Proposed Registration Decision PRD2015-08

Sulfoxaflor

(publié aussi en français)

24 March 2015

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

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

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

Canada

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

Catalogue number: H113-9/2015-08E (print version)
H113-9/2015-08E-PDF (PDF version)

Table of Contents

Overview

Proposed Registration Decision for Sulfoxaflor

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 Isoclast Active, Transform WG Insecticide and Closer Insecticide, containing the technical grade active ingredient sulfoxaflor, to control or suppress aphids, leafhoppers, San Jose scale and Lygus bug on field vegetable, cereal grain, oilseed, fruit and nut crops.

Isoclast Active (Registration Number 30824), previously known as Sulfoxaflor Technical Insecticide, Transform WG Insecticide (Registration Number 30825) and Closer Insecticide (Registration Number 30826), previously known as Closer SC Insecticide, are conditionally registered in Canada. The current applications were submitted to convert Isoclast Active, Transform WG Insecticide and Closer Insecticide from conditional registration to full registration.

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 sulfoxaflor, as well as Transform WG Insecticide and Closer Insecticide

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.

---

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."

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

Before making a final registration decision on sulfoxaflor, 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 sulfoxaflor, 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 Sulfoxaflor?

Sulfoxaflor is a compound in the sulfoximine class of chemistry. It is an insecticide with systemic activity in plants, being translocated through the xylem, and is effective against sap-feeding insects both on contact and through ingestion. It acts on the same type of insect nerve cell receptor as the neonicotinoid insecticides but in a different way, so it is considered to have a different mode of action and has been classified into a separate subgroup. Foliar application of end-use products containing sulfoxaflor provides control or suppression of aphids, leafhoppers, San Jose scale and Lygus bugs on field vegetable, cereal grain, oilseed, fruit and nut crops.

[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 Sulfoxaflor Affect Human Health?

Products containing sulfoxaflor are unlikely to affect your health when used according to label directions.

Potential exposure to Sulfoxaflor may occur through the diet (food and water), when handling and applying end-use products containing sulfoxaflor, or when re-entering treated areas. 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 products are used according to label directions.

In laboratory animals, sulfoxaflor was demonstrated to be of slight to moderate toxicity via the oral route; therefore, the signal word and hazard statement “WARNING – POISON” are required on the label. Sulfoxaflor was demonstrated to be of low toxicity via the dermal and inhalation routes. It was minimally irritating to eyes and skin, and did not cause an allergic skin reaction.

The end-use product, Transform WG Insecticide, was demonstrated to be of low toxicity via the oral, dermal and inhalation routes of exposure in laboratory animals. It was moderately irritating to eyes; therefore, the signal word and hazard statement “WARNING – EYE IRRITANT” are required on the label. Transform WG Insecticide was minimally irritating to the skin and did not cause an allergic skin reaction. Closer Insecticide was demonstrated to be of low acute toxicity via the oral and dermal routes in laboratory animals, and is not expected to pose an acute inhalation hazard. It was minimally irritating to the eyes and non-irritating to the skin, and did not cause an allergic skin reaction.

Health effects in animals given repeated doses of sulfoxaflor included effects on the liver, the nervous and muscular systems, and the male reproductive system. Sulfoxaflor did not damage genetic material. There was evidence of tumours of the male reproductive system (preputial gland and testis) in the rat, but the increased tumour response was either marginal or occurred at very high doses. Liver tumours observed in rodents were deemed to occur via a mode of action that is not relevant to humans.

When sulfoxaflor was given to pregnant or nursing animals, effects on the developing fetus (limb abnormalities) and juvenile animal (neonatal deaths) were observed at doses that were not toxic to the mother, indicating that the young were more sensitive to sulfoxaflor than the adult animal. The risk assessment takes this sensitivity into account in determining the allowable level of human exposure to sulfoxaflor.

The risk assessment protects against the effects of sulfoxaflor by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that infants, the subpopulation which would ingest the most sulfoxaflor relative to body weight, is expected to be exposed to less than 86 % of the acceptable daily intake (ADI). Based on these estimates, the chronic dietary risk from sulfoxaflor is not of concern for all population subgroups except for females 13-49 years. For this subgroup, the ADI from exposure to sulfoxaflor is not the same as that for water;hence, an aggregate dietary intake estimate (food plus water) could not be conducted. The chronic risks from food and water are less than 9 % and 20 % of the ADI, respectively. Sulfoxaflor is not carcinogenic; therefore, a cancer dietary exposure assessment is not required.

The acute reference dose (ARfD) for females 13-49 years from exposure to sulfoxaflor residues in water is not the same as that for food, hence an aggregate dietary intake estimate (food plus water) could not be conducted. For this subgroup, the acute dietary risk from food and water exposure to sulfoxaflor is 117 % and 6.61 %, respectively, at the 99.9^{th} percentile of exposure. For all other population subgroups, the deterministic acute dietary exposure (food plus water) is expected to be less than 21 % of the ARfD. Consequently, a single dose of sulfoxaflor is not likely to cause acute health effects to any population subgroup (including infants and children) in light of the conservatisms inherent in the risk assessment (that is, exposure to all treated crops co-occuring on the same day).

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

Residue trials conducted throughout Canada, the United States, the European Union, Australia, Brazil, and New Zealand using sulfoxaflor on various fruits, vegetables, oilseeds, cereal grains, tree nuts, and legumes were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Risks in Residential and Other Non-Occupational Environments

Exposures of the general public are considered acceptable when entering orchards to pick pome and stone fruits treated with Closer Insecticide.

Exposure of the general population to residues of sulfoxaflor from treated orchards could occur by participating in pick-your-own activities in pome fruit (apple and pear) and stone fruit (peach, nectarine, plums, and cherry) orchards. The exposures from such activities are considered acceptable for adults, youths, and children.

Occupational Risks From Handling Transform WG Insecticide and Closer Insecticide

Occupational risks are not of concern when Transform WG Insecticide and Closer Insecticide are used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Transform WG Insecticide and Closer Insecticide, as well as field workers re-entering freshly treated fields and orchards, can come in direct contact with sulfoxaflor residues on the skin. Therefore, the label specifies that anyone mixing and loading Transform WG Insecticide and Closer Insecticide, and during clean-up and repair must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes plus socks, and eye protection. In addition, when mixing and loading for aerial application, workers must also wear coveralls. Applicators must wear a long-sleeved shirt, long pants, and shoes plus socks. In addition, all mixers and loaders must wear eye protection, and for aerial applications, an added layer of coveralls must be worn for mixing and loading. The label also requires that workers not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications, and the duration of exposure for workers, the risks to these individuals are not a concern.

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

Environmental Considerations

What Happens When Sulfoxaflor Is Introduced Into the Environment?

When used according to label directions, sulfoxaflor is not expected to pose an unacceptable risk to the environment.

When sulfoxaflor is applied as a foliar spray, this compound will move from the surface of the leaf to internal leaf tissue. Sulfoxaflor can be deposited directly on pollen and nectar if applied when plants are in bloom. Sulfoxaflor is systemic and therefore can also reach pollen and nectar through its movement inside the plant. When spray droplets reach the soil, sulfoxaflor is rapidly broken down by soil microbes. Sulfoxaflor transformation products that are formed in soil are persistent and have the potential to leach through the soil profile and enter groundwater. When sulfoxaflor enters surface water, it also breaks down in the presence of microbes, albeit more slowly than in soil.

Sulfoxaflor poses negligible risk to birds and mammals, fish, terrestrial and aquatic plants and aquatic invertebrates. Because sulfoxaflor is an insecticide, it may cause adverse effects to certain non-target insects when they come in contact with high enough residue levels on plants. Therefore, in order to reduce exposure and minimize potential risk to beneficial arthropods precautionary statements appear on product labels. While sulfoxaflor is unlikely to pose a risk to bee colonies it may pose a potential risk to adult foraging bees exposed directly to spray droplets or to fresh residues on plants, however these effects are relatively short-lived, lasting approximately three days or less. When the risk reduction measures included on the label are followed, risks to bees are considered to be acceptable.

Value Considerations

What Is the Value of Transform WG Insecticide and Closer Insecticide?

Transform WG Insecticide and Closer Insecticide provide control or suppression of certain sap-feeding insect pests of listed field vegetable, cereal grain, oilseed, fruit and nut crops.

Transform WG Insecticide may be applied using either ground-based or aerial application equipment to control aphids and Lygus bugs on cereal grains and oilseeds. Closer Insecticide may be applied using ground-based application equipment, and also by aerial application equipment on potatoes, to control or suppress aphids, leafhoppers and San Jose scale on field vegetable, fruit and nut crops.

The active ingredient sulfoxaflor acts on the same type of insect nerve cell receptor as the neonicotinoid insecticides but in a different way, so it is considered to have a different mode of action and has been classified into a separate subgroup. Insects resistant to neonicotinoids have not shown cross-resistance to sulfoxaflor, giving this new active ingredient value for insecticide resistance management.

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 Transform WG Insecticide and Closer Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with sulfoxaflor on the skin or through inhalation of spray mists, anyone mixing and loading Transform WG Insecticide and Closer Insecticide, and during clean-up and repair, must wear a long-sleeved shirt, long pants, chemical-resistant gloves, shoes plus socks, and eye protection. In addition, when mixing and loading for aerial application, workers must also wear coveralls. Applicators must wear a long-sleeved shirt, long pants, and shoes plus socks. In addition, a standard label statement to protect against drift during application was added to the label. The label also requires that workers not enter treated fields for 12 hours after an application. Taking into consideration these label statements, the number of applications, and the duration of exposure for workers, the risks to these individuals are not a concern.

Environment

Sulfoxaflor product labels inform the user of the leaching potential of sulfoxaflor transformation products and of the hazard to bees and beneficial arthropods. To minimize the exposure to bees and bee brood, the label specifies that sulfoxaflor must be applied early in the morning or late in the evening when bees are not active and must not be applied during bloom on most crops. Taking these use restrictions into consideration, the risk to bees is not of concern.

Next Steps

Before making a final registration decision on sulfoxaflor, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please 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

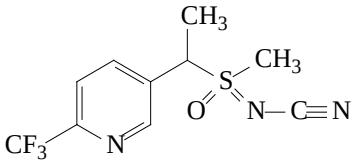
When the PMRA makes its registration decision, it will publish a Registration Decision on sulfoxaflor (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the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

Science Evaluation

Sulfoxaflor

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Sulfoxaflor
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	[methyl(oxo){1-[6-(trifluoromethyl)-3-pyridyl]ethyl}-λ^6-sulfanylidene]cyanamide
2. Chemical Abstracts Service (CAS)	*N*-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-λ^4-sulfanylidene]cyanamide
CAS number	946578-00-3
Molecular formula	$C_{10}H_{10}F_3N_3OS$
Molecular weight	277.3
Structural formula	
Purity of the active ingredient	97.9%

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

Technical Product – Isoclast Active

Property	Result
Colour and physical state	Off-white powder
Odour	Sharp odour
Melting range	112.94°C
Boiling point or range	N/A
Density	1.54 g/cm^3

Property	Result
Vapour pressure at 20°C	$\leq 1.4 \times 10^{-6}$ Pa
Henry's law constant at 20°C	6.7×10^{-12} atm m^3/mol
Ultraviolet (UV)-visible spectrum	λ_{max}, nm neutral: 192, 211, 260 acidic: 210, 260 basic: 218, 260
Solubility in water at 20°C	pH — Solubility (mg/L) Unbuffered — 670 5 — 1380 7 — 570 9 — 550
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Methanol — 93.1 Acetone — 217 Xylene — 0.743 1,2-Dichloroethane — 39.6 Ethyl acetate — 95.2 n-Heptane — 2.42×10^{-4} n-Octanol — 1.66
n-Octanol-water partition coefficient (K_{ow})	pH — $\log K_{ow}$ 5 — 0.806 7 — 0.802 9 — 0.799
Dissociation constant (pK_a)	No measurable ionization constant within environmentally relevant pH range (pH 2–10).
Stability (temperature, metal)	No chemical degradation of the test substance at 54 ± 2°C and in the presence of metals (copper, brass, 304 stainless steel, 316 stainless steel) and metal ions (copper (I) chloride and nickel (II) chloride) was noted through 14 days of storage. A substantial degradation of the test substance, ~50% of the initial assay, was noted in the presence of $FeCl_3 \cdot 6H_2O$.

