hamster V79 lung cells.
In vivo micronucleus assay PMRA 2181236	Negative in the rat (Wistar). ≥500 mg/kg bw: ↓ spontaneous activity, ruffled fur.
Methyl sulfone (Metabolite #3626)	
Acute oral (Acute Toxic Class) Rat (Wistar) PMRA 2181233	Moderate Toxicity LD_{50} = 300-2000 mg/kg bw (corresponding to LD_{50} cut-off of >500 mg/kg bw)

Study Type / Animal / PMRA #	Study Results
Bacterial reverse mutation PMRA 2181239	Positive (weakly): Gene mutations induced for *S. typhimurium* strain TA100 in the absence of metabolic activation (response exceeded twice the control response in 2/3 experiments). Negative in *S. typhimurium* strains TA98, TA102, TA1535, and TA1537 in the absence and presence of metabolic activation, and in *S. typhimurium* strain TA100 in the presence of metabolic activation.
In vitro forward mutation assay in mammalian cells PMRA 2181228	Negative in Chinese hamster V79 lung cells.
In vivo unscheduled DNA synthesis assay PMRA 2181231	Negative in the rat (Wistar). ≥250 mg/kg bw: ↓ spontaneous activity, ruffled fur. 500 mg/kg bw: 1 animal died, apathy.
In vivo micronucleus assay PMRA 2181237	Negative in the rat (Wistar). 500 mg/kg bw: ↓ spontaneous activity, ruffled fur.
Butene sulfonic acid (Metabolite #3627)	
Acute oral (Acute Toxic Class) Rat (Wistar) PMRA 2181234	Low Toxicity LD_{50} >2000 mg/kg bw
28-day oral (dietary) Rat (Wistar) PMRA 2407952	NOAEL not established (range-finding study) No adverse effects were observed up to 732/1024 mg/kg bw/day in ♂/♀.
Bacterial reverse mutation PMRA 2181240	Negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and in *E. Coli* strain WP2 uvrA, in the presence and absence of metabolic activation.
In vitro chromosome aberration assay PMRA 2181230	Negative in Chinese hamster V79 lung cells.
In vivo micronucleus assay PMRA 2181235	Negative in the rat (Wistar strain). Significant increase in micronucleated PCEs only at a cytotoxic dose (driven by one animal). ≥1000 mg/kg bw: ruffled fur.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Fluensulfone

Exposure Scenario(s)	Study	Point of Departure and Endpoint	CAF[1]
Acute dietary	Two-generation dietary reproductive toxicity study in the rat	NOAEL = 18 mg/kg bw/day, based on increased postnatal loss, observed in the presence of reduced toxicity in parental animals	300 (3-fold PCPA factor)
	ARfD = 0.06 mg/kg bw		
Repeated dietary	Two-year dietary chronic toxicity/oncogenicity study in the rat One-year dietary 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		
Cancer	18-month dietary oncogenicity study in the mouse	$q_1^* = 8.14 \times 10^{-2}$ (mg/kg bw/day)$^{-1}$, based on the combined incidence of alveolar/bronchiolar adenomas and carcinomas in female mice	N/A

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2181113	2012, Document JII (Technical Active Ingredient -- Confidential Information), DACO: 0.8.11,0.8.12,Document J
2181132	2012, Identity, Physical and Chemical Properties, and Further Information, DACO: 12.7,Document M
2181149	2008, MCW2 - Quantification of Active Ingredient and Impurities Present at or above 0.1% in Technical MCW2, DACO: 2.12.2,2.13.1,2.13.3,2.13.4,IIA 1.10.1,IIA 1.11.1,IIA 4.2.1,IIA 4.2.3,IIA 4.2.4 CBI
2181150	2010, Overview of Test Batches Used in the MCW-2 Toxicology Program, DACO: 2.13.3,IIA 1.11.2 CBI
2181178	2011, Analytical method to determine [CBI removed] in technical fluensulfone, DACO: 2.13.4,IIA 4.2.4 CBI
2257054	2011, Validation of analytical method for determination of [CBI info removed], DACO: 2.13.1,7.2.2 CBI
2181120	2012, Analytical Methods, DACO: 12.7,Document M
2257057	2008, Analytical Method for the Active Ingredient in Technical MCW2, DACO: 2.13.1
2181149	2008, MCW2 - Quantification of Active Ingredient and Impurities Present at or above 0.1% in Technical MCW2, DACO: 2.12.2,2.13.1,2.13.3,2.13.4,IIA 1.10.1,IIA 1.11.1,IIA 4.2.1,IIA 4.2.3,IIA 4.2.4 CBI
2181151	2008, MCW 2 Determination of the Melting Point / Melting Range, DACO: 2.14.4,IIA 2.1.1
2181152	2009, MCW 2 Technical Determination of the Melting Point - Melting Range and the Boiling Point - Boiling Range, DACO: 2.14.13,2.14.4,2.14.5,IIA 2.1.1,IIA 2.1.2,IIA 2.1.3
2181153	2008, MCW 2 Determination of the Boiling Point/Boiling Range, DACO: 2.14.5,IIA 2.1.2
2181166	2008, MCW 2 Determination of the Relative Density, DACO: 2.14.6,IIA 2.2
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