Proposed Registration Decision PRD2016-30

Sulfuryl Fluoride

(publié aussi en français)

30 September 2016

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2016-30E (print version)
H113-9/2016-30E-PDF (PDF version)

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Overview

Proposed Registration Decision for Sulfuryl Fluoride

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 Sulfuryl Fluoride Gas Fumigant and ProFume Gas Fumigant, containing the technical grade active ingredient sulfuryl fluoride, to control stored product pests in cereal grain mills, associated storage facilities and food processing plants.

Sulfuryl Fluoride Gas Fumigant (Registration Number 28240) and ProFume Gas Fumigant (Registration Number 28241) are conditionally registered in Canada for use in empty cereal grain mills, associated empty storage facilities and empty food processing plants. The detailed review for Sulfuryl Fluoride Gas Fumigant and ProFume Gas Fumigant can be found in Regulatory Note REG2006-15, *Sulfuryl Fluoride*. A Proposed Regulatory Decision PRD2008-10, *Sulfuryl Fluoride* to convert conditional registration for this use to full was published and no comments were received. However, subsequent to the publication of PRD2008-10 additional data and information were submitted and reviewed. The current applications are to convert Sulfuryl Fluoride Gas Fumigant and ProFume Gas Fumigant from conditional registration to full registration and to expand the uses to include food commodities.

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 Sulfuryl Fluoride Gas Fumigant and ProFume Fumigant Gas.

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 (for example, those most sensitive to environmental contaminants). 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.

Before making a final registration decision on sulfuryl fluoride, 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 sulfuryl fluoride, 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 Sulfuryl Fluoride?

Sulfuryl fluoride is a fumigant gas that kills insects. When formulated as ProFume Gas Fumigant, it kills all life stages of several insects found in certain stored food and feed commodities, and in cereal grain mills, storage facilities and food processing facilities.

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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."

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.*

Health Considerations

Can Approved Uses of Sulfuryl Fluoride Affect Human Health?

ProFume Gas Fumigant, containing sulfuryl fluoride, is unlikely to affect your health when used according to label directions.

Exposure to sulfuryl fluoride may occur through the diet and when the product is handled and applied. 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 pesticide-containing products are used according to label directions.

The technical grade active ingredient, sulfuryl fluoride, and the associated end-use product, ProFume Gas Fumigant, are considered of high acute toxicity by the oral and inhalation routes of exposure; consequently, the signal word and hazard statement “Danger Poison” are required on each label. The gas is stored under pressure in cylinders, resulting in a compressed liquid form, which causes burns if released. For this reason, the statement “Liquid is corrosive to eyes and skin” is required on both labels.

Registrant-supplied short-term and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of sulfuryl fluoride to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included effects on the lung, brain, and liver. It was not possible to completely characterize potential sensitivity of the young. The risk assessment takes this into account and is protective of the above-noted effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Food

Dietary risks from food are not of health concern.

Dietary intake estimates revealed that the general population and infants less than one year old, the subpopulation which would ingest the most sulfuryl fluoride relative to body weight, are expected to be exposed to less than 30% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from sulfuryl fluoride is not of health concern for all population subgroups. In addition, the chronic dietary exposure to fluoride, a degradation of sulfuryl fluoride, is also 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 2% 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.

Fumigation trials conducted in Canada and the United States using sulfuryl fluoride on various raw agricultural commodities and processed commodities are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Consultation Document.

Occupational risks are not of concern when ProFume Gas Fumigant is used according to label directions, which will include the following additional protective measures:

Fumigation workers must wear a long-sleeved shirt, long pants, shoes, and socks. During fumigation and aeration, workers must wear adequate positive pressure, self-contained breathing apparatus (SCBA) with a full face mask if the airborne concentration of sulfuryl fluoride in the fumigated area exceeds 1 part per million (ppm) in the breathing zone. Fumigations performed by any individual fumigation workers or crew member must be separated by a two-week interval, and no one may enter the treated structure without adequate respiratory protection until the airborne concentration of sulfuryl fluoride inside the structure is at or below 1 ppm.

Taking into consideration these label requirements, health risks to workers handling ProFume Gas Fumigant are not of concern.

Bystander risks are not of concern when ProFume Gas Fumigant is used according to label directions, which include protective measures and the requirement for a fumigant management plan.

A fumigation management plan is required for each fumigation event to ensure that concentrations of sulfuryl fluoride in the air around the fumigated structure do not exceed 1 ppm.

Environmental Considerations

What Happens When Sulfuryl Fluoride Is Introduced Into the Environment?

Sulfuryl fluoride is a methyl bromide replacement and will be used in the fumigation of structures and some food commodities. After fumigation, sulfuryl fluoride will enter the environment when released from the building, into the atmosphere.

The release to the environment will be slow and concentrations are not expected to pose an unacceptable risk to the environment.

Once in the atmosphere, however, sulfuryl fluoride is expected to last for a long period of time and it has been detected in remote areas around the world. Sulfuryl fluoride is a greenhouse gas.

Value Considerations

What Is the Value of ProFume Gas Fumigant?

ProFume Gas Fumigant (99.8% sulfuryl fluoride) controls several insects that damage food and animal feed, such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil. ProFume Gas Fumigant may be used to treat food and feed products listed on the label, as well as cereal grain mills, storage facilities and food processing facilities.

Sulfuryl fluoride is an alternative to methyl bromide which is being phased out under an international agreement. It is also an alternative to phosphine gas which damages certain metals. Carbon dioxide is another alternative to sulfuryl fluoride; however, it has a limited number of uses.

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 Profume Gas Fumigant to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Fumigation workers could be exposed to sulfuryl fluoride while performing fumigation and aeration activities. No mixing or loading is required because ProFume Gas Fumigant is introduced directly from the cylinder to the area requiring treatment through a suitable leak-proof tube. Because there is a concern with users coming into direct contact with sulfuryl fluoride on the skin or through inhalation of fumes, fumigation workers must wear a long-sleeved shirt, long pants, shoes, and socks. The label will indicate that during fumigation and aeration, workers must wear adequate positive pressure, self-contained breathing apparatus (SCBA) with a full face mask if the airborne concentration of sulfuryl fluoride in the fumigated area exceeds 1 ppm, or is unknown, in the breathing zone. It will also specify that fumigations performed by any individual fumigation workers or crew member must be separated by a two-week interval, and that no one may enter the treated structure without adequate respiratory protection until the concentration of sulfuryl fluoride inside the structure is at or below 1 ppm.

Next Steps

Before making a final registration decision on sulfuryl fluoride, the PMRA will consider all 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 note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. 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 sulfuryl fluoride (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

Sulfuryl Fluoride

1.0 The Active Ingredient, Its Properties and Uses

A detailed assessment of the chemical properties of sulfuryl fluoride and the end-use product ProFume Gas Fumigant are presented in Regulatory Note REG2006-15, *Sulfuryl Fluoride*.

1.1 Directions for Use

ProFume Gas Fumigant controls certain insects such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil that infest stored products in cereal grain mills, storage facilities and food processing facilities. The following commodities can be treated: barley, dried beef, cocoa bean, dried coconut, coffee bean, corn, dried eggs, ham, powdered milk, oats, popcorn, rice, sorghum grain, triticale grain, wheat and wild rice. The product must be applied by licensed applicators using the ProFume Fumiguide computer program, which identifies the parameters under which the fumigation can take place (for example, maximum dose and concentration, minimum length of fumigation and temperatures). Refer to the label for further information.

1.2 Mode of Action

Sulfuryl fluoride is a gas which is a non-specific target poison that belongs to the Insecticide Resistance Action Committee's Mode of Action (MOA) Group 8C. It kills insects by interfering with metabolic processes.

2.0 Methods of Analysis

Gas chromatography methods with mass spectrometric detection (GC-MS; Method GRM 01.12 in dried fruits and tree nuts and Method GRM 01.18 in cereals grains) 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 limits of quantitation. Acceptable recoveries (70–120%) were obtained in all tested food commodities. The proposed enforcement methods were successfully validated in food commodities 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 methods.

3.0 Impact on Human and Animal Health

A detailed review of the toxicological database for sulfuryl fluoride was conducted previously and is summarized in Regulatory Note REG2006-15, *Sulfuryl Fluoride*. The database consists 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 sulfuryl fluoride. Most of the toxicity studies were conducted via the inhalation route of exposure.

Results of the toxicology studies conducted on laboratory animals with sulfuryl fluoride and the associated end-use product, ProFume Gas Fumigant, are presented in REG2006-15, along with toxicology endpoints for use in human health risk assessment.

In summary, the key findings from the toxicological studies included clinical signs of toxicity in the form of tremors, lethargy, incapacitation, convulsions, tetany, and impaired respiratory function following both single and repeated inhalation exposures. Target tissues following repeated inhalation exposure included the brain, kidney, and respiratory tract. Effects on the teeth in the form of dental fluorosis and dental abnormalities were also noted after repeated exposure. Mortality occurred at high exposure levels. There was no evidence of oncogenic or genotoxic potential. Metabolism studies showed that sulfuryl fluoride undergoes rapid hydrolysis to form fluorosulfate and sulfate following the sequential loss of two fluorine atoms.

As indicated above, the brain was identified as a target tissue in several toxicity studies conducted with sulfuryl fluoride. Neuropathology was observed in mice and rabbits after only two weeks of inhalation exposure. Neurotoxicity studies conducted in rats demonstrated that repeated exposures of sulfuryl fluoride for 13 weeks resulted in slowed somatosensory and visual evoked potentials as well as auditory brainstem and cortical responses. Brain lesions were noted at exposure levels higher than those affecting evoked potentials, which appear to be a more sensitive indicator of neurotoxicity than neuropathology following sulfuryl fluoride exposure. The brain lesions noted in the toxicology database indicate that sulfuryl fluoride targets a specific region of the brain as opposed to a particular neural cell type. Lesions were generally seen in the basal ganglia region of the brain, primarily affecting the caudate-putamen region. The incidence and severity of brain lesions increased with exposure level, and the dose at which effects were observed generally decreased with increasing duration of exposure.

The results of the developmental and reproductive toxicity studies did not provide evidence of increased susceptibility of the young. However, fetal or pup brains were not examined histologically in these studies. Therefore, it was not known whether adverse effects on the brain would occur following in utero exposure or via exposure through milk, nor was it known how potential effects on the developing brain might translate to adverse functional outcome (for example, cognitive ability). Consequently, there was uncertainty regarding the potential for developmental neurotoxicity in humans. As outlined in REG2006-15, in the absence of a developmental neurotoxicity study or other such data to address this uncertainty, an additional factor of 3-fold was used to assess human health risk for some exposure scenarios.

In an effort to address this uncertainty with respect to developmental neurotoxicity, the registrant submitted additional pharmacokinetic (PK) studies conducted in adult, perinatal and weanling rats, as well as in adult rabbits. The results of these studies are summarized in Appendix I, Table 2. Most of the studies focused on the analysis of fluorosulfate and fluoride in plasma and tissues following various exposure regimens. Some studies also included an analysis of sulfuryl fluoride residues; however, sulfuryl fluoride was not detected in nasal or lung tissue or in plasma.

Levels of fluorosulfate and fluoride detected in rat tissues were comparable after either a single inhalation exposure or ten daily inhalation exposures, indicating minimal accumulation of sulfuryl fluoride metabolites following repeated exposures. When adult rats were exposed to sulfuryl fluoride via inhalation, fluorosulfate was not detected in the brain, and brain fluoride levels exceeded those in plasma and lungs. These results suggested that transfer of fluorosulfate across the blood-brain barrier was limited, whereas fluoride readily partitioned to the brain. Therefore, it can be concluded that the toxicity of sulfuryl fluoride is mediated primarily by the fluorine atoms that are formed from the breakdown of sulfuryl fluoride.