End-Use Products – Transform WG Insecticide and Closer Insecticide

Property	Transform WG Insecticide	Closer Insecticide
Colour	White	Tan
Odour	Mild odour	Mild odour
Physical state	Solid	Liquid
Formulation type	Wettable granules	Suspension

Property	Transform WG Insecticide	Closer Insecticide
Guarantee	50%	240 g/L
Container material and description	500 g, 1 kg and 5 kg HDPE bottles 500 g, 1 kg and 3 kg water soluble bags inside a cardboard carton	1 L, 5 L, 10 L, 20 L HDPE Jerrycans
Density	0.4–055 g/mL	1–1.2 g/mL
pH of 1% dispersion in water	6–8	3–5
Oxidizing or reducing action	None	None
Storage stability	Stable when stored for three years at warehouse temperatures ranging from -9.06°C to 48.84°C in high density polyethylene (HDPE) and polyethylene terephthalate (PET) bottles and foil laminate sachets.	Stable when stored for three years at warehouse temperatures ranging from -9.06°C to 48.84°C in high density polyethylene (HDPE) and polyethylene terephthalate (PET) bottles.
Corrosion characteristics	The formulation is chemically and physically compatible with HDPE and PET bottles and foil laminate sachets.	The formulation is chemically and physically compatible with HDPE and PET bottles.
Explodability	Not explosive	Not explosive

1.3 Directions for Use

The active ingredient sulfoxaflor is formulated into two commercial class end-use products for use in Canada, Transform WG Insecticide and Closer Insecticide. These products may be applied using ground-based foliar application equipment or, for some uses (potato, barley, wheat and oilseeds), aerial application equipment. Transform WG Insecticide is used to control cereal aphids and Russian wheat aphid on barley and wheat, and aphids and Lygus bugs on canola (rapeseed), flax seed and similar oilseeds (Crop Subgroup 20A). Closer Insecticide is used to control aphids on Brassica vegetables (Crop Group 5), leafy vegetables (Crop Group 4) and root and tuber vegetables (Crop Group 1); suppress leafhoppers on grapes; control green apple aphid, rosy apple aphid and San Jose scale and suppress woolly apple aphid on pome fruits (Crop Group 11-09); control green peach aphid, mealy plum aphid and San Jose scale on stone fruits (Crop Group 12-09); and control aphids and San Jose scale on tree nuts (Crop Group 14-11). For details of the directions for use, please refer to the product labels.

1.4 Mode of Action

Sulfoxaflor has systemic activity in plants, being translocated through the xylem, primarily by apoplastic movement, and is effective against sap-feeding insects both on contact and through

ingestion. Sulfoxaflor acts as an agonist at the insect nicotinic acetylcholine receptor, allowing ion flow through the associated ion channel and resulting in nervous excitation. There is physiological evidence that the mechanism of this action is different from that of neonicotinoid insecticides, and insects resistant to neonicotinoids show no cross-resistance to sulfoxaflor (Zhu *et al.* 2010). Therefore, the Insecticide Resistance Action Committee (IRAC) has placed sulfoxaflor in a separate subgroup (4C) within the mode-of-action group that includes the neonicotinoids (Group 4: Nicotinic Acetylcholine Receptor Agonists).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

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

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

In plant and animal commodities, HPLC/MS/MS methods 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 limits of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. Methods for residue analysis are summarized in Appendix I, Table 1. The proposed enforcement methods were successfully validated in several plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using the radiolabelled samples of lettuce, pea, rice, and tomato analyzed with the proposed enforcement method. Similar efficiencies were demonstrated for ruminant matrices containing bioincurred residues of the test substance and analyzed with the proposed enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Isoclast Active (also known as XDE-208, XR-208 and X11422208; hereinafter referred to as sulfoxaflor) is a member of a novel class of insecticides, the sulfoximines. Sulfoxaflor exerts its insecticidal activity as an agonist at the insect nicotinic acetylcholine receptor (nAChR), which plays a central role in the mediation of fast excitatory synaptic transmission in the insect central nervous system.

A detailed review of the toxicological database for sulfoxaflor was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Integrated toxicokinetic analyses were conducted in several core toxicology studies. Mechanistic studies to support the proposed modes of action (MOA) for liver tumours, Leydig cell tumours, preputial gland tumours and fetal abnormalities/neonatal deaths were also provided. Several studies (acute oral; dermal sensitization; toxicokinetics; 28-day and 90-day dietary studies in rats, rabbits and dogs; a battery of mutagenicity studies; and in vitro rat and human receptor binding studies) were also conducted with metabolite X11919474, a major degradate of sulfoxaflor with potential for human exposure through drinking water. Limited studies were also available for other substances that are either impurities from the formulation process or environmental degradates of concern. The toxicology studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Overall, 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 sulfoxaflor.

In acute toxicity testing, sulfoxaflor was demonstrated to be of slight toxicity via the oral route in rats and moderate toxicity via the oral route in mice. It was shown to be of low toxicity via the dermal and inhalation routes in rats. Sulfoxaflor was minimally irritating to eyes and skin of rabbits, and is not a dermal sensitizer based on results from a local lymph node assay in mice.

The end-use product, Transform WG Insecticide, was demonstrated to be of low toxicity via the oral, dermal and inhalation routes of exposure in rats. It was moderately irritating to eyes and minimally irritating to the skin of rabbits, and is not a dermal sensitizer based on results from a local lymph node assay conducted in mice.

The end-use product, Closer Insecticide, was demonstrated to be of low acute toxicity via the oral and dermal routes in rats. It was minimally irritating to the eyes and non-irritating to the skin of rabbits, and is not a dermal sensitizer based on results from a local lymph node assay conducted in mice. With respect to acute inhalation toxicity, a stable respirable aerosol could not be generated for Closer Insecticide. Based on the low potential for inhalation, as well as the low acute inhalation toxicity observed with Transform WG Insecticide, which contains a higher concentration of sulfoxaflor, Closer Insecticide is considered to be of low acute toxicity via the inhalation route.

Four metabolites (X11596066, X11721061, X11719474 and X11579457) were also evaluated for acute oral toxicity, and were found to be of low acute toxicity via the oral route in rats. A fifth metabolite (X11519540) was determined to be moderately toxic via the oral route in rats, with an LD_{50} that was 2-fold lower than that determined for the parent sulfoxaflor. In addition, metabolite X11719474 was not a dermal sensitizer based on the results of a local lymph node assay.

In the assessment of toxicokinetics, ^{14}C-radiolabelled sulfoxaflor was rapidly absorbed (approximately 92-96%) following oral administration in rats. Maximum plasma concentrations were reached at approximately two hours post-dosing. Plasma concentrations were dose-related indicating absorption was not saturated at 100 mg/kg bw following gavage administration. No significant differences in absorption amount were observed between sexes, or among the single low dose, single high dose, and repeated low dose groups.

Sulfoxaflor was widely distributed among tissues and organs, with highest levels of radioactivity detected in portal of entry and primary excretion tissues (in other words, the gastrointestinal tract, liver, kidney and urinary bladder). By 168 hours post-dosing, less than 1.5% of the administered dose remained in the body. Overall, the toxicokinetics data for sulfoxaflor did not suggest a potential for bioaccumulation.

Excretion of sulfoxaflor occurred primarily via the urine (>99%), with minimal elimination via the feces. The removal of sulfoxaflor from plasma occurred in two distinct phases following a single gavage dose; a rapid phase with a half-life of 4-6 hours followed by a much slower phase with a half-life of 39-45 hours.

The toxicokinetics data for sulfoxaflor indicated that it is resistant to in vivo metabolism, as the parent compound represented over 93% of the dose eliminated in the urine of rats. In the kidney, liver and plasma, only the parent compound was detected, further indicating a lack of metabolism. A glucuronide conjugate of metabolite X11721061, which is the urea metabolite of sulfoxaflor, was identified in urine at up to 4% of the administered dose. Other unidentified minor components in the urine and feces represented less than 1% of administered dose.

In a limited study in the mouse, sulfoxaflor was rapidly absorbed following a single oral dose, and was eliminated almost entirely as un-metabolized parent compound, primarily via the urine with minimal amounts in the feces.

In toxicokinetic analyses integrated into repeat-dose toxicology studies, plasma half-lives in male and female rats were 4-5 and 7-8 hours, respectively, after 28 days of dietary administration, and 8 and 9 hours, respectively, after 90 days of dietary administration.

The toxicokinetics of metabolite X11719474, which is a major metabolite found in plants and environmental matrices, was demonstrated in rats to be similar to the parent sulfoxaflor. Following a single oral dose, metabolite X11719474 was highly (95-98%) and rapidly absorbed, with maximum plasma concentrations attained within approximately one hour of dosing. It was rapidly eliminated in urine, with over 90% eliminated within 12 hours of dosing. Minimal fecal elimination (2-3%) occurred. Similar to sulfoxaflor, the removal of metabolite X11719474 from plasma occurred in two phases; a rapid phase with a half-life of less than two hours followed by a much slower phase with a half-life of 36-41 hours. Metabolite X11719474 was essentially un-metabolized in rats. The primary component found in urine was metabolite X11719474, while only two other minor metabolites, representing less than 1% of the administered dose, were detected.

The toxicity of sulfoxaflor was manifested in adult laboratory animals as generalized toxicity (for example, decreases in body weight, body weight gain, and/or food consumption), hepatotoxicity, adrenal gland effects, and effects on the male reproductive system. In the developing young, neuromuscular abnormalities and neonatal death were observed.

Decreased body weight, body weight gain, and food consumption were observed during the first few days of exposure in several oral studies for all test species. Animals generally recovered from these effects within several weeks. Sulfoxaflor has an unpleasant smell, which may have contributed to palatability issues thereby limiting the dose levels that could be tested via diet or gavage.

In the short- and long-term toxicity studies conducted in mice and rats, the primary target organ was the liver. Effects indicative of hepatotoxicity included clinical chemistry changes (elevated liver enzymes, cholesterol and triglycerides), increased liver weight, hepatocellular hypertrophy with altered tinctorial properties, liver foci, mitotic figures, vacuolization, fatty change, aggregates of macrophages and single cell necrosis. The effects noted at lower doses (increased liver weights, hepatocellular hypertrophy) were consistent with the induction of hepatic cytochrome P450. The longer-term carcinogenicity studies resulted in lower effect levels for hepatotoxicity compared to the short-term studies. Males appeared to be more sensitive to the hepatic effects from sulfoxaflor exposure than females.

There were no significant treatment-related findings reported in the toxicity studies conducted with the dog. It was concluded that higher dose levels could have been tolerated by the dogs in the 12-month study. However, based on the results of palatability and tolerability probe studies (via capsule and diet), the dose levels selected for the 12-month study were reasonable. Furthermore, the endpoints selected for risk assessment provide adequate margins (≥6-fold) to the highest dose tested in the 12-month study of 6 mg/kg bw/day.

Other notable findings in the toxicology database for sulfoxaflor included increased adrenal weight and hypertrophy and/or vacuolization of the adrenal gland zona fasciculata noted in the short-term toxicity study with mice, as well as effects on the male reproductive system (decreased epididymides weight with decreased spermatic elements; increased bilateral atrophy of seminiferous tubules; and decreased secretory material in coagulating gland, prostate and seminal vesicle) observed in the long-term toxicity study with rats.

In the reproductive toxicity studies, hepatotoxicity was apparent in male parental animals only. Reproductive effects, all of which occurred in the absence of maternal toxicity, included increased post-implantation loss and stillbirths, as well as delayed preputial separation in F_1 males in the two-generation reproduction study. An increased incidence of neonatal deaths occurred between post-natal day (PND) 1 and 4 in both F_1 and F_2 progeny at a dose that did not elicit maternal toxicity. Complete litter losses were noted at higher doses in the one-generation range-finding study. Reduced neonatal survival in the absence of maternal toxicity was also observed in the rat developmental neurotoxicity (DNT) study at a lower effect level than in the reproductive toxicity studies.

Following in utero exposure where maternal animals received sulfoxaflor in the diet, developmental effects were noted in rats at the highest dose tested and included reduced fetal weight, increased resorptions and post-implantation loss, and several developmental abnormalities (forelimb flexure, bent clavicle, hind limb rotation, convoluted/hydroureter and fused sternebrae). Maternal toxicity was evident at this dose in the form of decreased body weight, body weight gain, food consumption and gravid uterine weight. In the rabbit dietary developmental toxicity study, decreased body weight gain and food consumption were observed in maternal animals whereas no treatment-related effects were noted in the developing fetus. Preliminary studies demonstrated comparable systemic bioavailability in pregnant rabbits following dietary and gavage administration.

A cross-fostering reproduction study was conducted to assess whether the observed effects of sulfoxaflor on neonatal survival in rats resulted from in utero and/or lactational exposure. In that study, all offspring from dams exposed to sulfoxaflor prior to birth died by PND 4, irrespective of whether they were cross-fostered to control or treated foster dams. There was no effect on neonatal survival when exposure to sulfoxaflor occurred only post-natally (through lactation). Thus, it was demonstrated that the effect of sulfoxaflor on pup survival was due to in utero exposure.

To determine the critical window of developmental susceptibility of rat fetuses, a series of special studies was conducted. These studies demonstrated that the critical window of exposure for susceptibility was late gestation, specifically, from gestation day (GD) 20 to 21 or 22. Exposure of dams during this limited time period resulted in reduced neonatal survival and limb abnormalities in pups, whereas offspring from dams exposed up to GD 19 did not show any limb abnormalities or reduced neonatal survival.

Histopathological evaluation of fetal lung samples from the developmental toxicity study in rats did not reveal any morphological abnormalities that could have contributed to the sulfoxaflor-induced neonatal mortality in rat pups.

In the cross-fostering reproduction study in rats, sulfoxaflor blood concentrations determined on GD 21 were comparable between maternal and fetal animals, suggesting that sulfoxaflor moves readily across the placenta. Similar findings were reported in the rabbit developmental toxicity study, suggesting that the interspecies difference in developmental and reproductive toxicity between rats and rabbits was not due to toxicokinetic differences but rather toxicodynamic differences. Lactational transfer was also confirmed in the cross-fostering study, in which the levels of sulfoxaflor in milk on lactation day (LD) 0 were determined to be approximately half the corresponding plasma concentrations in sulfoxaflor-exposed dams. In the two-generation reproductive toxicity study, plasma concentrations of sulfoxaflor determined in offspring on PND 4 were 30% of maternal values. The results from these studies indicated that fetal plasma levels of sulfoxaflor were similar to those in maternal animals during gestation; however, after parturition when offspring exposure to sulfoxaflor was limited to lactational transfer, exposure to the rat neonates was 2 to 3-fold lower than maternal exposure levels.

It was proposed by the applicant that developmental abnormalities and neonatal deaths observed in rats were mediated by the pharmacological agonist action of sulfoxaflor at the fetal neuromuscular junction nAChR. There are two types of mammalian nAChRs: neuronal and muscular. The neuronal nAChRs are located principally in the central and peripheral nervous system and dysregulation is manifested in a variety of ways, including effects on cardiovascular function, cognitive performance, locomotor activity, and respiration. The muscular nAChRs are found in the intramuscular junctions of skeletal muscles and are involved in muscle contraction. Dysregulation of these receptors can result in muscle contraction and breathing difficulties due to sustained diaphragm contracture.

Two isoforms of the muscular nAChRs have been identified in mammals: a fetal isoform and an adult isoform. Five subunits are expressed in mammalian muscle nAChRs (α1, β1, γ, δ and ε). Transcription of the γ and ε subunit genes is regulated developmentally, whereby the γ subunit is expressed in fetal muscle and the ε subunit is expressed in adult muscle. In rodents, replacement of the (subunit by the γ subunit commences late during the first postnatal week and is largely complete by the end of the second postnatal week, whereas in humans, the switch from (to γ subunit expression occurs predominantly during the third trimester of gestation. The fetal muscle nAChR develops functional expression between GD 16 and 17 in the rat, resulting in synchronized fetal limb movements and diaphragmatic responsiveness, important for the transition to extra-uterine respiration.

The MOA proposed by the applicant for developmental abnormalities and neonatal death observed following exposure to sulfoxaflor involves sustained agonism at the fetal-type muscle nAChR and subsequent sustained muscle contracture of the limb, shoulder girdle and diaphragm. The transitioning of muscle nAChRs from the fetal to the adult isoforms and the timing of this shift provides insight into the potential role of the fetal nAChR in the developmental effects observed in rats after sulfoxaflor exposure. Both the skeletal effects and the offspring deaths in rats were limited to the very early post-natal period when the fetal isoform is the predominant isoform present. However, beyond PND 4, there was no increase in pup death and the skeletal effects noted shortly after birth (forelimb flexure, bent clavicles, and rotated hindlimbs) were no longer apparent.

To support the proposed MOA for sulfoxaflor-induced developmental and reproductive toxicity, several mechanistic studies were conducted. Radioligand-binding studies were performed with fetal muscle tissue isolated from the rat (GD 21) and rabbit (GD 28) forelimb and with human recombinant receptors expressed in cultured human embryonic kidney cells. A high level of non-specific binding was observed with sulfoxaflor, due to interaction with sites other than the receptor, such as lipid membranes. Competition binding was therefore employed to examine whether sulfoxaflor was able to displace binding of the high-affinity nAChR radioligand [^{3}H]-epibatidine. In a series of studies, sulfoxaflor was shown to bind to fetal isoforms of the muscular nicotinic receptors of rats, rabbits and humans.

The ability of sulfoxaflor to act as an agonist of muscle nAChRs was examined using two-electrode voltage clamp recording, which allows the flow of current through cell-surface nAChRs to be measured in response to agonist application. Changes in current, caused by the

opening of agonist-gated ion channels, can be measured. This study used the fetal isoform for rat and human muscle nAChR expressed in Xenopus oocytes. In addition to sulfoxaflor, the endogenous agonist acetylcholine was tested to ensure the integrity of the expressed receptors and for a quantitative comparison to sulfoxaflor-induced activity. A concentration of up to 3×10^{-3} M of sulfoxaflor (the limit of solubility) was tested with the human fetal and adult receptors and the rat adult receptor and did not produce any agonist activity, whereas a concentration of 3×10^{-4} M of sulfoxaflor induced a 10% response (% of maximum response to acetylcholine) in rat fetal receptors. This represents a10-fold difference in concentration eliciting no response in the human receptor with that eliciting a 10% response in the rat fetal receptor. The rabbit receptor was not tested as it was reported that the technology for cloning the rabbit muscle nAChR is not yet available. In addition, no agonist activity was observed with metabolite X11719474.

To determine if nAChR agonism could result in muscle contraction, preparations of rat fetal diaphragm muscle were tested for their response to sulfoxaflor. The results of this study revealed dose-dependent muscle contractions. These contractions were blocked by a potent nicotinic receptor antagonist (tubocurarine), demonstrating that sulfoxaflor acts directly upon the nicotinic receptor leading to muscle contractions. Furthermore, muscle contraction was only observed in the presence of sulfoxaflor. When sulfoxaflor was removed from the muscle preparations, contraction ceased.

These studies revealed that, qualitatively, sulfoxaflor has the ability to bind to the fetal isoforms of the muscle nAChR of rats, rabbits and humans. Despite binding, sulfoxaflor did not activate the adult or fetal human muscle nAChr, or the adult rat muscle nAChR. This was likely due to the different nAChR subtypes present in adult and fetal tissues. Sulfoxaflor interacted with fetal muscle nAChR, which is still present in the neonatal rat; however, it did not bind to the adult subtype, thereby conferring an enhanced susceptibility to the neonate relative to adults.

The applicant claimed that this MOA was not relevant to humans based upon available data demonstrating fundamental qualitative differences in sulfoxaflor agonism at the rat versus the human muscle nAChR where agonism occurs at the rat fetal subtype, but not the human fetal or adult subtype, muscle nAChR.

The proposed MOA was judged to be plausible, providing a reasonable explanation for the increased neonatal deaths and developmental abnormalities observed with sulfoxaflor. However, there is uncertainty with regard to dose and temporal concordance, as well as alternate MOAs, including the ability of sulfoxaflor to interact with neuronal nAChRs. Due to the severity of the endpoints and this residual uncertainty, the decreased neonatal survival and developmental abnormalities were still considered relevant for human health risk assessment.

Consideration was given to the potential impact of the information gleaned from the mechanistic studies on the uncertainty factor for interspecies extrapolation, which can be divided into separate factors for toxicokinetic and toxicodynamic effects. Although human relevance could not be discounted for the developmental abnormalities and neonatal deaths observed in rats, the available information comparing rat and human muscle nAChR response to sulfoxaflor has bearing on the uncertainty factor for interspecies extrapolation when assessing nAChR-mediated risks associated with sulfoxaflor exposure. There is evidence to suggest that the human muscular

nAChR is less sensitive than the rat receptor to perturbation by sulfoxaflor. Specifically, the radioligand binding and electrophysiological examinations revealed that sulfoxaflor had no agonist activity on the equivalent human fetal nAChR or on the rat or human adult muscle nAChR, whereas it was shown to be a partial agonist of the rat fetal muscle nAChR. Furthermore, a comparison of the amino acid sequence of the rat and human (subunit (specific to the fetus) revealed that although the two subunits are similar (approximately 90% identical), they contain 53 amino acid differences. There is evidence that as few as one or two amino acid differences can confer species-specific agonist activity upon nicotinic ligands. The (and γ subunits (fetal and adult isoforms, respectively), even from the same species, show even greater sequence differences than the human and rat (subunit, where the (and γ subunits of rats share only about 50% identity in amino acid sequence. In addition, known differences in ontogeny and timing of the transition from fetal-type to adult-type muscle nAChR between humans and rats contribute to the reduction of uncertainty with respect to interspecies extrapolation. This information was used to inform the toxicodynamic considerations as they relate to the standard 10-fold uncertainty factor for interspecies extrapolation. Notwithstanding the limitations associated with the proposed MOA, the standard interspecies uncertainty factor of 10-fold was reduced to 3-fold for risk assessments that are based on the endpoint of developmental abnormalities or neonatal death.