Adult rabbits, when compared to rats, demonstrated higher plasma fluoride levels but lower brain fluoride levels following a single inhalation exposure to the same concentration of sulfuryl fluoride. These results suggested that although more fluoride was absorbed by rabbits, less partitioned to the rabbit brain when compared to rat brain.

In studies in which pregnant female rats were exposed to sulfuryl fluoride via inhalation during gestation, levels of fluoride and fluorosulfate in fetal plasma were 12% and 19 to 42%, respectively, of the levels measured in plasma collected from dams. No fluoride was detected in fetal brain tissue. Fluorosulfate was detected in fetal brain tissue, but at a level equivalent to 35% of the fetal plasma level.

In female rats exposed to sulfuryl fluoride via inhalation during gestation and for a portion of the lactation period (lactation days [LD] 5 to 10), fluoride levels in the dam's milk immediately following the exposure period on LD 10 were 3-fold to 5-fold lower than fluorosulfate levels. Two hours after the termination of the exposure period on LD 10, levels of fluorosulfate in milk declined to 25% to 46% of the peak values that were measured immediately following the exposure period, whereas levels of fluoride in milk increased. Non-detectable or very low levels of fluoride were measured in the plasma of 10-day old pups receiving milk from dams exposed to sulfuryl fluoride via inhalation. These results indicated little carryover on a daily basis of free fluoride in pup plasma, despite daily exposures via milk from exposed dams.

Pups that were gavage-dosed with an exaggerated dose of fluoride in milk exhibited low levels of fluoride in the brain. In this study, the fluoride level in milk given to pups was up to four-times higher than levels in milk of maternal animals exposed via inhalation to sulfuryl fluoride. Fluoride was detected in the brain of pups at a level that was one-third the level in plasma.

In weanling rats exposed directly to sulfuryl fluoride via inhalation, fluoride was detected in plasma at eight hours after termination of the exposure, and not at earlier time points. This could have been the result of slow hydrolysis of fluorosulfate, rapid uptake of fluoride by bone, or analytical error. The levels of fluoride in the brains of weanling pups were 17-fold lower than those in adult rats exposed to similar concentrations of sulfuryl fluoride via inhalation.

In an in vitro study examining the hydrolysis of sulfuryl fluoride in rat and human tissue, the highest rate was observed in blood. The rate of hydrolysis in blood was similar in adult rats and 10-day old rats, whereas the rate was 2-fold higher in human blood when compared to rat blood.

Collectively, the results of these PK studies demonstrated that fetal and pup plasma fluoride levels were lower than those measured in the maternal plasma, and that fluoride was not detected in the brains of fetuses exposed to sulfuryl fluoride via the maternal animal. However, a key component missing from these additional PK investigations was an assessment of fluoride in the brains of pups exposed after birth via their mother's milk.

In an attempt to address this gap in the testing paradigm, brain fluoride levels in nursing pups over a 24-hour lactational exposure period were predicted by the registrant using a cross-species physiologically-based pharmacokinetic (PBPK) model, using parameters for rats, rabbits, and humans. The PBPK model predicted that fluoride would not accumulate in the brain of the young animal and that levels of fluoride would not increase with multiple exposures. It did, however, predict that fluoride would partition to the developing brain of the young exposed to sulfuryl fluoride metabolites via maternal milk, and that plasma and brain fluoride levels in nursing pups plateau and reach steady state within two hours.

Limitations in the submitted PBPK were identified. Input parameters in the model included data from the above-noted study in which pups were gavage-dosed with an exaggerated dose of fluoride in milk. However, in that study, the fluoride levels in the brains of gavage-dosed pups did not follow a dose response and the post-dosing time-course of the brain fluoride levels differed for the various dose levels. Furthermore, the data from the highest dose in that study were excluded from the model and values were based on a limited sample size (three pups per dose). It is also unknown how representative these data would be of lactational exposure, and there is uncertainty as to whether the kinetic profile would be similar following repeated exposures. In addition, some values from in vivo testing appear to be discordant with model predictions, and it does not appear as though input parameters and assumptions were altered to evaluate the sensitivity of the model. Finally, the parameters for the simulations for the ontogeny model came from in-house studies and could not be validated with independent sources.

Despite these limitations, the PBPK model did predict that fluoride would partition to the developing brain. It is not known if such distribution to the brain would result in neurological impairment since there is no assessment of cognition or functional outcome in the young in the sulfuryl fluoride toxicology database. For these reasons, there is still residual uncertainty with respect to potential developmental neurotoxicity. As such, an additional 3-fold database uncertainty factor for repeated exposure scenarios was retained. A re-examination of the acute exposure scenarios was also undertaken within the context of potential developmental neurotoxicity. Overall, the toxicology data, including the results of the additional PK studies, supported a low level of concern for acute exposure scenarios.

Additional supplemental information based on predictions using this PBPK model was also provided. The PBPK model was used to predict human plasma levels of fluoride of workers fumigating structures and re-entering fumigated structures. The model prediction showed that levels of fluoride in human plasma from exposure to sulfuryl fluoride would be well below those from exposure to other sources of fluoride, for example in drinking water. However, since the PBPK model could not be fully validated with independent data, this prediction alone was not considered sufficient to address the concern with respect to developmental neurotoxicity.

The results of the PK studies are summarized in Appendix I, Table 2. The toxicology endpoints for use in human health risk assessment are summarized in Appendix I, Table 3.

Incident Reports

As of 19 May 2016, the PMRA has received 10 human and 14 domestic animal incidents involving sulfuryl fluoride. All but one of these incidents occurred in the United States, where the uses of sulfuryl fluoride are more extensive than those in Canada. In the United States, the registered uses of sulfuryl fluoride include fumigation of houses and other residential structures, while in Canada the use is limited to cereal grain mills and food processing plants. The Canadian incident involved an individual who sustained minor effects (respiratory irritation) following the removal of the plastic covering of a mattress that had been fumigated in the United States prior to importation into Canada. Almost all of the incidents from the United States involved humans or pets that died after entering a fumigated home before it was cleared for re-entry.

An extensive fumigation management plan has to be in place for each fumigation event that occurs in Canada. This plan includes constant monitoring of sulfuryl fluoride levels in air around the fumigated structure and an evacuation plan in cases of sustained detectable levels of sulfuryl fluoride. Therefore, the likelihood of similar incidents occurring in Canada with the currently registered use pattern is low and the reported incidents have no impact on the regulatory decision relating to the Canadian product ProFume Gas Fumigant.

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, developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats, all conducted via inhalation, were available for sulfuryl fluoride. As discussed above, neurotoxicity was a critical endpoint identified in the supporting toxicology database, which triggered concern regarding potential cognitive impairment in the young. To address this concern, the registrant provided PK studies conducted via inhalation or gavage with adult, perinatal, and weanling rats, as well as PK studies conducted via inhalation with adult rabbits and results from PBPK modelling.

With respect to potential prenatal and postnatal toxicity, the results of the developmental and reproductive toxicity studies did not provide evidence of increased sensitivity of the young. In the reproductive toxicity study in the rat, effects at the offspring LOAEL were limited to the stomach being void of milk, with parental animals at this dose displaying body weight reductions, lung foci, and aggregates of alveolar macrophages. Brain vacuolation was noted in P and F1 animals sacrificed as adults at the end of their respective reproductive phases, but neither the incidence nor the severity of this lesion were increased in F1 animals compared to the

P generation. In the developmental toxicity studies, there were no adverse effects on rat fetuses at doses that were toxic to the maternal animal (reduced body weight gain) and the effects on rabbit fetuses (reduced fetal weights, pale liver) occurred at doses that were also toxic to the dams (body weight loss). In the PK studies, plasma fluoride levels were lower in the young animal compared to the maternal animal, and fluoride was not detected in the brains of fetuses exposed to sulfuryl fluoride in utero. However, fetal and pup brains were not examined histologically in any of the studies in the sulfuryl fluoride toxicology database, and no brain fluoride measurements were obtained for pups exposed postnatally via lactation. Furthermore, an assessment of cognitive function in the developing young after exposure to sulfuryl fluoride was not conducted.

Overall, residual uncertainty remains concerning susceptibility of the young to potential neurotoxic effects following repeated exposure to sulfuryl fluoride. This concern was reflected through the use of a database uncertainty factor of 3-fold in the risk assessment for scenarios involving repeated exposures. Since concern regarding potential sensitivity of the young is subsumed by the application of a database uncertainty factor, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

The ARfD for sulfuryl fluoride is summarized in REG2006-15.

3.3 Acceptable Daily Intake (ADI)

The ADI for sulfuryl fluoride is summarized in REG2006-15.

Cancer Assessment

As there was no evidence of carcinogenicity, a cancer risk assessment was not necessary.

3.4 Occupational and Residential Risk Assessment

3.4.1 Handler Exposure and Risk

Fumigation workers could be exposed to sulfuryl fluoride while performing fumigation and aeration activities. No mixing or loading is required because ProFume Gas Fumigant is introduced directly to the area requiring treatment from a cylinder through a suitable leak-proof tube. In the assessment of the exposure of, and risks to, fumigation workers conducted previously and summarized in REG2006-15, exposure of fumigation workers was expected to occur repeatedly but intermittently over an intermediate-term duration. This was based on information that suggested that each of approximately 50 mills is likely to be treated once per year, with a few mills being treated up to twice per year, over a period of approximately five months (from May to October) with fumigations normally scheduled over long weekends. The primary route of exposure is inhalation. Dermal exposure is not expected to be of concern due to the high vapour pressure of sulfuryl fluoride (1.6×10^6 Pa at 20ºC) and the proposed delivery system of ProFume Gas Fumigant.

Fumigation worker exposure was estimated using personal air monitoring data collected for fumigators and aerators at cereal mills in the United States fumigated with ProFume Gas Fumigant. Based on this estimated worker exposure and the toxicological endpoint selected for repeated exposure scenarios of intermediate-term duration, respiratory protection, in the form of a self-contained breathing apparatus (SCBA) was required to be worn by fumigation workers during the fumigation and aeration activities in order to achieve the target margin of exposure (MOE). Respiratory protection would also be required in order to achieve the target MOE if the exposure of fumigation workers was limited to a short-term duration when risk estimates are calculated using the toxicological endpoint selected for short-term repeated inhalation exposures.

However, more recently, the exposure scenario of fumigation workers was reconsidered and it was determined that exposure of fumigation workers could be characterized as being of acute duration provided that the frequency of fumigations performed by individual workers was limited via label statements. By limiting the frequency of fumigations performed by individual workers and using the toxicological endpoint selected for acute exposure scenarios, the need for respiratory protection during the fumigation and aeration activities was eliminated as the target MOE was achieved without respiratory protection.

As outlined in REG2006-15, the rat acute neurotoxicity study NOAEL of 291 ppm (equivalent to 291 mg/kg bw/day), the highest concentration tested, was considered the most appropriate effect level for acute inhalation risk assessment. No adverse effects were noted in this study, in which rats were exposed to sulfuryl fluoride for six hours/day over two days. This study evaluated the critical endpoint of neurotoxicity. Neuropathology was not evaluated in this study, but an assessment of sensory evoked potentials was conducted. Sensory evoked potentials were a more sensitive indicator of neurotoxicity than neuropathology following sulfuryl fluoride exposure in the 13-week neurotoxicity study. The target MOE is 100, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As discussed above, the additional 3-fold factor to account for the uncertainty regarding developmental neurotoxicity was not considered applicable to acute exposure scenarios.

The target MOE was achieved for fumigation workers without respiratory protection using the acute endpoint. Acute inhalation MOEs of 142 and 729 were calculated for fumigators and aerators, respectively, and the acute inhalation MOE for combined fumigation and aeration activities was 119. Based on these revised MOEs, SCBA respiratory protection for fumigation workers in the vicinity of the treated structure is not required unless the concentration of sulfuryl fluoride exceeds 1 ppm. However, since these risk estimates are based on an acute endpoint, a label statement limiting exposure for any individual to once every two weeks is required on the ProFume Gas Fumigant label. Based on the rapid clearance of fluoride from the plasma demonstrated in the PK data, an interval of approximately two weeks between fumigations was considered sufficient to protect workers from the cumulative effects of sulfuryl fluoride exposure.