In the acute neurotoxicity study, decreased motor activity was apparent in both sexes of rats, while clinical signs of neurotoxicity were observed at the highest dose tested and only on the day of dosing. No evidence of neurotoxicity was seen in the short-term dietary study in rats in which additional neurotoxicity assessments were conducted. In addition to reduced neonatal survival, effects noted in offspring in the DNT study included reduced body weight, a delay in attainment of surface righting response, changes in brain length and weight at study termination, and malrotation of the forelimb. All of these offspring findings occurred in the absence of maternal toxicity.

Sulfoxaflor was tested in a battery of in vitro and in vivo genotoxicity studies. In addition, several sulfoxaflor metabolites (X11596066, X11721061, X11719474, X11579457 and X1159540) were tested in a battery of in vitro genotoxicity studies. There was no evidence of genotoxicity observed in any of the studies with sulfoxaflor or its metabolites.

In the 18-month dietary oncogenicity study in mice, increased incidences of liver adenomas and carcinomas were observed in both males and females. Increased incidences of liver adenomas, Leydig cell adenomas and preputial gland carcinomas were also observed in male rats in the two-year dietary combined chronic toxicity/oncogenicity study. The applicant proposed a constitutive androstane receptor (CAR)-mediated MOA for the liver tumours in rats and mice, and a dopamine agonism/enhancement-mediated MOA for Leydig cell adenomas and preputial gland carcinomas in rats.

The postulated MOA for sulfoxaflor-induced liver tumours is via a nuclear-receptor-mediated MOA that involves CAR activation, leading to increased hepatocellular proliferation and ultimately hepatocellular tumours. Activation of rodent CAR, and to a lesser extent the pregnane X receptor (PXR), produces a cascade of alterations in gene transcription that leads to increased

hepatocellular proliferation, a critical event in the development of liver tumours. In a series of mechanistic studies in mice, including C57BL/6J "knockout" mice for PXR and CAR, and C57BL/J6 mice "humanized" for PXR and CAR, it was demonstrated that sulfoxaflor was a relatively potent inducer of hepatic P450 enzymes via activation of CAR and possibly, to some extent, PXR. This was apparent at the messenger ribonucleic acid, protein (Cyp2b10, Cyp3a11) and enzyme level. Activation of the mouse CAR (and possibly PXR) resulted in increased hepatocyte hypertrophy and proliferation. The human CAR (and possibly PXR) supported modest P450 induction and hepatocyte hypertrophy by sulfoxaflor, but did not support an effect on hepatocyte proliferation.

In a mechanistic study on liver tumourigenesis in rats, 3-day or 7-day exposure to sulfoxaflor at dietary concentrations up to 1500 ppm resulted in increased liver weights, increased cell proliferation in the centrilobular and midzonal regions of the hepatic lobules, marked induction of Cyp2b1 gene expression and hepatic activities of 7-pentoxyresorufin-O-deethylase (PROD) and benzyloxyresorufin-P-deethylase (BROD), and moderate induction of Cyp2b2 and Cyp3a3 expression levels.

When taken together, the mechanistic and repeat-dose toxicity studies for both mice and rats clearly demonstrated a dose-related increase in the Cyp2b/CAR-associated transcript and associated increase in specific Cyp2b protein (Cyp2b10 in mice and Cyp2b1 in rats) and enzymatic activity (PROD/BROD). These results are consistent with direct activation of the CAR nuclear receptor. Furthermore, the Cyp2b/CAR-associated gene expression and protein data from the MOA experiments in both mice and rats define a very specific MOA for sulfoxaflor while simultaneously ruling out other nuclear-receptor MOAs for rodent hepatic carcinogenesis such as activation of peroxisome proliferator-activated receptors or aryl hydrocarbon receptor agonism. Overall, there was sufficient evidence to support the proposed MOA. Moreover, sulfoxaflor caused higher expression of CAR in rodents than in humans. The marked qualitative and quantitative species differences in the key events in the MOA for neoplasia in response to CAR activation allowed for the conclusion that the sulfoxaflor-induced liver tumours in rats and mice are not relevant to humans.

For the induction of Leydig cell tumours in the Fischer 344 rat, it was postulated by the applicant that sulfoxaflor acts as a dopamine agonist in the central nervous system, inhibiting prolactin release in the pituitary, which results in transient decreases in serum testosterone and increased serum luteinizing hormone (LH) levels. This, in turn, leads to Leydig cell hyperplasia and proliferation. This MOA for the induction of Leydig cell tumours is generally considered to be not relevant to humans. To support this MOA, several mechanistic studies were conducted. An 8-week dietary study in male Fischer 344 rats demonstrated that exposure to sulfoxaflor resulted in decreased serum prolactin and increased serum LH and testosterone levels, as well as decreased testis LH receptor (LHR) and prolactin receptor gene expression at week 4, but not at week 2 or week 8. Exposure to sulfoxaflor had no effect on the percentage of Leydig cells with intracellular staining of LHR, biliary excretion of [^{14}C]testosterone, serum 17∃-estradiol levels or any measured gene in the steroidogenic pathway. Because Fischer 344 rats are particularly susceptible to effects on Leydig cells, analogous treatment of male Sprague-Dawley rats was

performed, resulting in increased serum LH and testosterone levels at week 2 and a decrease in serum prolactin level at week 4.

In a mechanistic study using intracerebral microdialysis in rats, sulfoxaflor infusion evoked dose-related increases in the extracellular level of dopamine in the mediobasal hypothalamus, with a maximal rise of 39%, occurring 40 minutes after the onset of infusion. In a further mechanistic study, sulfoxaflor did not bind to the estrogen receptor (ER) alpha and had weak binding affinity to the androgen receptor (AnR), whereas it did not show any agonism or antagonism in the ER and AnR transactivation assays. In addition, there was no evidence for aromatase inhibition by sulfoxaflor.

Overall, these studies were not sufficient to support the proposed MOA for Leydig cell tumours. In particular, there was a lack of consistency in the hormone measurements and gene expression results over the sampling intervals in the 8-week dietary study. The applicant failed to demonstrate that increased dopamine release from the hypothalamus inhibits prolactin release from the anterior pituitary. Also, there was a lack of dose-response and/or temporal concordance with key precursor events (for example, decrease in serum prolactin level, down-regulation of LHR on Leydig cells, decrease in serum testosterone and compensatory increase in serum LH level).

Despite the limitations associated with the proposed MOA, overall concern for the increased incidence of bilateral Leydig cell adenomas was low. There are large qualitative and quantitative differences between rats and humans regarding Leydig cell responses to hormonal stimuli. Rat Leydig cells contain >10-fold more LH receptors than their human counterparts, which confers greater sensitivity of the rat to slight changes in LH levels. Leydig cells in rats, but not in humans, have both prolactin and gonadotropin-releasing hormone (GnRH) receptors on their surface; stimulation of rat Leydig cells through both prolactin and GnRH receptors is a rat-specific mechanism by which Leydig cell tumours can occur. In addition, there was a high incidence of Leydig cell tumours in all dose groups, including controls (88-92%); Leydig cell tumours are common age-related legions in Fischer 344 rats (with a background incidence of 75-100%). Furthermore, the increased incidence of bilateral Leydig cell tumours (88% compared to 64% in controls) was observed only at the highest dose tested, and an increase in Leydig cell tumours was not observed in mice. Finally, the induction of Leydig cell tumours is generally anticipated to exhibit a threshold. Overall, the endpoints selected for risk assessment are considered protective of this endpoint.

In the two-year dietary combined chronic toxicity/oncogenicity study in rats, an apparent increase in the incidence of preputial gland carcinomas was observed in male rats at all dose levels. The applicant postulated that sulfoxaflor promoted the formation of preputial gland carcinomas through the same MOA proposed for the induction of Leydig cell tumours, namely, exposure to sulfoxaflor causes an increase in neuronal dopamine release via agonism of the nAChR. This results in reduced serum prolactin levels and downstream perturbations of LHR gene expression and serum levels of testosterone and LH. Increased activity of the hypothalamus-pituitary axis follows, which leads to continuous dopamine release and subsequent increases in testosterone production. The concerns identified above for the Leydig cell tumour MOA (in other words, a lack of dose-response and/or temporal concordance) apply to the

postulated MOA for the induction of preputial gland carcinomas. In addition, there was no direct evidence to support alterations of the hypothalamus-pituitary axis. However, the preputial gland was not examined for all animals on study and the true incidence of this lesion is unknown. Thus, it was not possible to determine whether the preputial gland tumours were due to treatment. Concern for the preputial gland carcinomas noted at the low dose was minimized by the lack of other toxicological effects at that dose. At the mid dose, other treatment-related findings were noted, including several testicular effects; therefore, the tumour response at this dose was considered equivocal. The endpoints selected for the non-cancer risk assessment are considered protective of the equivocal response at the mid-dose level.

In toxicity studies conducted with metabolite X11719474 (a plant and soil metabolite), effects on the liver were noted in 28- and 90-day dietary studies in the rat. No effects were noted in dogs in a 90-day gavage study, nor were any reproductive or offspring effects noted in a one-generation reproductive toxicity study in the rat. In a developmental toxicity study in the rat, effects on the developing fetus were limited to a slightly increased incidence of wavy ribs at a dose that resulted in reduced body weight in maternal animals. All treatment-related effects noted in the studies conducted with metabolite X11719474 occurred at higher doses than those tested in comparable studies conducted with the parent sulfoxaflor.

Other than acute toxicity and genotoxicity studies, testing with metabolite X11519540 (a minor soil and livestock metabolite not detected in the rat; also a low-level impurity of the manufacturing process) was limited to a 28-day dietary study in rats. In that study, effects occurred down to the lowest dose tested and included hepatotoxicity and adrenal gland effects (increased weight, vacuolization of the cortex). At higher doses, renal toxicity (tubule degeneration), thyroid gland effects (follicular cell hypertrophy), and additional adrenal gland effects (vacuolization of zona fasciculata) were observed. This metabolite demonstrated increased short-term toxicity when compared to the parent sulfoxaflor. The 28-day rat study also indicated that metabolite X11519540 has a longer half-life of elimination (24-35 hours) than sulfoxaflor (4-8 hours), which could contribute to its increased toxicity.

Results of the toxicology studies conducted on laboratory animals with sulfoxaflor, its metabolites, and its associated end-use products, are summarized in Appendix I, Tables 2, 3 and 4. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada’swebsite. As of 21 September 2012, no incident reports involving sulfoxaflor have been submitted to the PMRA.

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, extensive data were available for sulfoxaflor. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits, a reproductive toxicity study in rats, and a developmental neurotoxicity study in rats. Additional studies, including cross-fostering and critical window studies in rats, a neonatal survival study in rabbits, and mechanistic studies examining receptor agonism, were conducted to elucidate the mode of action relating to developmental and reproductive effects in rats and rabbits.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the rabbit. No effects were observed in rabbit fetuses born by caesarian section at the end of gestation or in rabbit neonates reared until PND 4 at doses that caused reductions in maternal growth. In the rat, evidence of sensitivity of the young was noted in several studies. In the rat developmental toxicity study, an increase in resorptions and post-implantation loss, resulting in a decrease in the number of viable fetuses, in addition to developmental abnormalities (forelimb flexure, hindlimb rotation, convoluted ureter, hydroureter, bent clavicle, fused sternebrae) were observed in rat fetuses at a dose that caused moderate toxicity (reduced body weight and body weight gain, increased liver weight) in maternal animals. In both the two-generation reproductive toxicity study and the DNT study, decreased neonatal survival was observed in the absence of maternal toxicity, with the latter study producing the lowest NOAEL for neonatal death in the database. Through various special studies it was determined that the developmental abnormalities and neonatal deaths occurred as a result of in utero exposure and not lactational exposure. Additional findings that were observed at a higher dose in the DNT study, but still in the absence of maternal toxicity, included forelimb malrotation, delay in attainment of surface righting response, and slight changes in brain weight and brain length at study termination (adult offspring).