3.4.2 Postapplication Exposure and Risk

The exposure of, and risks to, workers entering treated structures to perform regular work tasks after fumigation and aeration were assessed previously and are summarized in REG2006-15. The exposure duration for these workers is expected to be acute (24 hours or less) because vapours of sulfuryl fluoride dissipate rapidly. The label for ProFume Gas Fumigant also states that fumigated structures must be aerated to a concentration of 1 ppm prior to entering the building. Provided that the label directions are followed, there is no health risk of concern related to postapplication exposure.

3.4.3 Bystander Exposure

The exposure of, and risks to, bystanders during fumigation and aeration as well as after aeration while sulfuryl fluoride vapours disperse from the treated site was assessed previously and are summarized in REG2006-15. Exposure of bystanders (adults and children living in residences near a mill or food processing plant) could occur up to twice per year. The exposure duration is expected to be acute (up to 24 hours).

Due to uncertainties identified in the initial bystander exposure and risk assessment, additional air monitoring data collected around mills or food processing plants treated with ProFume Gas Fumigant representative of Canadian climatic conditions were required. These data were submitted and summarized in PRD2008-10, *Sulfuryl Fluoride*.

Health risks to bystanders are not of concern provided that label directions and a fumigation management plan are followed for each fumigation event. The label requires that scheduled monitoring of ambient air must be conducted up to 25 metres from the fumigated structure to prevent worker and bystander exposure to sustained concentrations of sulfuryl fluoride in excess of 1 ppm during the introduction, fumigation, and aeration phase. Air concentrations should be measured at several locations, especially downwind from the fumigated structure, and in the direction of neighbouring off-site structures, recreational areas, or areas where bystanders may be exposed. A fumigation management plan is required for each fumigation event with ProFume Gas Fumigant; it involves an organized, documented description of the steps required to ensure a safe and effective fumigation. The fumigation management plan for ProFume Gas Fumigant is site-specific, and includes an evacuation action to be executed when sustained sulfuryl fluoride levels exceed 1 ppm for one hour, or exceed 5 ppm for 30 minutes.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in food commodities is sulfuryl fluoride. The data gathering/enforcement analytical method is valid for the quantitation of sulfuryl fluoride residues in raw agricultural commodities (RACs) and processed food commodities. Quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Fumigation trials conducted in Canada and the United States, using end-use products containing sulfuryl fluoride, at exaggerated rates in or on various RACs and processed food commodities are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

A chronic (non-cancer) dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the refined chronic non-cancer analysis for sulfuryl fluoride: residues of sulfuryl fluoride or fluoride in/on several RACs and processed food commodities based on supervised trial median/mean residue values, default and experimental processing factors (where available) and US percent crop treated. The refined chronic dietary exposure from all supported sulfuryl fluoride food uses for the total population, including infants and children, and all representative population subgroups is less than 30% of the acceptable daily intake (ADI) of sulfuryl fluoride. In addition, the chronic dietary exposure to fluoride, a degradation of sulfuryl fluoride, is also not of health concern for all population subgroups. Therefore, exposure from food is considered acceptable.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the refined acute analysis for sulfuryl fluoride: maximum residues in/on several RACs and processed food commodities, default and experimental processing factors (where available), and 100% crop treated. The refined acute dietary exposure for all supported sulfuryl fluoride food uses is estimated to be <2% of the Acute Reference Dose (ARfD) for all population subgroups (95^{th} percentile, deterministic).

3.5.3 Aggregate Exposure and Risk

The risks to sulfuryl fluoride consist of exposure from food only; there are no uses that may result in residues in drinking water and there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Tree Nuts (Crop Group 14-11) except almonds	3
All processed foods not otherwise listed	2
Peanuts	0.5
Cacao beans	0.2
Cereal grains (Crop Group 15) except sweet corn kernels plus cobs with husks removed	0.1
Almonds	0.04
Raisins	0.01

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.

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

The nature of the residues in plant matrices, analytical methodologies, fumigation trial data, and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 4 and 5.

4.0 Impact on the Environment

A detailed environmental risk assessment of Sulfuryl Fluoride Gas Fumigant and ProFume Gas Fumigant are presented in REG2006-15. No additional environmental data were required as a condition of registration in 2006; therefore, no amendments or additions to the previous environmental review were necessary.

5.0 Value

ProFume Gas Fumigant (99.8% sulfuryl fluoride) controls stored product pests such as Indian meal moth, confused flour beetle, saw-toothed grain beetle, warehouse beetle and granary weevil in cereal grain mills, associated storage facilities and food processing facilities. For further information, refer to REG2006-15, *Sulfuryl fluoride*.

To support the addition of commodities to the label of Profume Gas Fumigant, value information was provided. One laboratory and three field trials demonstrated that sulfuryl fluoride is able to penetrate various commodities to control the listed stored product insects. A laboratory trial demonstrated that ProFume Gas Fumigant controlled confused flour beetle adults and black carpet beetle larvae in seven different substrates. The level of control observed in the trial was similar to or better than that of methyl bromide, which is a broad-spectrum fumigant. The field trials demonstrated that ProFume Gas Fumigant effectively penetrates wooden blocks or flour to control Mediterranean flour moth egg hatch. These data were used to extrapolate to the remaining uses.

Sulfuryl fluoride is an alternative to methyl bromide (MOA Group 8A) which is being phased out under the Montreal Protocol on Substances that Deplete the Ozone Layer. Sulfuryl fluoride is not an ozone depleting substance. It is also an alternative to phosphine gas which corrodes certain metals and has a different mode of action (MOA Group 24A). Carbon dioxide is a non-conventional alternative to sulfuryl fluoride; however, its use is limited to certain beetles in grain and flour storage areas. Sulfuryl fluoride can be used with other pest management practices such as inspection of food commodities for pests, sealing up entry points within a structure and good sanitation practices.

6.0 Pest Control Product Policy Considerations

Canada will continue to actively participate in international fora, such as the risk reduction initiatives under the United Nations, North American Free Trade Agreement, and the Organisation for Economic Co-operation and Development Pesticide Programme. These activities address health and environmental problems associated with pesticide use as well as concerns about risks to users and the general public.

The long-range transport of persistent organic pollutants (POPs) is a high priority issue for the Government of Canada, particularly the Ministers of Health and Indigenous and Northern Affairs Canada.

The TSMP is critical to Canada's position in discussions and negotiations with the world community on managing toxic substances. The clarification of how the TSMP will be implemented by the PMRA will facilitate the development of consistent national positions and provide increased opportunities to influence approaches taken in international fora, and indeed, in other countries. (Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*)

***Canadian Environmental Protection Act* (CEPA)**

The *Canadian Environmental Protection Act* (CEPA), administered jointly by the Ministers of Health and Environment, provides a federal regulatory role in the management of toxic substances. CEPA was developed to ensure coverage of substances not captured under other federal legislation. Section 11 of CEPA defines "toxic" as follows:

For the purposes of this Part, a substance is toxic if it is entering or may enter the environment in a **quantity or concentration** or under conditions

a) having or that may have an immediate or long-term harmful effect on the environment;

Concentrations are not at a level to have harmful effect

b) constituting or that may constitute a danger to the environment on which human life depends; or

Concentrations are not at a level to have harmful effect

c) constituting or that may constitute a danger in Canada to human life or health.

Concentrations are not at a level to have harmful effect

Kyoto Protocol

The Kyoto Protocol is an international agreement linked to the United Nations Framework Convention on Climate Change, which commits its Parties by setting internationally binding emission reduction targets (United Nations, 2014). Canada repealed the Kyoto Protocol on 29 June 2012 citing that the two largest contributors, United States and China, are not part of the Protocol.

Sulfuryl fluoride is a greenhouse gas. It was identified as such by MIT in 2009 with an atmospheric lifetime of 40 years and is 4800 times more effective at trapping heat per molecule than CO_2 (Chandler, 2009). The European Chemicals Agency (ECHA) lists the contribution of sulfuryl fluoride to global warming as small and approximately 0.03%, when compared to the total anthropogenic emissions of greenhouse cased into the atmosphere (ECHA, 2015). The PMRA does not have a mandate to address greenhouse gases, therefore, upon reviewing this product a letter was sent to Environment Canada, Greenhouse Gas Division, to inform them of the potential as they do have a mandate to address greenhouse gases.

Montreal Protocol

The Montreal Protocol on Substances that Deplete the Ozone Layer was designed to reduce the production and consumption of ozone depleting substances in order to reduce their abundance in the atmosphere, and thereby protect the earth's fragile ozone Layer. The original Montreal Protocol was agreed on 16 September 1987 and entered into force on 1 January 1989 (Ozone Secretariat, 2016).

Sulfuryl fluoride is not an ozone depleting compound.

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, sulfuryl fluoride was assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. Based on an assessment of the data package, the PMRA has reached the conclusion that sulfuryl fluoride does not meet TSMP Track 1 criteria.

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

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for sulfuryl fluoride is adequate to define the majority of toxic effects that may result from exposure. Clinical signs of toxicity were observed following acute and repeated exposures via inhalation and included tremors, lethargy, incapacitation, convulsions, tetany, and impaired respiratory function. Target tissues following repeated inhalation exposure included the brain, kidney, teeth, and respiratory tract. Mortality occurred at high exposure levels. There was no evidence of oncogenic or genotoxic potential. No developmental or reproductive toxicity was observed following exposure to sulfuryl fluoride. There is uncertainty with respect to the potential for sulfuryl fluoride to cause developmental neurotoxicity. 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.

Fumigation workers handling ProFume Gas Fumigant and workers re-entering treated areas are not expected to be exposed to levels of sulfuryl fluoride that will result in health risks of concern when ProFume Gas Fumigant is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants is adequately understood. The residue definition for enforcement in plant products is sulfuryl fluoride. The proposed fumigation use of sulfuryl fluoride on RACs and processed food commodities does not constitute a risk of concern from acute exposure to sulfuryl fluoride or chronic dietary exposure to sulfuryl fluoride to any segment of the population, including infants, children, adults and seniors. Sufficient residue data have been reviewed to recommend the following MRLs for residues of sulfuryl fluoride.

Commodity	Recommended MRL (ppm)
Tree Nuts (Crop Group 14-11) except almonds	3
All processed foods not otherwise listed	2
Peanuts	0.5
Cacao beans	0.2
Cereal grains (Crop Group 15) except sweet corn kernels plus cobs with husks removed	0.1
Almonds	0.04
Raisins	0.01

7.2 Environmental Risk

For a summary of the environmental risk assessment, please refer to REG2006-15.

7.3 Value

No further value information was required to support the claim that Profume Gas Fumigant controls certain stored product pests in cereal grain mills, food processing plants and storage facilities. Additional value information demonstrated that ProFume Gas Fumigant also controls these pests within stored products as listed on the label.

Sulfuryl fluoride is an alternative to methyl bromide which is being phased out under the Montreal Protocol. It is also an alternative to phosphine gas which damages certain metals, and carbon dioxide, which has a limited number of uses.

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 Sulfuryl Fluoride Gas and ProFume Gas Fumigant, containing the technical grade active ingredient sulfuryl fluoride, to control stored product pests in cereal grain mills, associated storage facilities and food processing plants.

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

ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
ºC	degree(s) Celsius
CAF	composite assessment factor
CEPA	*Canadian Environmental Protection Act*
CO_2	carbon dioxide
ECHA	European Chemicals Agency
EEC	estimated environmental concentration
F	fluoride
FDA	*Food and Drugs Act*
FSO_3	fluorosulfate
g	gram
GC-MS	gas chromatography with mass spectrometry
GD	gestation day
hr	hour
i.v.	intravenous
$KFSO_3$	potassium fluorosulfate
kg	kilogram
L	litre
LD	lactation day
LOAEL	lowest observed adverse effect level
mg	milligram
min	minute
MOA	mode of action
MOE	margin of exposure
MIT	Massachusetts Institute of Technology
MRL	maximum residue limit
NA	not applicable
NAFTA	North American Free Trade Agreement
NAP	natural atmospheric pressure
NOAEL	no observed adverse effect level
NZW	New Zealand white
Pa	Pascal(s)
PBPK	physiologically-based pharmacokinetic
PCPA	*Pest Control Products Act*
PK	pharmacokinetic
PMRA	Pest Management Regulatory Agency
PND	post-natal day
POP	persistent organic pollutants
ppm	part(s) per million
RAC	raw agricultural commodity
RBC	red blood cell(s)
SCBA	self-contained breathing apparatus

SD	standard deviation
SF	sulfuryl fluoride
TSMP	Toxic Substances Management Policy
$T_{(1/2)}$	half-life of elimination

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Dried fruits and tree nuts	GRM01.12	Sulfuryl fluoride	GC-MS	0.01 ppm		PMRA# 774899,774900, 774901, 774909, 774910,1448731
Cereal grains	GRM01.18	Sulfuryl fluoride	GC-MS	0.01 ppm		PMRA# 774898, 774902, 774923, 1448731

Table 2 Summary of Additional Pharmacokinetic Studies for Sulfuryl Fluoride

[Unless otherwise specified, tissues were analyzed for fluorosulfate (FSO_3) and fluoride (F), and sometimes sulfuryl fluoride (SF)]

Study Type / Animal / PMRA #	Methods	Study Results
In Vitro – Rat & Human		
In vitro determination of sites and rates of hydrolysis PMRA #1908782	SF or FSO_3 incubated with various tissues from adult rat, PND 10 rat, human Adult rat: liver, lung, plasma, RBC, nasal tissue, lung lavage fluid, whole blood PND 10 rat: whole blood Human: liver, lung, whole blood	Minimal hydrolysis (<10%) by portal of entry tissues (nasal tissue, lung lavage) and metabolizing tissues (liver, lung). Blood components effective in hydrolyzing SF (60-80%). Rates of SF hydrolysis similar between adult and PND 10 rat blood; rate of hydrolysis in human blood 2-fold higher than in rat blood. No hydrolysis of FSO_3 in blood, liver or lung from adult rat or human.
Adult Male F344 Rats		
Limited PK – single exposure PMRA #2078940	0, 30, 300 ppm; 4 ♂/group Single 4 hour, nose-only inhalation exposure Blood, kidney, brain collected after 2 hours of exposure and at 0, 2, 4, 8 hours post-exposure.	**30 ppm:** No F detected in plasma. No FSO_3 detected in kidney or brain. FSO_3 detected in plasma. **300 ppm:** FSO_3 levels in brain very low compared to plasma and kidney and detected immediately after exposure only. FSO_3 detected in kidney up to 4 hours post-exposure. F detected in plasma up to 4 hours post-exposure. Brain and kidney could not be analyzed for F.
Quantitation of metabolites in selected tissues PMRA #2078941	0, 3, 30, 300 ppm; 10 ♂/group Single 4 hour, nose-only inhalation exposure. Blood, kidney, cerebrum, olfactory bulb, nasal and lung tissues collected 0, 2, 4, 8	**3 ppm:** FSO_3 detected in plasma immediately after exposure only. FSO_3 detected in kidney up to 2 hours post-exposure and in lung up to 8 hours post-exposure. FSO_3 not detected in brain or nasal tissue. F not detected in plasma, lung or cerebrum. F detected in nasal tissue up to 8 hours post-exposure (bone present in nasal tissue samples). F detected in kidney immediately

	hours post-exposure.	after exposure only. **30 ppm:** FSO_3 detected in plasma and kidney up to 4 hours post-exposure. FSO_3 detected in lung up to 8 hours post-exposure. FSO_3 detected in nasal tissue immediately following exposure only. $T_{(1/2)}$ FSO_3 = 1.2 hours in plasma, 5.6 hours in kidney, 11.3 hours in lung. F not detected in plasma. F detected in lung immediately after exposure only and in cerebrum up to 2 hours post-exposure. F detected in nasal tissue up to 8 hours post-exposure (bone present in nasal tissue samples). F detected in kidney up to 4 hours post-exposure. $T_{(1/2)}$ F = 0.97 hours in cerebrum. **300 ppm:** FSO_3 detected in plasma and lung up to 8 hours post-exposure. FSO_3 detected in kidneys and nasal tissue up to 4 hours post-exposure. $T_{(1/2)}$ FSO_3 = 1.5 hours in plasma, 1.0 hour in kidney, 1.8 hours in lung, 1.5 hours in nasal tissue. F detected in all tissues up to 8 hours post-exposure. $T_{(1/2)}$ F = 2.6 hours in plasma, 2.7 hours in lung, 2.1 hours in cerebrum. --- FSO_3 not detected in cerebrum at any exposure level; transfer across blood-brain barrier is likely limited. F levels in cerebrum exposure-dependent and higher than in plasma and lungs. Elimination of FSO_3 and F rapid from all tissues except nasal tissue (which included bone).
Nasal and pulmonary uptake and metabolism PMRA #1908781 Phase I: Nasal and pulmonary uptake	300 ppm; 3-9 ♂/group Single 4 hour, nose-only inhalation exposure, Animals surgically modified to separate nasal and pulmonary air flows; SF uptake by nasal cavity determined. Nasal and lung lavage fluid, plasma, nasal and pulmonary tissues, kidney, cerebrum, olfactory bulb, urine collected immediately after exposure. Nasal and lung lavage fluid and plasma analyzed for SF.	Overall absorption of SF from upper respiratory tract = 4.9% (absorption from lower respiratory tract estimated to be 7.6%). No SF detected in headspace of nasal or lung lavage fluid or blood (SF is rapidly hydrolyzed at portal of entry and not available systemically). Surgically modified rats had significantly lower levels of FSO_3 in plasma, olfactory bulb and nasal tissues than non-modified rats. FSO_3 detected in lung and nasal lavage of surgically non-modified rats but not of surgically modified rats. No FSO_3 detected in cerebrum of surgically modified or non-modified rats. Tissue samples could not be analyzed for F.
Nasal and pulmonary uptake and metabolism	0, 3, 30, 300 ppm; 4 ♂/group Single 4 hour, nose-only	FSO_3 detected in urine collected 0-6 hours at all exposure concentrations and in urine collected up to 24 hours at 300 ppm only.

PMRA #1908781 Phase II: Urinary Excretion	inhalation exposure. Urine collected 0-6, 6-12, 12-24 hours post-exposure.	FSO_3 and F rapidly excreted (92% and 68% of excreted FSO_3 and F recovered in 0-6 hours). Approximately 13% of predicted internal dose excreted 0-6 hours post-exposure. $T_{(1/2)}$ FSO_3 = 2.0 hours; F = 4.1 hours
Nasal and pulmonary uptake and metabolism PMRA #1908781 Phase III: Metabolism of FSO_3	25 mg/kg bw i.v. dose of $KFSO_3$ (equivalent to the dose from a 4-hour exposure to SF at 200 ppm); 3 ♂/group Urine collected 0-12, 12-24, 24-48 hours post-dosing.	Approximately 41% of administered FSO_3 was hydrolyzed to F and excreted in urine during 48-hour period following injection. 96% of FSO_3 recovered in urine was excreted during first 12 hours.
Nasal and pulmonary uptake and metabolism PMRA #1908781 Phase IV: FSO_2-Albumin Adducts	0, 3, 30, 300 ppm; 4 ♂/group Single 4 hour, nose-only inhalation exposure. Plasma, nasal and lung lavage fluid collected immediately after exposure and analyzed for FSO_2-albumin adducts.	Formation of FSO_2-albumin adducts represents a minor degradation pathway (0.5-2.7%) compared to hydrolysis to FSO_3 (97.3-99.5%). A higher ratio of FSO_2-albumin adducts / FSO_3 in lung lavage vs. plasma indicates that SF is rapidly hydrolyzed at the portal of entry and tissues of the upper and lower respiratory tract.
Limited pharmacokinetics – repeated exposure PMRA #2078945	0, 3, 30, 300 ppm; 5-8 ♂/group; Repeated 6 hour, whole-body inhalation exposures, 5 days/week for 2 weeks. Urine and plasma collected up to 18 hours after first and last exposures. Cerebrum and kidney collected immediately or 18 hours after first and last exposures.	Levels of FSO_3 and F detected in tissues after one exposure comparable to levels detected after 10^{th} exposure. FSO_3 not detected in cerebrum at any exposure concentration. Plasma time course profiles for FSO_3 and F similar between rats exposed for one or 10 days. $T_{(1/2)}$ after one exposure F = 2.3 hours, FSO_3 = 1.7 hours $T_{(1/2)}$ after 10 exposures F = 2.6 hours, FSO_3 = 1.6 hours Levels of FSO_3 and F in urine slightly higher after 10 exposures, but relative levels of F versus FSO_3 similar.
Pharmacokinetics in pregnant and lactating SD rats, fetuses, and pups		
PK in dams, fetuses, & pups PMRA #2078942 Phase I: Gestational Exposure	0, 5, 30, 150 ppm; 12 dams/group Repeated 6 hour, whole-body inhalation exposures, GD 6-20. Urine collected from dams up to 18 hours post-exposure on GD 18. Blood collected from dams & fetuses immediately after exposure on GD 20.	**<u>Dams</u>** **5 ppm:** FSO_3 detected in urine 0-6 hours post-exposure only. $T_{(1/2)}$ F in urine = 4.8 hours. **30 ppm:** FSO_3 detected in urine 0-6 hours post-exposure only. $T_{(1/2)}$ F in urine = 3.9 hours **150 ppm:** No SF detected in plasma. $T_{(1/2)}$ FSO_3 in urine = 1.8 hours. 91% of FSO_3 excreted during first 6 hours. $T_{(1/2)}$ F in urine = 4.5 hours. **<u>Fetuses</u>** **5 ppm:** No FSO_3 detected in plasma. Level of F in plasma 19% of level in dams. No FSO_3 detected in brain or kidney tissue. No F detected in brain tissue.