Overall, the database is adequate for determining the sensitivity of the young. There is a high level of concern for prenatal toxicity / sensitivity of the young based on the seriousness of the endpoint (death) observed in the absence of maternal toxicity. Therefore, the 10-fold *Pest Control Products Act* factor was retained for scenarios in which the endpoint of neonatal death was used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other subpopulations, including children, the risk was considered well-characterized and the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

For females 13 to 49 years of age, the most appropriate study endpoint for assessing risk following acute dietary exposure to sulfoxaflor was from the DNT study in rats. A NOAEL of 1.9 mg/kg bw/day was determined based on neonatal mortality at the LOAEL of 7.1 mg/kg bw/day. The toxicological effects noted in offspring in this study may occur following a single in utero exposure; therefore, these effects are relevant to the selection of the ARfD for this subpopulation.

The standard uncertainty factor of 10-fold for interspecies extrapolation was reduced to 3-fold. As discussed above, this was based on available evidence indicating that humans may be less sensitive than rats to sulfoxaflor-mediated toxicity stemming from interaction with the nicotinic acetylcholine receptor in muscle, which likely plays a role in the neonatal mortality observed in rats. Therefore, uncertainty factors of 3-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied in the setting of the ARfD. The 10-fold *Pest Control Products Act* factor was retained for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. This results in a Composite Assessment Factor (CAF) of 300. The ARfD is considered to be protective of sensitive subpopulations such as unborn children.

The ARfD (for females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.9 \text{ mg/kg bw}}{300} = 0.006 \text{ mg/kg bw}$$

For the general population, the most appropriate endpoint for assessing risk following acute dietary exposure to sulfoxaflor was from the acute neurotoxicity study. A NOAEL of 25 mg/kg bw was determined in male and female rats based on decreased motor activity at the LOAEL of 75 mg/kg bw. The toxicological effect noted in animals in this study occurred following a single exposure; therefore this effect is relevant to the selection of the ARfD.

Uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied in the setting of the ARfD. For the reasons outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. This results in a CAF of 100.

The ARfD (for the general population) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{25 \text{ mg/kg bw}}{100} = 0.25 \text{ mg/kg bw}$$

The above ARfD is also appropriate for assessing the risk to all populations, including females 13 to 49 years of age, from exposure to sulfoxaflor residues in drinking water, which consist primarily of metabolite X1179474 (98%) with a small contribution (2%) from metabolite X11519540. The parent sulfoxaflor is not expected to be present in drinking water. Metabolite X1179474 was demonstrated to be less toxic than sulfoxaflor based on a limited number of toxicity studies. Neonatal deaths and developmental abnormalities were not observed in the

studies conducted with metabolite X1179474; therefore, these endpoints are not appropriate to use in the drinking water risk assessment. Although the available toxicology studies demonstrated that metabolite X1159540 is more toxic than sulfoxaflor, concern regarding this metabolite is lessened by its minimal contribution to the drinking water residues. Furthermore, the endpoint used was derived from studies conducted with sulfoxaflor, which is more toxic than the principal metabolite X1179474.

3.3 Acceptable Daily Intake (ADI)

For females 13 to 49 years of age, the endpoint and CAF selected for the establishment of the ARfD for this subpopulation were considered most appropriate for the setting of the ADI (see above).

The ADI (for females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.9 \text{ mg/kg bw/day}}{300} = 0.006 \text{ mg/kg bw/day}$$

For the general population, the most appropriate endpoint for assessing risk following chronic dietary exposure to sulfoxaflor was from the two-year combined chronic/oncogenicity study in the rat. A NOAEL of 1.04 mg/kg bw/day was determined in males based on decreased food consumption, epididymal weight and spermatic elements in the epididymides, as well as increased liver weight and bilateral atrophy of the seminiferous tubule at the LOAEL of 4.24 mg/kg bw/day. This is the lowest NOAEL in the toxicology database.

Uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied in the setting of the ADI. For the reasons outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. This results in a CAF of 100.

The ADI (for the general population) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.04 \text{ mg/kg bw/day}}{100} = 0.01 \text{ mg/kg bw/day}$$

This ADI provides a margin of approximately 400 to the dose at which an equivocal increase in preputial gland tumours was observed in male rats, and a margin of approximately 2100 to the dose that elicited an increase in bilateral Leydig cell tumours in male rats.

The above ADI is also appropriate to use in assessing the risk to all populations, including females 13 to 49 years of age, from exposure to sulfoxaflor residues in drinking water, for the reasons outlined above under the ARfD.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints for Occupational & Residential Exposure Assessments

Occupational exposures to Transform WG Insecticide and Closer Insecticide are characterized as short-term to intermediate-term for farmers and custom applicators who mix, load, and apply, and are predominantly by the dermal and inhalation routes. Postapplication exposures for re-entry workers are expected to be short-term to intermediate-term, and occur primarily by the dermal route.

For short- , intermediate- and long-term occupational exposures via the dermal and inhalation routes, the NOAEL of 1.9 mg/kg bw/day from the DNT study in rats was selected. Offspring toxicity was observed in this study in the form of mortality. Worker populations could include women of reproductive age and therefore this endpoint was considered appropriate for the occupational risk assessment. The available 28-day dermal study did not assess the relevant endpoints of concern (in other words, developmental effects in pups following pre-natal and/or post-natal exposure). Repeat-dose inhalation toxicity studies were not available.

For “pick-your-own” scenarios, which involve both acute dermal and dietary exposure, the NOAEL of 1.9 mg/kg bw/day from the DNT study in rats was selected. Offspring toxicity was observed in this study in the form of mortality. “Pick your own” scenarios could involve women of reproductive age and therefore this endpoint was considered appropriate for this risk assessment.

For occupational exposure scenarios, the target margin of exposure (MOE) is 300, which includes uncertainty factors of 3-fold for interspecies extrapolation (for the reasons explained above) and 10-fold for intraspecies variability. The concerns outlined in the *Pest Control Products Act* Hazard Characterization section regarding this endpoint are also relevant to the worker population. For these reasons, an additional factor of 10-fold was applied to these risk assessments to protect for sensitive subpopulations such as unborn children.

For residential exposure scenarios, the target MOE is 300, which includes uncertainty factors of 3-fold for interspecies extrapolation (for the reasons explained above) and 10-fold for intraspecies variability, as well as a 10-fold *Pest Control Products Act* factor (for the reasons outlined above under the *Pest Control Products Act* Hazard Characterization section).

The selection of this endpoint and MOE is considered to be protective of sensitive subpopulations, such as unborn children.

Cancer Assessment

Liver tumours in rats and mice exposed to sulfoxaflor were determined to be not relevant to human health. The increased incidence of bilateral Leydig cell tumours in rats were determined to be of low concern, while there was some residual uncertainty regarding the potential for sulfoxaflor to stimulate the production of preputial gland carcinomas. Overall, the endpoints selected for non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of sulfoxaflor.

3.4.1.1 Dermal Absorption

In the in vivo rat dermal absorption study, male rats were treated with nominal doses of 2400 µg/cm^2 (high dose), 4.8 µg/cm^2 (medium dose), and 0.24 µg/cm^2 (low dose) sulfoxaflor. Animals were exposed for 10 hours, after which time the skin was washed to remove the non-absorbed dose. Animals were terminated at 24, 48, 96, 144 and 192 hours after treatment. The potentially absorbed dose was calculated by summing residues in urine, feces, cage wash, treated skin including up to 20 tape strips (skin-bound residue), surrounding skin, blood and carcass. The maximum potentially absorbed dose was 2.1% (at 48 hours) at the high dose, while the medium dose absorption of 14.3% (at 24 hours) continued to 22% (at 192 hours), and the low dose absorption of 11.0% (at 24 hours) continued to 21% (at 192 hours).

An in vitro dermal penetration study with rat and human skin was conducted concurrently with the same doses as those used in the in vivo study. Human skin and rat dorsal skin were attached to flow-through diffusion cells. Skin samples were exposed for 10 hours after which time the skin was washed. At the end of the study (24 hours), the skin was washed again, and then tape stripped. The potentially absorbed dose was calculated by summing residues in receptor fluid, receptor chamber rinse, and skin (including all tape strips and unexposed skin). The maximum mean potentially absorbed dose occurred at the low dose for both rat (8.3%) and human (2.5%). This study suggests that, generally, the human skin appears to be less permeable than the rat skin.

The dermal absorption studies for sulfoxaflor generally met the requirements and ‘minimal standards’ of the draft NAFTA triple pack approach. Therefore, it was considered appropriate to apply the ‘triple pack’ approach to this active ingredient. Although there are uncertainties regarding in vitro reproducibility, variability in the in vitro human dermal absorption data and regional variability in human skin, the mean value of the human in vitro results (2.5%) from the low dose was considered acceptable to use as a dermal absorption value. However, the in vivo data suggest that the skin-bound residue continues to be absorbed after the exposure period. Therefore, the residue (1.6%) from the 24-hour human in vitro skin wash was considered to be available for absorption. Consequently, a dermal absorption value of 4.1% (rounded to 4%) was selected for use in the risk assessment for sulfoxaflor.

The dermal absorption value of 4% may need to be reconsidered for formulations and uses other than those currently proposed for registration.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Transform WG Insecticide and Closer Insecticide during mixing, loading and application. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. However, dermal and inhalation exposure for workers mixing and loading dry flowable (Transform WG Insecticide) and liquid (Closer Insecticide) products, were generated from the Pesticide Handlers' Exposure Database (PHED) version 1.1, in conjunction with area-treated-per-day information, and application rates.

Exposures to workers mixing, loading and applying Transform WG Insecticide (Appendix I, Table 6) and Closer Insecticide (Appendix I, Table 7) are expected to be short-term to intermediate-term in duration, and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixers, loaders, and applicators of Transform WG Insecticide to wheat, barley and canola (representing oilseeds) using aerial and ground equipment. Exposure estimates were derived for mixers, loaders, and applicators of Closer Insecticide to brassica and leafy vegetables, pome and stone fruits, root and tuber vegetables, tree nuts (including pistachios) and grapes. The exposure estimates are based on mixers, loaders, and applicators wearing a long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. In addition, all mixers and loaders must wear eye protection, and for aerial applications, an added layer of coveralls must be worn for mixing and loading. Chemical-resistant gloves were not expected to be worn by aerial applicators.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint (no observed adverse effects level) to obtain the MOE; the target MOE is 300.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Transform WG Insecticide and Closer Insecticide. Various postapplication crop maintenance activities and harvesting are performed for each crop. For cereals and oilseed crops treated with Transform WG Insecticide (Appendix I, Table 8), these activities include scouting, and irrigation. For vegetable, orchard and grape crops treated with Closer Insecticide (Appendix I, Table 9), these activities include scouting, irrigation, and harvesting of all crops, tying, pinching, pruning, training, thinning of vegetables, and cane turning and girdling for grapes. Given the nature of activities performed, postapplication inhalation exposure is not a significant route of exposure compared to the dermal route, since sulfoxaflor is not volatile (vapour pressure $\leq 2.5 \times 10^{-9}$ kPa at 25°C; $\leq 1.4 \times 10^{-9}$ kPa at 20°C). The duration of exposure is considered to be short-term to intermediate-term for all workers, and assumed to be eight hours per day.