	Brain and kidney collected from fetuses immediately after exposure on GD 20.	**30 ppm:** Level of FSO_3 in plasma 12% of level in dams. Level of free F in plasma 32% level in dams. No FSO_3 or F detected in brain tissue. FSO_3 in kidney 2.6x greater than in plasma. F in kidney 32% of FSO_3 level. **150 ppm:** No SF detected in plasma. Level of FSO_3 in plasma 12% of level in dams. Level of F in plasma 42% level in dams. Level of FSO_3 in brain tissue 35% of level in fetal plasma. F detected in one brain tissue sample. FSO_3 in kidney 2x greater than in plasma. F in kidney 39% of FSO_3 level. FSO_3 in fetal brain may reflect incomplete formation of blood-brain barrier
PK in dams, fetuses, & pups PMRA #2078942 Phase II: Lactational Exposure	0, 5, 30, 150 ppm; 3 dams/group Repeated 6 hour, whole-body inhalation exposures, GD 6-20 and LD 5-10 (dams only). Blood and milk collected from dams 0 and 2 hours post-exposure on LD 10 Blood collected from pups PND 10 following 2 hours of lactational exposure (blood also collected prior to lactational exposure). No assessment of FSO_3 or F levels in pup brains.	**<u>Dams</u>** **≥ 5 ppm:** FSO_3 in milk at 2 hours 25-46% of peak level. FSO_3 and F in milk 2-4x level in plasma. F in milk at 2 hours higher than at time 0. FSO_3 in milk 3-5x higher than F. <u>Pups</u> **5 ppm:** No FSO_3 or F in plasma prior to lactational exposure (after 6-hour separation from dams). No FSO_3 or F in plasma after 2 hours of lactational exposure. **30 ppm:** No FSO_3 of F in plasma prior to lactational exposure. Level of FSO_3 in plasma after lactational exposure 17% of level in dam plasma and 1% of peak level in milk. Level of F in plasma after lactational exposure 12% of level in dam plasma, and 7% of peak level in milk. **150 ppm:** No FSO_3 in plasma prior to lactational exposure. F detected in plasma from only one litter prior to lactation exposure. Level of FSO_3 in plasma after lactational exposure 16% of level in dam plasma and 2% of peak level in milk. Level of F in plasma after lactational exposure 4% of level in dam plasma, and 2% of peak level in milk. Pups may have consumed less milk than at lower exposure concentration.
PK in dams, fetuses, & pups PMRA #2078942 Phase III: Direct Dosing of Pups	4, 20, 40 µg FSO_3 and F; 27 PND 10 pups/group (samples pooled from 9 pups yielding a sample size of 3) Single gavage dose in rat milk. Blood, kidney and brain tissue collected from pups at 1, 3, 6 hours post-dosing.	**4 µg:** FSO_3 and F detected in plasma at 1 hour post-dosing only. No FSO_3 detected in brain or kidney. F detected in in brain of 1/3 samples (9x higher than plasma level) and kidney up to 6 hours post-dosing. **20 µg:** FSO_3 and F detected in plasma up to 6 hour post-dosing. No FSO_3 detected in brain. FSO_3 detected in kidney up to 3 hours post-dosing. F detected in brain of 1/3 samples (6-14x lower than plasma level) up to 3 hours post-dosing. $T_{(1/2)}$ FSO_3 in plasma = 2.3 hours. $T_{(1/2)}$ F in plasma = 1.9 hours. F detected in kidney up to 6 hours post-dosing. **40 µg:** FSO_3 and F detected in plasma up to 6 hour post-

		dosing. No FSO_3 detected in brain. FSO_3 and F detected in kidney up to 6 hours post-dosing. F detected in brain (2-13x lower than plasma level) up to 6 hours post-dosing. $T_{(1/2)}$ FSO_3 in plasma = 5.0 hours. $T_{(1/2)}$ F in plasma = 3.1 hours.
PK in weanlings PMRA # 2078943	0, 3, 30, 300 ppm; 8 ♂ PND 22 weanlings /group) Single 4 hour, whole-body inhalation exposure. Blood, brain and kidney collected at 0, 2, 4, 8 hours post-exposure.	**3 ppm:** FSO_3 detected in plasma up to 4 hours post-exposure. No F detected in plasma. No FSO_3 or F detected in brain. FSO_3 detected in kidney up to 2 hours post-exposure. F detected in kidney up to 8 hours post-exposure. **30 ppm:** FSO_3 detected in plasma up to 8 hours post-exposure (declining 18-fold from time 0). No F detected in plasma. $T_{(1/2)}$ elimination FSO_3 from plasma = 2.0 hours. No FSO_3 detected in brain. F detected in brain up to 2 hours post-dosing. FSO_3 detected in kidney up to 4 hours post-exposure. F detected in kidney up to 8 hours post-exposure. **300 ppm:** No SF detected in plasma. FSO_3 detected in plasma up to 8 hours post-exposure (declining 13-fold from time 0). F detected in plasma at 8 hours post-dosing only (slow, partial hydrolysis of FSO_3). $T_{(1/2)}$ FSO_3 in plasma = 2.3 hours. FSO3 detected in brain immediately after exposure only (4% of level in plasma). F detected in brain up to 8 hours post-exposure. FSO_3 and F detected in kidney up to 8 hours post-exposure. Lack of F in plasma of weanlings represents analytical error or rapid uptake by bone in young rats. Weanling brain F levels > FSO_3 – impermeability of weanling blood-brain barrier to FSO_3. Kidney F levels similar or lower than kidney FSO_3 levels – sequestration of fluoride into bone during development.

2

Species Comparison – Rats (F344) & Rabbits (NZW)		
Limited PK in rabbits PMRA #2078944	0, 600 ppm; 3 ♂/group Single 6 hour, nose-only inhalation exposure. Blood collected before, during and immediately after exposure. Urine collected during and up to 18 hours post-exposure. Kidney, lung, cerebrum, olfactory bulb, nasal mucosa, nasal tissues	No SF detected in plasma. FSO_3 and F detected in plasma up to 18 hours post-exposure. $T_{(1/2)}$ FSO_3 in plasma = 2.1 hours; $T_{(1/2)}$ F in plasma = 3.4 hours. FSO_3 and F detected in urine up to 18 hours post-exposure. F detected in cerebrum, lung kidney, olfactory bulb, and nasal tissue up to 18 hours post-exposure. F detected in nasal mucosa immediately after exposure only. Level of F in cerebrum 70% of level in plasma immediately after exposure. Levels of F in cerebrum, lung and kidney declined rapidly (1%, 14%, and 6% of initial levels by 18 hours post-exposure). FSO_3 detected in kidney, lung, cerebrum, nasal mucosa,

	collected at 0 and 18 hours post-exposure.	and nasal tissue immediately after exposure only. Level of FSO_3 in cerebrum 10x lower than level of F in cerebrum immediately after exposure. Level of FSO_3 in cerebrum lower than level in plasma (17x), kidney (12x) and lung (8x) immediately after exposure. Analysis of nasal tissue, nasal mucosa, olfactory bulb complicated by possible contamination with bone fragments.
Species comparison -rats & rabbits PMRA #2078946	0, 3, 30, 300 ppm; 5 ♂ rats/group, 3 ♀ rabbits/group Single 6 hour, whole-body inhalation exposure. Blood collected before and immediately after exposure. Kidney and cerebrum collected immediately after exposure.	**3 ppm:** F detected in plasma of rabbits but not rats. Plasma levels of FSO_3 similar between rats and rabbits. F detected in kidney of rabbits but not rats. No FSO_3 detected in kidney of rats or rabbits. F detected in cerebrum of rats but not rabbits. No FSO_3 detected in cerebrum of rats or rabbits. **30 ppm:** Level of F in plasma of rabbits 3x higher than in rats. Plasma levels of FSO_3 similar between rats and rabbits. FSO_3 detected in kidney of rabbits but not rats. F detected in cerebrum of rats but not rabbits. No FSO_3 detected in cerebrum of rats or rabbits. **300 ppm:** Level of F in plasma of rabbits 3x higher than in rats. Plasma levels of FSO_3 similar between rats and rabbits. Level of FSO_3 in kidney of rats 6% of level in rabbits. Similar levels of F detected in cerebrum of rats and rabbits. No FSO_3 detected in cerebrum of rats. Level of FSO_3 in cerebrum of rabbits 7% of level of F in cerebrum. Levels of FSO_3 in rat plasma 2-3x higher than levels of F. Levels of FSO_3 in rabbit plasma similar to levels of F. Linear increase in level of F in kidney of rats. Non-linear increase in level of F in kidney of rabbits.

Table 3 Toxicology Endpoints for Use in Human Health Risk Assessments for Sulfuryl Fluoride

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary[2]	Acute inhalation neurotoxicity study in rats	NOAEL = 291 ppm (highest concentration tested); this level is equivalent to 291 mg/kg bw No evidence of adverse effects, including sensory evoked potentials which are sensitive indicators of neurotoxicity for sulfuryl fluoride	100
	ARfD = 2.91 mg/kg bw		

Repeated dietary[2]	2-year inhalation combined toxicity / carcinogenicity study in rats	NOAEL = 5 ppm; this level is equivalent to 5 mg/kg bw/day Lung foci, decreased body weight gain, hematological and clinical chemistry findings, and dental fluorosis	300
	ADI = 0.017 mg/kg bw/day		
Acute inhalation	Acute inhalation neurotoxicity study in rats	NOAEL = 291 ppm (highest concentration tested); this level is equivalent to 291 mg/kg bw No evidence of adverse effects, including sensory evoked potentials which are sensitive indicators of neurotoxicity for sulfuryl fluoride	100
Short-term inhalation	2-week inhalation toxicity study in rabbits	NOAEL = 100 ppm; this level is equivalent to 59 mg/kg bw/day Elevated white blood cell counts, decreased liver weights (males only), cerebral vacuolation and malacia (necrosis), altered hepatocellular cytoplasmic homogeneity, inflammation of the nasal mucosa, and hyperplasia of the spleen	300
Intermediate-term inhalation	13-week inhalation toxicity study in rabbits	NOAEL= 30 ppm; this level is equivalent to 18 mg/kg bw/day Decreased body weight gain, elevated serum fluoride levels, decreased liver weight, and cerebral vacuolation	300

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for occupational and bystander assessments.
[2] An oral absorption factor of 100% was used in route-to-route extrapolation.

Table 4 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE - Graham flour	**PMRA # 853013**
Radiolabel Position	^{35}S-labelled sulfuryl fluoride
Test Site	Fumigation chamber
Treatment	Fumigation under reduced pressure for 92 hours at room temperature
Total Rate	2944 mg-hr/L
Formulation	Liquid
Aeration period	Not specified
Proposed Metabolic Pathway in graham flour Based on the properties of the treated flour, anionic residues resulting from sulfuryl fluoride are covalently bound to some components of the flour such as amino acids and proteins. The results of the analysis confirmed that radioactivity was associated with at least 8 amino acids; however, none were identified. It was proposed that the most likely amino acids are those found in proteins: phenylalanine, histidine, and lysine. Free sulfate was also identified.	

NATURE OF THE RESIDUE - Various commodities (apples, dried beef, dry dog food, non-fat dry milk, snack cakes, vegetable oil and wheat flour)	**PMRA # 728290, 845081**
Radiolabel Position	^{35}S-labelled sulfuryl fluoride
Test Site	Fumigation chamber
Treatment	Fumigation under reduced pressure for 20 hours at room temperature
Total Rate	36 to 360 mg-hr/L for 20 hours for a total of 7200 mg-hr/L
Formulation	Liquid
Aeration period	1, 8 or 15 days

Proposed Metabolic Pathway

Measurable residues of fluoride and sulfate ions were observed in all tested commodities and no trend was identified with increased aeration time. These results suggest that the anions, formed during the fumigation procedure as a result of degradation of sulfuryl fluoride, did not dissipate over the 15-day aeration period. The anion levels in the various commodities were not proportional to the treatment rate, and the ratios of F^- to SO_4^{2-} ions were highly variable between commodities, suggesting that the non-metabolic degradation pathway is commodity-specific. In addition, the ratios of F^- to SO_4^{2-} ions were generally higher than expected based on complete degradation of sulfuryl fluoride to free anions. The greatest anion residues were found in the high-protein matrices (dried beef, dog food, milk and wheat). These observations support the proposed pathway of residue binding to protein via the sulfate group, with release of fluoride.

In general, sulfuryl fluoride reacts with the amino-terminal nitrogen atoms of free amino acids, peptides, and proteins to produce N-fluorosulfonyl derivatives as intermediates, and then forms N-substituted sulfamates and N,N=-disubstituted sulfamides. Non-specific binding of anions to other matrix components could not be ruled out.

CONFINED AND FIELD ACCUMULATION IN ROTATIONAL CROPS

As the petitioned use is for post-harvest fumigation, no confined or field accumulation in rotational crops are required.

NATURE OF THE RESIDUE IN LIVESTOCK	**PMRA# 1448729, 1448730**

Sulfuryl fluoride residues are expected to be dissipated to below the limit of quantitation by the time any potential feed items are fed to livestock. Therefore, nature of the residue studies in livestock are not required at this time.

FREEZER STORAGE STABILITY	**PMRA# 774905, 845214**

The freezer storage stability data indicated that residues of sulfuryl fluoride were stable in SKC 1g Anasorb CSC tubes, under ambient (15.6 to 17.8°C) and freezer (-19 to -21°C) storage conditions for up to 46 and 180 days, respectively.

In the submitted fumigation trial studies, all treated samples were analysed for residues of sulfuryl fluoride within 2 days of completion of aeration. Since samples were analysed less than 30 days after treatment, storage stability data for sulfuryl fluoride is not required.

CROP FIELD TRIALS & RESIDUE DECLINE ON CEREAL GRAINS AND PROCESSED COMMODITIES	PMRA # 774907, 845215, 845216, 845217

Controlled laboratory and operational grain mill fumigations using sulfuryl fluoride were conducted with whole cereal grains (hard red winter wheat, soft red winter wheat, durum wheat, medium grain brown rice, medium grain white rice, white field corn, popcorn, barley, and oats) and representative processed commodities (wheat germ, wheat flour, and corn meal; grain mill fumigations only) in order to determine the magnitude of sulfuryl fluoride residues that occur following treatment with sulfuryl fluoride. In the laboratory, commodities were fumigated for 24 hours at either 200 mg-hr/L or 1500 mg-hr/L and then aerated for 24 hours prior to analysis. In the grain mills, the duration of the fumigations was 24 hours at either ~280, ~1000, or ~1800 mg-hr/L followed by a 24-hour aeration interval. Sulfuryl fluoride analysis was completed immediately after the 24-hour aeration period.

Crop	Commodity	Temp. (ºC)	Application rate (mg-hr/L) / No. of applications	Aeration (days)	n	Sulfuryl Fluoride Residues (ppm)			
						Min	Max	Mean	SD
Corn	cornstarch	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Corn	flour	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Corn	grain	22	1500 / 1	1	2	<0.020	0.026	0.023	0.004
Corn	grits	22	1500 / 1	1	2	<0.008	0.014	0.011	0.005
Corn	meal	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Corn	oil	22	1500 / 1	1	2	5.848	7.840	6.844	1.409
Rice	bran	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Rice	hulls	22	1500 / 1	1	2	0.056	0.057	0.057	0.001
Rice	paddy rice grain	22	1500 / 1	1	2	0.016	0.025	0.021	0.007
Rice	polished	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	bran	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	10	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	30	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	22	250, 1000 or 2500 / 1	1	6	<0.008	0.008	0.008	0.001
Wheat	flour	22	1500 / 1	1	2	0.013	0.015	0.014	0.002
Wheat	germ	10	1500 / 1	1	2	<0.020	<0.020	<0.020	0.000
Wheat	germ	30	1500 / 1	1	2	<0.020	<0.020	<0.020	0.000
Wheat	germ	22	1500 / 1	1	2	<0.020	<0.020	<0.020	0.000
Wheat	germ	22	250, 1000 or 2500 / 1	1	6	<0.020	<0.020	<0.020	0.000
Wheat	grain	10	1500 / 1	1	2	0.032	0.033	0.033	0.000
Wheat	grain	30	1500 / 1	1	2	0.013	0.014	0.013	0.001
Wheat	grain	22	1500 / 1	1	10	<0.008	0.090	0.021	0.026
Wheat	grain	22	250, 1000 or 2500 / 1	1	6	<0.008	0.036	0.028	0.004
Wheat	red dog	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Wheat	shorts	22	1500 / 1	1	2	<0.008	<0.008	<0.008	0.000
Corn	cornstarch	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000

Corn	flour	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Corn	grain	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Corn	grits	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Corn	meal	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Corn	oil	22	1500 / 1	4	2	2.511	2.664	2.588	0.108
Rice	bran	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Rice	hulls	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Rice	paddy rice grain	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Rice	polished	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	bran	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	10	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	30	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	flour	22	1500 / 1	4	10	<0.008	<0.008	<0.008	0.000
Wheat	flour	22	250, 1000 or 2500 / 1	4	6	<0.008	<0.008	<0.008	0.000
Wheat	germ	10	1500 / 1	4	2	<0.020	<0.020	<0.020	0.000
Wheat	germ	30	1500 / 1	4	2	<0.020	<0.020	<0.020	0.000
Wheat	germ	22	1500 / 1	4	10	<0.020	<0.020	<0.020	0.000
Wheat	germ	22	250, 1000 or 2500 / 1	4	6	<0.020	<0.020	<0.020	0.000
Wheat	grain	10	1500 / 1	4	2	0.042	0.044	0.043	0.001
Wheat	grain	30	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	grain	22	1500 / 1	4	10	<0.008	<0.008	<0.008	0.000
Wheat	grain	22	250, 1000 or 2500 / 1	4	6	<0.008	<0.008	<0.008	0.000
Wheat	red dog	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Wheat	shorts	22	1500 / 1	4	2	<0.008	<0.008	<0.008	0.000
Corn	cornstarch	22	1500 / 1	7	2	NA	NA	NA	NA
Corn	flour	22	1500 / 1	7	2	<0.008	<0.008	<0.008	0.000
Corn	grain	22	1500 / 1	7	2	<0.008	<0.008	<0.008	0.000
Corn	grits	22	1500 / 1	7	2	NA	NA	NA	NA
Corn	meal	22	1500 / 1	7	2	NA	NA	NA	NA
Corn	oil	22	1500 / 1	7	2	3.128	4.384	3.756	0.888
Rice	bran	22	1500 / 1	7	2	NA	NA	NA	NA
Rice	hulls	22	1500 / 1	7	2	<0.008	<0.008	<0.008	0.000
Rice	Paddy rice grain	22	1500 / 1	7	2	NA	NA	NA	NA
Rice	polished	22	1500 / 1	7	2	NA	NA	NA	NA
Wheat	bran	22	1500 / 1	7	2	NA	NA	NA	NA
Wheat	flour	10	1500 / 1	7	2	NA	NA	NA	NA
Wheat	flour	30	1500 / 1	7	2	NA	NA	NA	NA
Wheat	flour	22	1500 / 1	7	20	NA	NA	NA	NA
Wheat	flour	22	250, 1000 or	7	6	NA	NA	NA	NA

			2500 / 1						
Wheat	germ	10	1500 / 1	7	2	NA	NA	NA	NA
Wheat	germ	30	1500 / 1	7	2	NA	NA	NA	NA
Wheat	germ	22	1500 / 1	7	20	NA	NA	NA	NA
Wheat	germ	22	250, 1000 or 2500 / 1	7	6	NA	NA	NA	NA
Wheat	grain	10	1500 / 1	7	2	0.019	0.021	0.02	0.001
Wheat	grain	30	1500 / 1	7	2	NA	NA	NA	NA
Wheat	grain	22	1500 / 1	7	26	NA	NA	NA	NA
Wheat	grain	22	250, 1000 or 2500 / 1	7	6	NA	NA	NA	NA
Wheat	red dog	22	1500 / 1	7	2	NA	NA	NA	NA
Wheat	shorts	22	1500 / 1	7	2	NA	NA	NA	NA

CROP FIELD TRIALS & RESIDUE DECLINE ON NUTS AND DRIED FRUITS **PMRA# 774912**

Supervised post-harvest fumigation trials were conducted with walnuts, pistachios, pecans, almonds, dates, figs, dried plums and raisins. Single fumigations were carried out at normal atmospheric pressure (Treatment A) or under vacuum conditions (Treatment B) at rates of approximately 200 mg-hr/L. Additionally, multiple fumigations (2-5) were conducted, each at approximately 1500 mg-hr/L (Treatment C). All samples were aerated for at least 24 hours prior to the first sample being collected for analysis.

Treatment ID - Crop	Fumigation Number	Fumigation Rate, mg-hr/L (cumulative rate)	Aeration Time, days	Sulfuryl Fluoride Residues (ppm)				
				n	Min.	Max.	Mean	Std. Dev.
A - Almond	1	203	1	4	0.009	0.012	0.011	0.002
A - Almond	1		2	5	0.001	0.002	0.001	0.0005
A - Dates	1	208	1	4	0.001	0.001	0.001	0.00
A - Dried Plums	1	219	1	4	0.001	0.001	0.001	0.00
A - Figs	1	197	1	5	0.001	0.007	0.004	0.002
A - Pecans	1	199	1	5	0.032	0.060	0.046	0.011
A - Pecans	1		2	4	0.017	0.025	0.022	0.003
A - Pecans	1		5	4	0.005	0.007	0.006	0.001
A - Pecans	1		8	4	0.001	0.001	0.001	0.00
A - Pistachios	1	214	1	4	0.001	0.001	0.001	0.00
A - Raisins	1	221	1	4	0.001	0.001	0.001	0.00
A - Walnuts	1	217	1	4	0.068	0.079	0.073	0.005
A - Walnuts	1		5	4	0.001	0.002	0.002	0.0005
A - Walnuts	1		8	4	0.001	0.001	0.001	0.00
B - Almond	1	1534	1	4	0.028	0.040	0.034	0.005
B - Almond	2	1538 (3072)	1	4	0.044	0.075	0.058	0.014
B - Almond	2		2	5	0.022	0.055	0.035	0.014
B - Almond	2		5	2	0.007	0.008	0.008	0.001
B - Almond	3	1488 (4560)	1	4	0.107	0.128	0.121	0.009
B - Almond	3		5	4	0.014	0.018	0.016	0.002
B - Almond	3		8	4	0.001	0.002	0.002	0.0005
B - Almond	3		15	4	0.001	0.001	0.001	0.00
B - Dates	1	1484	1	4	0.006	0.008	0.007	0.001
B - Dates	2	1504 (2988)	1	4	0.001	0.002	0.002	0.0001
B - Dates	3	1493 (4481)	1	4	0.005	0.007	0.006	0.0008

B - Dates	4	1503 (5984)	1	4	0.009	0.015	0.012	0.003
B - Dates	4		5	4	0.008	0.011	0.009	0.001
B - Dates	5	1491 (7475)	1	4	0.013	0.023	0.017	0.004
B - Dates	5		2	4	0.008	0.019	0.014	0.006
B - Dates	5		5	4	0.006	0.016	0.009	0.005
B - Dates	5		8	6	0.001	0.008	0.004	0.003
B - Dates	5		15	4	0.001	0.001	0.001	0.00
B - Dried Plums	1	1575	1	4	0.001	0.001	0.001	0.00
B - Dried Plums	2	1504	1	5	0.001	0.001	0.001	0.00
B - Dried Plums	3	1516	1	5	0.001	0.002	0.001	0.0006
B - Dried Plums	4	1521	1	4	0.001	0.001	0.001	0.00
B - Figs	1	1462	1	4	0.033	0.041	0.037	0.004
B - Figs	2	1498 (2960)	1	4	0.011	0.015	0.013	0.002
B - Figs	2		2	4	0.002	0.009	0.006	0.004
B - Figs	2		5	2	0.004	0.006	0.005	0.0008
B - Pecans	1	1533	1	4	2.224	2.688	2.408	0.200
B - Pecans	1		5	4	0.099	0.105	0.103	0.003
B - Pecans	1		15	4	0.015	0.020	0.016	0.002
B - Pecans	2	1452 (2985)	1	3	4.146	5.532	4.906	0.703
B - Pecans	2		15	4	0.012	0.016	0.014	0.002
B - Pecans	3	1510 (4495)	1	4	4276.00	6.030	4.950	0.842
B - Pecans	3		2	4	1.304	3.915	2.564	1.188
B - Pecans	3		5	4	0.199	0.261	0.228	0.028
B - Pecans	3		8	4	0.057	0.069	0.063	0.007
B - Pecans	3		15	4	0.001	0.001	0.001	0.00
B - Pistachios	1	1517	1	4	0.252	0.303	0.277	0.022
B - Pistachios	1		5	4	0.018	0.029	0.023	0.004
B - Pistachios	2	1507 (3024)	1	4	0.051	0.070	0.063	0.009
B - Pistachios	2		5	4	0.001	0.001	0.001	0.00
B - Pistachios	3	1506 (4530)	1	4	0.035	0.056	0.045	0.011
B - Pistachios	3		2	4	0.081	0.016	0.012	0.004
B - Pistachios	3		5	4	0.001	0.001	0.001	0.00
C - Almond	1	218	1	4	0.012	0.020	0.016	0.004
C - Almond	1		2	4	0.001	0.009	0.005	0.004
C - Almond	1		4	4	0.001	0.001	0.001	0.00
C - Pecans	1	206	1	4	1.095	1.306	1.182	0.091
C - Pecans	1		2	4	0.369	0.462	0.420	0.046
C - Pecans	1		5	4	0.039	0.055	0.048	0.007
C - Pecans	1		8	5	0.004	0.007	0.006	0.001
C - Pecans	1		15	4	0.001	0.001	0.001	0.00
C - Pistachios	1	202	1	5	0.013	0.026	0.018	0.005
C - Pistachios	1		2	4	0.001	0.001	0.001	0.00
C - Walnuts	1	183	1	4	0.569	0.640	0.602	0.030
C - Walnuts	1		2	4	0.290	0.425	0.362	0.057
C - Walnuts	1		5	4	0.090	0.101	0.094	0.005
C - Walnuts	1		8	4	0.024	0.029	0.027	0.003
C - Walnuts	1		15	4	0.001	0.001	0.001	0.00