3.4.2.2.1 Postapplication Entry into Crops Treated with Transform WG Insecticide

A chemical-specific dislodgeable foliar residues (DFR) study was submitted. Sulfoxaflor formulated as a 49.9% water dispersible granular (500 WDG) was applied via groundboom to wheat at two trial sites, each consisting of one control plot and two treatment plots. Each treatment plot received two foliar broadcast spray applications of the test substance at an application rate of 50 g sulfoxaflor per hectare. The re-treatment interval was 14 days. Applications were made in a spray volume of approximately 180 - 190 L per hectare and an adjuvant was added into the spray mixture for all applications.

Samples were collected: 1) prior to each application; 2) as soon as the spray dried after each application (0 to 8 hours); and 3) at intervals of 1, 2, 4, 7, 10, 14, and 21 days at the California site, and additionally at 28 and 35 days after the final treatment at the Georgia site. At each sampling interval, one sample was collected from the control plot and three samples were collected from the treated plots. Field-fortified samples prepared using samples from the control plot were prepared on days 1 and 14 after the last application at the California site, and on days 1, 14, and 28 after the last application at the Georgia site. As some field fortification analytical recoveries from the Georgia site were less than 95%, field sample results were adjusted accordingly. No adjustments to data were required for results from the California site.

The PMRA assumed pseudo first-order dissipation kinetics to generate dissipation curves for sulfoxaflor, and conducted a linear regression analysis using the natural logarithm of the average foliar residue values.

For the California site, average DFR values initially declined rapidly, followed by slower dissipation for the remainder of the monitoring. The maximum average DFR values were observed immediately after the first application (0.044 µg/cm^2), and after the second application (0.119 µg/cm^2). Based on the regression analyses, calculated half-lives for sulfoxaflor on treated wheat leaves was 3.92 days (R^2 = 0.56) for the 500 WDG product at the California site.

In Georgia, residue levels steadily declined after the second application (20% daily dissipation) and were equal to, or less than, the LOQ by the end of the sampling period. Peak residues occurred on the day of each treatment, 0.049 µg/cm^2 and 0.028 µg/cm^2, respectively. Based on the regression analyses, calculated half-lives for sulfoxaflor on treated wheat leaves was 3.1 days (R^2 = 0.99). Rainfall (5.8 cm) occurred on the day prior to sample collection on day 10 after the second treatment. Residues had already declined significantly by then; therefore, it is expected that the rainfall did not significantly affect the results.

The most appropriate data to use for assessment purposes was concluded to be the maximum measured residue on day 0 after the 2nd application of the test product (0.119 µg/cm^2) at the California site. This value represented the most conservative residue level, for the day on which the exposure is calculated.

There is a difference between cereal and oilseed morphology, maximum application rates, and re-treatment intervals. Therefore, for the cereal and oilseed crops, the study peak residue directly after the second application, 0.119 µg/cm^2 is the most appropriate dislodgeable foliar residue value for the postapplication exposure assessment.

Dermal exposure to workers entering treated areas is estimated by coupling appropriate chemical-specific DFR values, or default dislodgeable foliar residue values (20% of the application rate with 10% daily dissipation), with activity-specific transfer coefficients. Activity-specific transfer coefficients are based on Agricultural Re-entry Task Force reviewed studies.

Dermal exposure estimates were compared to the toxicological endpoint to obtain the MOE. The target MOE is 300.

3.4.2.2.2 Postapplication Entry into Crops Treated with Closer Insecticide

A chemical-specific DFR study was submitted. Sulfoxaflor, formulated as a 22.5% active ingredient as a suspension concentrate, as applied to broccoli at two trial sites, each consisting of one control plot and one treatment plot. The treatment plots received three groundboom broadcast foliar spray applications of the test substance, at a nominal application rate of 100 g sulfoxaflor per hectare. The re-treatment interval was seven days. Spray volumes were approximately 187 L/ha, with an adjuvant (surfactant) added to the spray mixture for all applications.

One control and three treated samples were collected: 1) prior to each application; 2) after each application as soon as the spray dried (0 to 8 hours); and 3) at intervals of 1, 2, 3/4, 7, 10, 14, 20/21, 27, and 35 days after the final treatment (27 and 35 day samples were only collected at the Georgia site). Field-fortified samples from the untreated control plot were prepared on days 1 and 14 after the last application at the California site, and on days 1, 14, and 27 after the last application at the Georgia site. Samples were adjusted for field fortification analytical recoveries less than 95%.

Pseudo first-order kinetics to generate dissipation curves for sulfoxaflor was assumed. The linear regression analysis used the natural logarithm of the average foliar residue values collected immediately after the third application through the last day of sampling (day 21 for California trial, and day 35 for Georgia trial). Based on linear regression of the transformed data, the half-lives for sulfoxaflor treated broccoli leaves were 2.9 days (R^2 = 0.94) for the California site and 1.2 days (R^2 = 0.94) for the Georgia site.

For the California site, the maximum average DFR values occurred on the day of application: 0.147 µg/cm^2 after first treatment, 0.120 µg/cm^2 after second treatment, and 0.163 µg/cm^2 after third treatment. Residues were still above the LOQ prior to the third application (0.0067 µg/cm^2). After the third application, the average DFR declined to 0.0017 µg/cm^2 after 21 days.

For the Georgia site, the maximum average DFR values after each treatment occurred on the day of application: 0.319 µg/cm^2 after first treatment, 0.191 µg/cm^2 after the second treatment, and 0.139 µg/cm^2 after the third treatment. Residues were still above the LOQ prior to the third application (0.00057 µg/cm^2). After the third application, the average DFR declined rapidly to 0.013 µg/cm^2 after 1 day and residues less than LOQ were observed by day 10.

The product used in the study is essentially the same as the suspension concentrate product (Closer Insecticide) proposed for registration. In the study, three applications of 100 g a.i./ha (1 µg/cm^2) were applied to broccoli, but the label only specifies two applications of 36 g a.i./ha (0.36 µg/cm^2). The retreatment intervals were the same. An adjuvant was added into the treatments for the study, but no adjuvants are on the Canadian label. Broccoli has a waxy leaf texture, so treatments are more likely to bead and run off. Without an adjuvant to aid in the retention of the product on broccoli, the results of this DFR study potentially over-estimate available dislodgeable residues. Therefore, the study can be used as a surrogate for the treatment of brassica crops in Canada when the application rate is adjusted. The most appropriate dislodgeable foliar residue for this assessment was the peak dislodgeable residue on the day of the first application at the Georgia site (0.319 µg/cm^2). The estimated residue for brassica crops is based on the application rate of 0.36 µg/cm^2 (0.319 × 36/100), resulting in a DFR value of 0.115 µg/cm^2.

Leafy, root and tuber vegetables, pome and stone fruit, and grapes have a smooth leaf texture. Dislodgeable residues on all other non-brassica crops on the proposed label are assessed using the default values of 20% dislodgeable residues on the day of application, and 10% daily dissipation.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

There are no domestic products; therefore, no residential handler risk assessment is required.

3.4.3.2 Bystander Exposure and Risk

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

3.4.3.3 Postapplication Exposure and Risk

There is potential for postapplication exposure to the general population entering treated orchards or coming in contact with residential fruit trees treated with Closer Insecticide.

3.4.3.3.1 Acute Aggregate Exposure Assessment for Pick-Your-Own fruit

The public could be exposed to residues of sulfoxaflor after foliar treatment of orchard crops. Pome fruit (apple and pear) and stone fruits (peach, nectarine, plum, and cherry (tart and sweet)) are considered to be ‘pick-your-own= crops. The acute dermal exposures alone for adults, youth, and children in pick-your-own facilities are not considered to be of concern. An acute aggregate assessment is typically required where there is potential for acute dietary exposure to sulfoxaflor residue (fresh, commodity-specific) to co-occur with the acute dermal exposure (from picking). There is no appropriate aggregation endpoint except for the females 13-49 years of age which is considered to be the most at-risk subpopulation. Therefore, the acute aggregate assessment is conducted only for the females 13-49 years of age group (Appendix I, Table 10).

The acute dietary exposure to treated peaches, representing the most conservative scenario of the pick-your-own crops (apples, pears, peaches, nectarines, cherries and plums), was added to the acute dermal exposure from hand harvesting, to give a single-day estimate of aggregate exposure to an individual that picks the fruit and eats it on the same day. An individual is considered to pick fruit for a two hour duration, at the time of the pre-harvest interval, after the last application.

The fresh fruit, acute, commodity-specific values are presented as a single-day exposure (mg/kg bw).

The oral NOAEL of 1.9 mg/kg bw/day from the rat developmental neurotoxicity study was considered appropriate for acute/short-term exposure by the oral and dermal routes, with a target MOE of 300. Acute dietary exposure is based on the fresh fruit, crop-specific, 95th percentile user-only maximum residues. The acute dermal exposure is based on maximum application rate, a transfer coefficient for hand harvesting (at the time of the pre-harvest interval of 7 days), and the amount of dislodgeable foliar residue.

3.4.3.3.2 Residential Fruit Trees

This commercial product could potentially be used on residential/private fruit trees. Children are not expected to engage in activities associated with the treated trees. Dermal exposures to adults and youths, through contact with transferable residues, are represented by hand harvesting and are expected to be short-term to intermediate-term in duration. Dermal exposures alone for adults and youth are not considered to be of concern. The chronic dietary (food + drinking water) exposures are considered to be addressed by the dietary risk assessment. There is no appropriate aggregation endpoint for dermal exposures and chronic dietary exposures except for the females, 13-49 years of age group, which is considered to be the most at-risk subpopulation. Therefore, the assessment is conducted for only this group (Appendix I, Table 11).

The exposure scenario for the risk assessment combines dislodgeable foliar residue on the day of application of 20%; daily dissipation of 10%, maximum application rate, minimum retreatment interval, and contact with treated trees on the day of the last treatment, and the transfer co-efficient for hand harvesting pome and stone fruit (1500 cm^2/h) and is considered acceptable to address postapplication activities in residential settings. Exposure time is 0.67 hours, and dermal absorption is 4%.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is sulfoxaflor. The HPLC/MS/MS data gathering/enforcement analytical methods are valid for the quantification of sulfoxaflor residues in a variety of crops (dry crops, wet crops, acidic crops, and oily crops) and livestock matrices. The residues of sulfoxaflor are stable when stored in a freezer at -20°C for 680 days in plants, and at least 56-64 days in livestock commodities. Raw agricultural commodities were processed, and residues in processed commodities were analyzed. Processing factors were determined, and the majority of processed commodities showed a reduction in residues upon processing. However, for raisins, tomato paste, tomato puree, and sugarbeet molasses, sulfoxaflor residues concentrated (2-10X). Quantifiable residues of sulfoxaflor are expected in ruminant and poultry commodities when exposed to treated feed. Supervised residue trials were conducted throughout the United States, Canada, the European Union, Australia, Brazil, and New Zealand using end-use products containing sulfoxaflor at exaggerated rates on a variety of fruits, vegetables, oilseeds, cereal grains, legumes, and tree nuts.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The assumptions made in the refined chronic analysis included median residue values for all crops, experimental processing factors (where available), projected percent crop treated information, and anticipated residues in/on animal commodities based on the More Reasonably Balanced Diet (MRBD). The refined chronic dietary exposure, from all supported sulfoxaflor food uses (alone) for all representative population subgroups, including infants and children, is <39 % of the ADI. The highest aggregate (food and water) exposure and risk estimate is for all infants (<1 year) at 86% of the ADI. Therefore, aggregate exposure from food and water is considered acceptable. The chronic dietary exposure to sulfoxaflor from food is 9 % of the ADI and from water is 19.3% of the ADI for females 13-49 years. The exposure from food and water cannot be aggregated for females 13-49 years since the ADI for food (0.0063 mg/kg bw/d) is not the same as for water (0.01 mg/kg bw/d).