CROP FIELD TRIALS & RESIDUE DECLINE ON NUTS AND DRIED FRUITS	PMRA#774908, 1448732

Dried fruit (raisins, dried plums, figs) and tree nuts (walnuts, almonds, pecans, hazelnuts) were fumigated with sulfuryl fluoride at three different commercial fumigation sites during 2004. At each test location, natural atmospheric pressure (NAP) fumigation chambers were used with an application rate of 1500 mg-hr/L. One set of hazelnut samples received three repeat applications of 1500 mg-hr/L. In addition to the NAP chambers used at one test site, vacuum fumigation chambers were used with an application rate of 200 mg-hr/L. Samples were retrieved and immediately shipped as is (shipped on the day of aeration and prior to the full 24 hour aeration period). Some samples were prepared in the field (i.e., without the 24 hour aeration period) in an attempt to maximize the SF residues.

Commodity	Total Applic. Rate (mg-hr/L)	Aeration Period (days)	Sulfuryl Fluoride Residues (ppm)					
			n	Min.	Max.	Median	Mean	Std. Dev.
Raisins	1500	1	7	0.02	0.48	0.03	0.09	0.17
Figs	1500		7	0.3	4.3	1.4	2	1.6
Dried Plums	1500		6	0.5	1.9	0.6	0.7	0.6
Walnuts (WS)	1500		8	0.8	2.6	1.5	1.6	0.7
Walnuts (IS)	1500		8	0.9	2.3	1.9	1.7	0.5
Walnuts (VWS)	200		7	0.1	1	0.5	0.5	0.3
Walnuts (VIS)	200		7	0.2	0.9	0.5	0.5	0.3
Almonds (WS)	1500		8	0.1	1	0.4	0.5	0.3
Almonds (IS)	1500		8	0.2	1.5	0.5	0.6	0.5
Pecans (WS)	1500		8	0.9	10.3	3.3	3.5	3.1
Pecans (IS)	1500		8	1.0	11.5	4.9	5.3	3.7
Hazelnuts (WS)	1500		10	0.8	5.4	1.9	2.3	1.4
Hazelnuts (IS)	1500		10	0.6	4	1.5	1.7	1.1
Hazelnuts (RWS)	3 × 1500	3	6	1.6	3	2.1	2.1	0.5
Hazelnuts (RIS)	3 × 1500		6	1.2	2.9	1.9	1.9	0.8

WS: without shell
IS: in shell
VWS: vacuum without shell
VIS: vacuum in shell
RWS: repeated application without shell
RIS: repeat application with shell

CROP FIELD TRIALS & RESIDUE DECLINE ON FINISHED PRODUCTS	PMRA#774925

Several finished products, in their retail packaging (packaged configuration) and removed from their packaging (open configuration), as well as cocoa beans, coffee, ham, and other key ingredients were fumigated once at a rate of 1414 to 1734 g hr/L at 30°C followed by a 23- to 27-hour aeration period at 5 to 10 L/min.

Commodity	Configuration	n	Sulfuryl Fluoride Residues (ppm)			
			Min	Max	Mean	SD
Cheezits7	Open	2	< 0.004	< 0.004	< 0.004	0.000
Cheezits7	Packaged	2	0.021	0.029	0.025	0.005
Fritos7	Open	2	< 0.004	0.004	0.003	0.002
Fritos7	Packaged	2	< 0.004	0.005	0.004	0.002
Doritos7	Open	2	0.123	0.153	0.138	0.021
Doritos7	Packaged	2	0.009	0.406	0.208	0.281
Spaghetti	Open	2	< 0.004	< 0.004	< 0.004	0.000
Spaghetti	Packaged	2	< 0.004	< 0.004	< 0.004	0.000
Egg Noodles	Open	2	< 0.004	< 0.004	< 0.004	0.000
Egg Noodles	Packaged	2	< 0.004	< 0.004	< 0.004	0.000
Chocolate Cake Mix	Open	2	< 0.004	< 0.004	< 0.004	0.000
Chocolate Cake Mix	Packaged	2	< 0.004	0.013	0.007	0.007
White Cake Mix	Open	2	0.013	0.020	0.017	0.005
White Cake Mix	Packaged	2	0.026	0.038	0.032	0.009
Corn Flakes	Open	2	0.277	1.993	1.135	1.213
Corn Flakes	Packaged	2	0.085	0.087	0.086	0.002
Granola	Open	2	0.011	0.032	0.022	0.015
Granola	Packaged	2	0.106	0.136	0.121	0.021
Flour Tortilla	Open	2	0.004	0.004	0.004	0.000
Flour Tortilla	Packaged	2	0.011	0.025	0.018	0.010
Corn Tortilla	Open	2	0.019	0.047	0.033	0.020
Corn Tortilla	Packaged	2	0.005	0.006	0.005	0.001
Pecan Sandies7	Open	2	0.061	0.065	0.063	0.003
Pecan Sandies7	Packaged	2	0.101	0.199	0.150	0.069
Peanut Butter Cookies	Open	2	< 0.004	< 0.004	< 0.004	0.000
Peanut Butter Cookies	Packaged	2	< 0.004	0.011	0.006	0.006
Coconut Flakes	Open	2	0.808	0.991	0.900	0.129
Coconut Flakes	Packaged	2	0.166	0.203	0.185	0.026
Oreo7 Cookies	Open	2	0.161	0.197	0.179	0.025
Oreo7 Cookies	Packaged	2	0.075	0.129	0.102	0.038
Coffee Beans	Open	2	0.011	0.011	0.011	0.000
Ground Coffee	Open	2	0.799	0.832	0.816	0.023
Beef Jerky	Open	2	< 0.004	0.007	0.005	0.004

CROP FIELD TRIALS & RESIDUE DECLINE ON FINISHED PRODUCTS					PMRA#774925	
Beef Jerky	Packaged	2	< 0.004	< 0.004	< 0.004	0.000
Powdered Nonfat Milk2	Open	2	< 0.004	< 0.004	< 0.004	0.000
Powdered Whole Milk	Open	2	1.439	1.466	1.453	0.019
Powdered Cheese	Open	2	0.344	0.472	0.408	0.091
Powdered Eggs	Open	2	0.253	0.634	0.444	0.269
Garlic Powder	Open	2	< 0.004	< 0.004	< 0.004	0.000
Onion Powder	Open	2	< 0.004	< 0.004	< 0.004	0.000
Peppercorns	Open	2	0.012	0.018	0.015	0.004
Parsley	Open	2	0.120	0.204	0.162	0.059
Baking Powder	Open	2	0.027	0.036	0.032	0.007
Baking Soda	Open	2	< 0.004	< 0.004	< 0.004	0.000
Salt	Open	2	< 0.004	< 0.004	< 0.004	0.000
Sugar	Open	2	< 0.004	< 0.004	< 0.004	0.000
Basil	Open	2	0.008	0.013	0.010	0.004
Peanuts	Open	2	0.082	0.209	0.145	0.090
Chilis	Open	2	0.229	0.264	0.247	0.025
Ham	Open	2	< 0.004	< 0.004	< 0.004	0.000
Cocoa Beans	Open	2	0.113	0.121	0.117	0.006

Shaded entries in the table are for commodity/analyte combinations with unacceptable method performance based on concurrent recovery. As there is uncertainty in the values reported, these were not considered further in the estimation of the MRL.

CROP FIELD TRIALS & RESIDUE DECLINE ON WALNUTS AND RAISINS								PMRA#774908	
Sulfuryl fluoride was applied to stored walnuts and raisins as a gas fumigant, once or up to 5 times at a total rate of 2500 mg-hr/L and with an aeration period of 24 hours.									
Load	**Temperature (°C)**	**Total Rate (mg-hr/L)**	**Post-Aeration (Days)**	**Sulfuryl Fluoride Residues (ppm)**					
				n	**Min**	**Max**	**Median**	**Mean**	**Std. Dev.**
Raisins									
Top	10	2511-2534	4	9	<0.0042	<0.0042	<0.0042	<0.0042	-
Middle				10	<0.0042	<0.0042	<0.0042	<0.0042	-
Bottom				10	<0.0042	<0.0042	<0.0042	<0.0042	-
Middle	10	2511-2534	7	4	<0.0042	<0.0042	<0.0042	<0.0042	-
Middle	21	2529-2535	4	4	<0.0042	<0.0042	<0.0042	<0.0042	-
			7	4	<0.0042	<0.0042	<0.0042	<0.0042	-
Middle	32.2	2464-2549	4	4	<0.0042	<0.0042	<0.0042	<0.0042	-
			7	4	<0.0042	<0.0042	<0.0042	<0.0042	-
Walnuts									
Top	10	2494-2514	4	10	0.119	0.259	0.177	0.184	0.044
Middle				6	0.285	0.386	0.336	0.332	0.040
Bottom				6	0.245	0.289	0.275	0.271	0.017
			7						

Middle	10	2494-2514		6	<0.0042	0.0042	-	-	-
Middle	21	2549-2550	4	6	0.036	0.052	0.045	0.044	0.006
			7	4	<0.0042	0.007	-	-	-
Middle	32.2	2495-2501	4	4	0.194	0.229	0.212	0.212	0.016
			7	4	0.048	0.073	0.063	0.062	0.010

CROP FIELD TRIALS & RESIDUE DECLINE ON CEREALS AND PROCESSED COMMODITIES	**PMRA#774913**

Sulfuryl fluoride was applied as a gas fumigant in a test mill where wheat bran, flour (corn and wheat) and grains (barley, rice and wheat) were stored. The stored commodities were treated for 15 hours at a rate of 1761 g-hr/L followed by an aeration period of 12 hrs. The mill was started up 21 hours after the aeration was completed.

Commodity	**Temperature (ºC)**	**Total Applic. Rate, (g hr/L)**	**Sulfuryl Fluoride Residues (ppm)**					
			n	**Min.**	**Max.**	**Median**	**Mean**	**Std. Dev.**
Corn, Flour	24.1	1761	2	0.036	0.039	-	0.037	-
Wheat, Flour			1	-	0.043	-	-	-
Barley, Grain			4	0.018	0.019	0.018	0.018	0.0008
Rice, Grain			2	0.008	0.008	-	0.008	-
Wheat, Grain			2	0.008	0.009	-	0.009	-

PROCESSED FOOD AND FEED	
See crop field trials.	
LIVESTOCK FEEDING	**PMRA # 72828**
Due to the nature of the molecule, sulfuryl fluoride is expected to hydrolyse to form sulfate and fluoride anion. It is unlikely that secondary residues of sulfuryl fluoride will occur in livestock commodities. Therefore, feeding studies in livestock are not required at this time.	

Table 5 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT	Sulfuryl fluoride
RESIDUE DEFINITION FOR RISK ASSESSMENT	Sulfuryl fluoride
METABOLIC PROFILE IN DIVERSE CROPS	Similar in various processed and unprocessed commodities.
ANIMAL STUDIES	
Not applicable.	

DIETARY RISK FROM FOOD AND WATER		
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**
		Food Alone
Refined chronic non-cancer dietary exposure analysis **ADI = 0.017 mg/kg bw/day** **Estimated chronic drinking water concentration = Not applicable**	**All infants < 1 year**	10
	Children 1–2 years	4
	Children 3 to 5 years	3
	Children 6–12 years	2
	Youth 13–19 years	1
	Adults 20–49 years	1
	Adults 50+ years	1
	Females 13-49 years	1
	Total population	1
	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**
		Food Alone
Refined acute dietary exposure analysis, 95th percentile **ARfD = 0.098 mg/kg bw** **Estimated acute drinking water concentration = Not applicable**	**All infants < 1 year**	1.7
	Children 1–2 years	1.1
	Children 3 to 5 years	1.0
	Children 6–12 years	<1
	Youth 13–19 years	<1
	Adults 20–49 years	<1
	Adults 50+ years	<1
	Females 13-49 years	<1
	Total population	<1

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

Differences Between MRLs in Canada and in Other Jurisdictions

Sulfuryl fluoride is a new active ingredient. Table 1 compares the MRLs proposed for sulfuryl fluoride in Canada with corresponding American tolerances and Codex MRLs[6]. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. A listing of established Codex MRLs is available on the Codex Alimentarius Pesticide Residues in Food and Feed website, by pesticide or commodity.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Tree Nuts (Crop Group 14-11) except almonds	3	3	3
All processed foods not otherwise listed	2	2	Various MRLs for different cereal processed commodities
Peanuts	0.5	0.5	Not established
Cacao beans	0.2	0.2	Not established
Cereal grains (Crop Group 15) except sweet corn kernels plus cobs with husks removed	0.1	0.1 (barley, oat, sorghum, triticale, wheat grains) 0.05 (field and popcorn grain) 0.04 (rice grain)	0.05
Almonds	0.04	3 (tree nuts)	3 (tree nuts)
Raisins	0.01	Not established	0.06 (dried fruits)

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the crop field trials used to generate residue chemistry data.

[6] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
1908780	2008, Limited Pharmacokinetics and Metabolism in F344DUCRL Rats, DACO: 4.5.9
1908781	2008, Nasal and Pulmonary Uptake and Metabolism of inhaled Sulfuryl Fluoride in Male F344/DuCrl Rats, DACO: 4.5.9
1908782	2009, In Vitro Determinations of the sites and rates of Hydrolysis of Sulfuryl Fluoride and Fluorosulfate in the rat and human, DACO: 4.5.9
1908783	2009, Pharmacokinetics in Rat Dams, Fetuses and Pups following vapor inhalation or gavage exposure during gestation and lactation, DACO: 4.5.14
1908784	2009, Pharmacokinetics in Rat Weanlings following inhalation exposure on postnatal day, DACO: 4.5.14
2078938	2005, Revised Report for: Evaluation of Sulfuryl Fluoride in an In-vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.5.9
2078939	2002, Evaluation of sulfuryl fluoride in the mouse lymphoma (L5178Y TK +/-) forward mutation assay/, DACO: 4.5.9
2078940	2011, Sulfuryl Fluoride: Limited Pharmacokinetics and Metabolism in F344/DuCrl Rats., DACO: 4.5.9
2078941	2011, Quantification of fluorosulfate and fluoride in selected tissues following inhalation exposure to sulfuryl fluoride in male F344/DuCrl rats., DACO: 4.5.9
2078942	2011, Sulfuryl Fluoride: Pharmacokinetics in CRL:CD(SD) rat dams, fetuses, and pups following vapor inhalation or gavage exposure during gestation and lactation., DACO: 4.5.9
2078943	2009, Sulfuryl Fluoride: Pharmacokinetics in CRL:CD(SD) Rat Weanlings Following Inhalation Exposure on Postnatal Day (PND) 22., DACO: 4.5.9
2078944	2011, Sulfuryl Fluoride: Probe Study to Evaluate Absorption and Limited Pharmacokinetics Following a Single, 6-hour, 600 ppm Exposure in New Zealand White Rabbits., DACO: 4.5.9

2078945	2011, Sulfuryl Fluoride: Limited Pharmacokinetics of Repeated, 6-hour/day, Inhalation Exposures Conducted for Two Weeks in F344/DuCrl Rats., DACO: 4.5.9
2078946	2011, Sulfuryl Fluoride: Species Comparison of Limited Pharmacokinetics Following a Single, 6-hour Inhalation, Exposures of F344/DuCrl Rats and New Zealand White Rabbits., DACO: 4.5.9
2078947	2011, Cover letter, DACO: 0.8
2078948	2011, Sulfuryl Fluoride cross-species PBPK model: Age and species-related pharmacokinetics of sulfuryl fluoride and its metabolites., DACO: 4.5.9
2078949	2011, Sulfuryl Fluoride Scientific basis for removal of the database uncertainty factor and continuation of a waiver for a developmental neurotoxicity study., DACO: 4.5.9
2232944	2012, Additional Information in Response to PMRA Health Canada Review of Sulfuryl Fluoride Pharmacokinetics and Physiologically Based Pharmacokinetic Model, DACO: 4.5.9
728288	Waiver
728290	Fluoride and Sulfate Residues in Foods Fumigated with Sulfuryl Fluoride
1448729	Fluorine Metabolism in the Bovine Organism
1448730	Fluorine Concentration and Distribution in Hens Eggs From the Aspect of Selected Biological Parameters
774896	Summary
774897	Assessment and Interpretative Summary of Results from Sulfuryl Fluoride Residue Studies, 1987 and 1989
849450	Report Summaries. Various. 53 pages.
774924	Diffusion Fluoride-Ion Selective Probe Analysis Method by Direct Comparison to the Total Fluoride Neutron Activation Analysis Technique Comments: 7.2.2
774898	Independent Validation for Corn Oil and Raisins using Dow AgroSciences Method GRM 01.17 Determination of Fluoride Anion in Corn, Wheat, Corn Oil and Flour Comments: 7.2.3, 7.2.4
774899	Independent Laboratory Validation of Dow AgroSciences LLC Method GRM 01.12 Determination of Residues of Sulfuryl Fluoride in Dried Fruit and Tree Nuts by Gas Chromatography with Electron Capture Detection Comments: 7.2.3, 7.2.4

774900	Independent Laboratory Validation of Dow AgroSciences LLC Method GRM 01.11 Determination of Residues of Sulfuryl Fluoride as Fluoride in Dried Fruit and Tree Nuts Using a Fluoride-Selective Electrode with a Double Known Addition Calibration Technique Dow AgroSciences LLC Comments: 7.2.3, 7.2.4
774901	Independent Laboratory Validation of Dow AgroSciences LLC Method GRM 01.11 Determination of Residues of Sulfuryl Fluoride as Fluoride in Dried Fruit and Tree Nuts Using a Fluoride-Selective Electrode with a Double Known Addition Calibration Technique Dow AgroSciences LLC Comments: 7.2.3, 7.2.4
774902	Independent Laboratory Validation of Dow AgroSciences LLC Method Residue Method Validation for the Determination of Fluoride Anion in Corn, Wheat, Corn oil and Flour, as included in Lab Report Code: , Appendix A, Magnitude of the Terminal Fluoride Ion Level in Cereal Grain Commodities Fumigated with Sulfuryl Fluoride. Comments: 7.2.3, 7.2.4
774923	Independent Laboratory Validation of Dow AgroSciences LLC Method Determination of Residues of Sulfuryl Fluoride in Corn, Wheat and Rice Commodities by Gas Chromatography with Electron Capture Detection Comments: 7.2.3, 7.2.4
774903	Applicability of Multi Residue Methods for Sulfuryl Fluoride
774904	Storage Stability of Fluoride in Cereal Grain and Flour, Dried Fruit (Raisins), Nuts (Walnuts), and Corn Grain and Meal
774905	Interim Report Storage Stability of Sulfuryl Fluoride on SKC 1g Anasorb CSC Tubes at Ambient and Frozen Temperature Conditions
845214	Waiver. Comments: Submitted July 21, 2004
774907	Evaluation of Sulfuryl Fluoride Fumigation Variables on Residue Levels in Crop Commodities
774908	To Determine and Evaluate the Significance of Sulfuryl Fluoride Residues in Dried Fruit and Tree Nuts Following Treatments with Sulfuryl Fluoride at Different Temperatures, Sampling Locations, Desorption Rates, Repeated Fumigations, and a Comparison of Treatments Done Under Vacuum or Normal Atmospheric Pressure Phase 1
774909	Interim Report for the Magnitude of Sulfuryl Fluoride and Fluoride Residues in Dried Fruit and Tree Nuts Method Validation for the Determination of Sulfuryl Fluoride in Dried Fruit and Tree Nuts Using Method GRM 01.12

774910	Interim Report for the Magnitude of Sulfuryl Fluoride and Fluoride Residues in Dried Fruit and Tree Nuts Method Validation for the Determination of Residues of Sulfuryl Fluoride as Fluoride by Dow AgroSciences Method GRM 01.11
774912	Magnitude of the Sulfuryl Fluoride and Terminal Fluoride Ion Levels in Dried Fruit and Tree Nut Commodities Fumigated with Sulfuryl Fluoride
774913	Residue of Fluoride Ion Following Fumigation of a Mill with Sulfuryl Fluoride in Grain, Flour and Bran Produced Immediately After Restart of Production, and in Commodities Placed in the Mill Prior to Fumigation, North America 2002
774925	Magnitude of the Terminal Fluoride Ion Level in Finished Food Products Fumigated with Sulfuryl Fluoride
845215	Duration of storage and storage temperature for study: Magnitude of the Terminal Fluoride Ion Level in Cereal Grain Commodities Fumigated with Sulfuryl Fluoride.
845216	Duration of storage and storage temperature for study: Evaluation of Sulfuryl Fluoride Fumigation Variables on Residue Levels in Crop Commodities.
845217	Data on residues of parent sulfuryl fluoride in processed commodities.
774917	A Critical Review of Scientific Publications Related to Fluoride and a Response to Comments on Risk Assessment
1337762	Summary
1448731	A Study to Assess the Specificity of Dow AgroSciences Methods GRM 01.12 and GRM 01.18 for the Determination of Sulfuryl Fluoride in Agricultural Commodities
1448732	Sulfuryl Fluoride and Fluoride Anion Residue Levels in Dried Fruit and Tree Nuts Commercially Fumigated with Sulfuryl Fluoride
1448733	Sulfuryl Fluoride and Fluoride Anion Residue Levels in Cereal Grain Commodities in Commercial Flour Mills Fumigated with ProFume

2.0 Value

PMRA Document Number	Reference
577905	Efficacy Table Summaries, DACO: 10.2.3.1
577932	Value Summaries, DACO: 10.1
577934	Value Summaries, DACO: 10.1

774920	2002, Biological Dossier to Support Provisional Authorisation of Profume, a New Fumigant Containing 99.8% Sulfuryl Fluoride for the Control of Insect Pests in Food Processing and Storage Areas Document M-III, Annex III, Tier 2 Summary, DACO: 10.2, 10.2.3.1, 10.2.3.2,1 0.2.3.4, 10.3.1, 10.3.2, 10.5.1, 10.5.2, 10.5.3
774921	Sulfuryl Fluoride: Dow AgroSciences Response to Questions Arising During Evaluation of the Dossier, DACO: 10.6
774920	Biological Dossier to Support Provisional Authorization of ProFume for the Control of Insects Pests in Food Processing and Storage Areas, EF33. DACO: 10.2.3.3.

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA Document Number	Reference
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845081	The Fate of Sulfuryl Fluoride in Wheat Flour. J. Agric. Food Chem., 12:464-467. Comments: Submitted July 21, 2004

2.0 Environment

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