3.5.2.2 Acute Dietary Exposure Results and Characterization

While the ARfD for drinking water was the same for all population subgroups (0.25 mg/kg bw/d), the subgroup of females 13–49 years old had an ARfD value for food (0.0063 mg/kg bw/d) that was different than all other population subgroups (0.25 mg/kg bw/d). Therefore, the exposure from food and water for females 13-49 years old could not be aggregated considering the different ARfD's.

For all population subgroups, except females 13-40 years old, the aggregate deterministic acute dietary risk from food and water is acceptable (≤ 21% ARfD).

For females 13–49 years old, the refined acute dietary exposure to water is 6.61% of the ARfD. The assumptions made in the refined probabilistic acute analysis (99.9^{th} percentile) to food included the field trial residue distributions, adjustments of residues for approved Canadian application rates, projected percent crop treated together with domestic production, experimental processing factors (where available) and anticipated residues in/on animal commodities based on MRBD. The refined acute dietary exposure (food alone) to sulfoxaflor residues in all supported commodities is estimated to be 117% of the ARfD for females 13–49 years old.

In light of the conservatisms inherent in the risk assessment (in other words, exposure to all treated crops co-occurring on the same day, see Table 3.5.1 below), and taking into consideration that a single dose of sulfoxaflor is not likely to cause acute health effects to any population subgroup (including infants and children), this risk is considered acceptable.

3.5.3 Aggregate Exposure and Risk

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

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits (MRLs)

Commodity	Recommended MRL (ppm)
Cirtus Fruits (CG 10)	0.7
Root and Tuber Vegetables (CG 1)	0.05
Leafy Vegetables, brassica (CG 5), except, cauliflower	2.0
Cauliflower	0.08
Leafy greens (CSG 4A), watercress	6.0
Leaf petioles (CSG 4B)	2.0
Cucurbit Vegetables (CG 9)	0.4

Commodity	Recommended MRL (ppm)
Pome Fruits (CG11-09)	0.5
Dry shelled beans	0.2
Succulent edible podded beans	4.0
Rapeseed (CSG 20A)	0.4
Wheat	0.08
Barley	0.4
Stone Fruits (CG 12-09)	3.0
Small Fruit Vine Climbing (CSG 13-07F)	2.0
Low Growing Berry, except fuzzy kiwi fruit (CSG 13-07G)	0.7
Cotton seed (CSG 20C)	0.2
Tree Nuts (CG14-11)	0.015
Fruiting Vegetables (CG 8-09)	0.7
Green onion (CSG 3-07B)	0.7
Bulb onion (CSG 3-07A)	0.01
Soybeans	0.2
Sugar Beet Molasses	0.25
Raisins	6.0
Tomato paste	2.6
Tomato puree	1.2
Leaves of Root and Tuber Vegetables, (CG 2), except turnip forage	3
Meat of cattle, goats, horses, and sheep	0.02
Fat of cattle, goats, horses, and sheep	0.01
Meat byproducts of cattle, goats, horses, and sheep	0.05
Milk	0.06
Eggs, Fat, and Meat, of hogs and poultry, meat byproducts of hogs	0.01
Meat byproducts of poultry	0.02

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 MRLs in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 12 and 13.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate and behaviour of sulfoxaflor and its major transformation products is summarized in Appendix I, Table 14. The chemical name and structure of transformation products formed in the environment, as well as a summary of their occurrence in environmental fate studies, are presented in Appendix I, Table 15.

Sulfoxaflor is introduced in the environment when it is applied as a foliar spray to a variety of field and orchard crops. Sulfoxaflor spray droplets deposited on the surface of the plant will rapidly move to internal plant tissue. Once inside the plant, sulfoxaflor is transported via the xylem. Sulfoxaflor levels in plant tissue will decrease with time as sulfoxaflor metabolizes to compounds such as X11719474 and X1172106.

Sulfoxaflor spray droplets can be deposited directly on pollen and nectar when plants are in bloom. Sulfoxaflor can also reach pollen and nectar via translocation from other parts of the plant. Relatively small amounts of sulfoxaflor are found in pollen and nectar from translocation when compared to the direct application on open flowers.

Sulfoxaflor could reach the soil surface upon application when foliage is not very dense. In addition, given its high solubility in water, this compound could also reach the soil through wash-off from the leaves. Abiotic transformation processes are not expected to contribute significantly to the dissipation of sulfoxaflor. This compound is stable to hydrolysis and phototransformation is slow when compared to biotransformation. Biotransformation is very rapid in soil and is the primary route of dissipation for sulfoxaflor in the terrestrial environment. In both aerobic and anaerobic soils, sulfoxaflor transforms to X11719474 which is persistent. Under aerobic conditions, X11719474 then transforms slowly to X11579457 and X11419540 which are also persistent. X11719474 was the only transformation product identified under anaerobic conditions.

Sulfoxaflor and its transformation products are expected to be mobile in soil based on low adsorption coefficients. In addition, sulfoxaflor and X11719474 are very soluble in water, exhibit limited phototransformation on soil and have a low potential for volatilisation. Such characteristics typically increase the potential for leaching. However, because sulfoxaflor transforms quickly in soil, it is not expected that this compound will persist long enough to leach through the soil profile and enter groundwater under most conditions. Conversely, transformation products are more persistent in soil and could therefore reach groundwater. The groundwater ubiquity scores (GUS) calculated for sulfoxaflor and its transformation products based on their persistence and mobility indicates that sulfoxaflor is a non-leacher and that X11719474, X11579457 and X11519540 are probable leachers. This is consistent with results

from field studies in which very low amounts of sulfoxaflor were detected in deeper soil layers and in soil pore water. X11719474, X11579457 and X11519540 were all found in deeper soil layers and in soil pore water, but with X11719474 concentrations being much greater than for X11579457 and X11519540. Results from field studies also showed that X11719474 can carry over to the next growing season and will be taken up from the soil by the roots of rotational crops. Sulfoxaflor was not found in rotational crops, likely due to its rapid transformation in soil.

Sulfoxaflor could reach surface water from spray drift. Both sulfoxaflor and X11719474 could enter surface water from runoff. Limited amounts of X11579457 and X11519540 are expected to reach surface water through runoff when compared to X11719474, as these are likely to be formed in deeper soil layers rather than in the surface soil due to the high mobility and persistence of their precursor X11719474. Once in the aquatic environment, sulfoxaflor and X11719474 are not expected to hydrolyze and will undergo limited phototransformation. Biotransformation is the main route of transformation for sulfoxaflor in water, even though it transforms more slowly in water than in soil. X11719474 was the only major transformation product identified in aquatic systems.

Residues of sulfoxaflor and its transformation products are not expected to be found in air. Sulfoxaflor and X11719474 exhibit low volatility. In addition, it is predicted that the degradation of sulfoxaflor in the atmosphere from photochemical oxidation will occur in a matter of hours.

4.2 Environmental Risk Characterization

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

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1 in most cases except for bees and certain beneficial arthropods where the level of concern is 0.4 and 2, respectively). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or

greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A risk assessment for sulfoxaflor and its transformation products was undertaken for terrestrial organisms based on available toxicity data. A summary of terrestrial toxicity data is presented in Appendix I, Table 16. Results of the accompanying risk assessment are presented in Appendix I, Tables 17-21.

Earthworms: Earthworms could be exposed to sulfoxaflor when this compound reaches the soil upon application. The expected environmental concentration is therefore calculated based on a direct application of sulfoxaflor to bare soil at the maximum cumulative application rate. The maximum cumulative application rate takes into account the maximum labelled application rate, the application interval and the dissipation of the compound between applications. Given that sulfoxaflor transforms rapidly in soil, the expected environmental concentration of this compound in soil is relatively low.

At levels higher than those expected in the Canadian environment, the acute exposure of earthworms to sulfoxaflor has been shown to cause mortality and sub-lethal effects such as lesions, slow response to tactile stimulus, and decreased weight. Chronic exposure to sulfoxaflor may also cause mortality and adverse effects on earthworm reproduction. However, given the low expected environmental concentration, risk quotients calculated for acute and chronic exposure to sulfoxaflor do not exceed the level of concern. The X11719474 transformation product was not acutely toxic to earthworms. There is therefore no concern from acute exposure to X11719474.

Bees (pollinators):
Foraging bees could be exposed directly to sulfoxaflor spray droplets during application or to sulfoxaflor residues found on the surface of leaves (contact exposure). Foraging bees could also be exposed to sulfoxaflor, X11719474 and X11721061 through the ingestion of pollen and nectar contaminated from direct spray or the systemic movement in the plant (oral exposure). In addition, brood may be exposed to sulfoxaflor and its metabolites as foraging bees bring contaminated pollen and nectar back to the hive.

A tiered approach was used to assess the risk from these routes of exposure. For the screening level (Tier I) assessment, risk quotients were calculated for the contact and oral routes of exposure using toxicity data from laboratory studies. For the Tier II assessment, risk at the colony level was evaluated based on results from semi-field studies.

While laboratory data indicated that sulfoxaflor may be hazardous to adult bees and larvae, semi-field studies indicate that effects on adult bees are transient and suggest that bee brood would not be significantly affected. Details are provided below. Use restrictions were added to the label to minimize the exposure to bees. When these are followed, risks to bees are not of concern.

Tier I assessment, contact exposure: In laboratory tests, mortality was observed in adult honey bees when sulfoxaflor, Closer Insecticide or Transform WG Insecticide was applied directly on the bee. Mortality was also observed when Closer Insecticide was applied directly on adult bumble bees. When toxicity was compared to the expected level of exposure in the risk assessment, a potential concern was identified for bees that are directly sprayed by sulfoxaflor while foraging. The risk to bees coming into contact with residues on foliage is expected to decrease within a relatively short period. This conclusion is based on results from a laboratory test showing that sulfoxaflor residues on alfalfa foliage from one application at a rate equal to or below 200 g a.i./ha would no longer be hazardous to bees after three hours.

Tier I assessment, oral exposure: In laboratory tests, mortality and sublethal effects such as lethargy were observed when adult honey bees were fed sulfoxaflor or Closer Insecticide. Effects on diet consumption were also observed suggesting that sulfoxaflor may not be palatable to honey bees. Conversely, X11719474 and X11721061 did not cause adult honey bee mortality and no effects on palatability were noted for these compounds.

When honey bee larvae were incubated with diet treated with sulfoxaflor, an increase in larvae mortality as well as a decrease in emergence was observed. No morphological differences were noted during any of the lifestages.

To assess the risk from the consumption of pollen and nectar containing sulfoxaflor, exposure estimates were based on measured sulfoxaflor concentrations in pollen and nectar as well as food consumption rates of pollen and nectar for larvae and adult worker bees. Residues in pollen and nectar were measured in many different crops; the most conservative concentrations were used in the risk assessment. Risk quotients calculated for honey bee larvae and adults that consume pollen and nectar containing sulfoxaflor exceed the level of concern ; further risk characterization is thus warranted. Because Closer Insecticide is more toxic to bumblebees than it is to honey bees, it was concluded that bumblebees may also be at risk from the consumption of nectar and pollen containing residues of sulfoxaflor.

Risk quotients were calculated for sulfoxaflor only. Minimal risk to bees is expected from oral exposure to X11719474 and X1172106, as these compounds are not acutely toxic to bees and are found in plant tissue in lower amounts relative to sulfoxaflor.

Tier II assessment: Because a potential for concern was identified during the screening level (Tier I) assessment, the risk was further characterized using results from studies carried out under more realistic use conditions. For the Tier II assessment, risk at the colony level was evaluated based on results from semi-field studies (tunnel tests, in which small colonies were introduced inside mesh tunnels placed on treated crops thereby restricting the foraging activity of the bees to the treated crop). Depending on the study, applications of sulfoxaflor were made during bloom when bees were actively foraging (oral exposure through the consumption of

contaminated pollen and nectar and contact exposure through direct exposure to spray droplets and to residues on the plant), during bloom after bee flight (primarily oral exposure, as bees do not come in direct contact with spray and residues on foliage are no longer harmful to bees by the time bee flight resumes in the morning due to the low residual toxicity of sulfoxaflor) or during the pre-bloom period (oral exposure only, with relatively low residue levels in pollen and nectar).

Semi-field studies showed that effects on adult foraging bees were transient. When sulfoxaflor was applied to flowering crops, a sharp increase in forager bee mortality occurred on the day of application. Mortality then returned to control levels after a period of approximately three days or less. Mortality was generally higher when sulfoxaflor was applied during bee flight compared to an application in the evening after bee flight, likely a result of the compounded effects from both the oral and contact exposure routes upon direct application during bee flight. In addition, when comparing results from semi-field studies with a similar application timing, a general increase in mortality with increasing application rate was apparent. Conversely, when sulfoxaflor was applied pre-bloom, the increase in forager bee mortality was minimal. In all studies, a decrease in foraging activity was noted on the day of application but returned to control levels within a period of three days or less. In a few cases where sulfoxaflor was applied during bloom, some behavioural abnormalities were observed shortly after application, such as lack of coordination, cramping, and intensive cleaning.

There was no evidence of brood effects in the semi-field studies. However, many of these studies presented some limitations or confounding factors that prevented reaching a definitive conclusion with regards to the potential effects of sulfoxaflor on brood. Examples of confounding factors observed in one or more studies include an observation period too short to evaluate potential effects over an entire brood cycle; a pre-application period inside the tunnel longer than recommended by test guidelines, thereby causing undue stress to the colony; and a mite infestation potentially affecting control performance. In two of the submitted studies, the observation period was long enough to detect potential brood effects and therefore, these studies provided some useful information on the effects of sulfoxaflor on bee brood. In these studies, the compensation index, the brood termination rate and colony strength in all groups treated with sulfoxaflor was similar to the control. However, it is important to note that the brood termination rate was high in the sulfoxaflor treatment groups and in the controls and this may have masked potential brood effects in the sulfoxaflor treatment groups. In comparison, severe brood effects were observed in groups treated with the reference toxicants fenoxycarb and dimethoate. Reference toxicants are specifically intended to cause severe effects on developing brood in order to demonstrate the sensitivity of the test system. As such, results from groups exposed to the reference toxicants indicate that severe effects could in fact be detected despite the generally low brood performance. Therefore, while uncertainty remains regarding the potential effects of sulfoxaflor on brood given the poor brood performance, severe effects on brood from the use of sulfoxaflor are not expected.

Based on the results of the risk assessment, use restrictions were included on the label to minimize the exposure to sulfoxaflor. To mitigate risks to adult bees, all applications must be made early in the morning or late in the evening when bees are not active. This restriction reduces the probability of having bees present on the field during application and allows time for

foliar residues to reach less harzardous levels before the bees resume foraging activities. Furthermore, sulfoxaflor products must not be applied during the crop flowering period for most of the labelled crops. This restriction was added as a precautionary measure given the uncertainties identified with the brood data. Without applications during the crop flowering period, sulfoxaflor would not be directly sprayed on pollen and nectar, thus limiting exposure to adult bees as well as brood.

Beneficial arthropods:
The risk assessment for beneficial arthropods considers that the main route of exposure for these non-target organisms is from contact with treated plant material both on the treated area (from direct spray on the crop) and at the margins of the treated field (from spray drift). The expected concentration of sulfoxaflor residues on foliage within the treated field is calculated as the cumulative application rate, which takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves. To calculate the concentration of sulfoxaflor residues on foliage found outside the treated area, the maximum cumulative rate is adjusted according to the projected drift deposition at one metre downwind from the site of application. Drift deposition values of 74% (early season airblast, fine spray) and 54% (late season airblast, fine spray) were selected for the risk assessment given that the maximum labelled rates for sulfoxaflor are associated with airblast applications on pome fruit, stone fruits and grapes. In addition, beneficial arthropods are likely to be present in the vicinity of these crops as they may be part of an integrated pest management program.

In screening level laboratory tests carried out with freshly dried residues on a glass plate, Closer Insecticide was shown to be toxic to the parasitic wasp but not to the predatory mite. In extended laboratory tests with the parasitic wasp, mortality was observed following exposure to freshly dried and aged residues of Closer Insecticide on leaf substrate. With aged residues, mortality decreased as the weathering time increased; residues were no longer harmful after 3 to 14 days of weathering, depending on the test rate. In another extended laboratory test, mortality was observed in ladybird beetles exposed to freshly dried residue on leaf substrate. Parasitic wasps and ladybird beetles were not repelled by Closer residues on foliage. No effects on reproduction were observed in any of the tests.

The screening level risk assessment for beneficial arthropods is based on toxicity data carried out on glass plates with the predatory mite and the parasitic wasp. For spray applications, the level of concern for the screening level assessment is two based on an empirical comparison of risk quotients and known effects from field and semi-field studies for these two species. The level of concern for higher-tier tests and for other test species is one.

The screening level risk quotients calculated for the predatory mite based on results from a glass plate test are below the level of concern. However, screening level risk quotients for the parasitic wasp greatly exceed the level of concern for both on- and off-field exposures. When considering results from extended laboratory tests (freshly dried residues on leaf substrate), on-field and off-field risk quotients also exceed the level of concern for the parasitic wasp and for the ladybird beetle.

To further characterize the risk to the parasitic wasp and the ladybird beetle, exposure estimates were refined by applying crop deposition factors ranging from 20 to 80% (on-field) and a vegetation distribution factor of 0.1 (off-field habitats). When comparing refined exposure estimates to results of extended laboratory tests on leaf substrate, on-field risk quotients still exceed the level of concern for both species. Off-field risk quotients exceed the level of concern for the parasitic wasp but not for the ladybird beetle.

Results of the aged residue study support the conclusions of the refined risk assessment which indicate a potential for concern for the parasitic wasp. In this study, high parasitic wasp mortality was observed at rates that are comparable to the exposure estimates used in the refined risk assessment (100% corrected mortality on the day of application at rates ranging from 6.2 to 45 g a.i./ha; the lowest off-field rate used in the refined risk assessment is 9.2 g a.i./ha).

Results of the aged residue study also suggest that the risk could decrease as residues on the surface of the leaf are weathered. Residues were no longer harmful to the parasitic wasp after a period ranging between 3 and 14 days after treatment depending on the application rate. The rates used in this study are however well below the maximum labelled rate for sulfoxaflor. Therefore, it is not possible to draw clear conclusions with regards to the length of time sulfoxaflor residues could continue to pose a risk to beneficial arthropods after application at Canadian use rates. Residues may potentially continue to affect beneficial arthropods for a longer period than the 3 to 14 days observed in the aged residues test.

Birds and mammals: For the bird and mammal risk assessment, the ingestion of food items contaminated by spray droplets is considered to be the main route of exposure. The risk assessment is, thus, based on the estimated daily exposure which takes into account the expected concentration of sulfoxaflor on various food items immediately after the last application and the food ingestion rate of different sizes of birds and mammals. At the screening level, the most conservative exposure estimate is used (associated with food items showing the highest level of contamination after application in the treated area). In addition, acute toxicity values are divided by an uncertainty factor of 10 to account for differences in inter- and intra-species sensitivity.

At high enough doses, acute oral exposure to sulfoxaflor caused mortality and a reduction in body weight in bobwhite quails. Mortality was also observed in an acute oral test carried out with the zebra finch, although a reliable endpoint could not be determined for this species due to regurgitation shortly after dosing. Acute oral exposure to X11719474 caused no adverse effects to bobwhite quails. When sulfoxaflor was administered in the diet, less than 50% mortality was observed up to the highest concentrations tested for both bobwhite quail and mallard duck. However, reduced body weight gain was a notable concentration-dependent sublethal effect in both test species. In reproductive tests, no subchronic or reproductive effects were observed at the highest concentrations tested for either bobwhite quail or mallard duck.

The acute oral toxicity of sulfoxaflor and X11719474 to small mammals is described in detail in Section 3.0 of this document. Laboratory studies indicated that sulfoxaflor was slightly to moderately toxic to small mammals on an acute oral basis. X11719474 was considered to be of low acute toxicity. Among effects observed in a two-generation dietary reproduction study with rats, the reduction in pup survival was considered to be environmentally relevant.

For birds, risk quotients calculated at the screening level for sulfoxaflor do not exceed the level of concern on an acute and reproductive basis. For mammals, the screening level risk quotients do not exceed the level of concern for sulfoxaflor on an acute basis, but exceed the level of concern on a reproductive basis. The reproductive risk to mammals was thus further assessed.

To further characterize the reproductive risk to mammals, the assessment was expanded to include a range of sulfoxaflor residue concentrations on all relevant food items. Also, both on- and off-field exposure estimates were considered. The off-field exposure takes into account the projected drift deposition at one metre downwind from the site of application, as discussed above for beneficial arthropods.

When considering maximum sulfoxaflor residues, reproductive risk quotients exceed the level of concern for medium and large sized herbivorous mammals feeding on the treated area and for medium sized herbivorous mammals feeding off the treated area. The level of concern is not exceeded when considering mean sulfoxaflor residues. Given that risk quotients exceed the level of concern by a relatively small margin when considering maximum residues, and that risk quotients are below the level of concern when considering mean residues, the probability that adverse reproductive effects would occur following exposure to residues on food items is considered to be relatively low.

While X11719474 could be found in plants from the metabolism of sulfoxaflor and also from soil uptake, this compound is not acutely toxic to birds and mammals and the risk is expected to be negligible.

Non-target plants: For the risk assessment, the cumulative application rate is compared to plant toxicity endpoints. The cumulative application rate takes into account the maximum labelled application rate, the application interval and the dissipation of the compound on the surface of the leaves. For the off-field assessment, the rate is adjusted according to the projected drift deposition at one metre downwind from the site of application.

The toxicity of Closer Insecticide to non-target plants was determined through vegetative vigour and seedling emergence assays using standard crop species. No significant adverse effects were observed in any plant species at the highest application rate tested (400 g a.i./ha for seedling emergence and up to 200 g a.i./ha for vegetative vigour). Risk quotients do not exceed the level of concern.

4.2.2 Risks to Aquatic Organisms

A risk assessment of sulfoxaflor and the major transformation product X11719474 was undertaken for freshwater and marine aquatic organisms based on available toxicity data. A summary of aquatic toxicity data is presented in Appendix I, Table 22. The accompanying risk assessment is presented in Appendix I, Table 23.

Aquatic organisms could be exposed to sulfoxaflor from drift or runoff. At the screening level, expected environmental concentrations are calculated based on a direct application to water at the maximum cumulative rate, thus taking into account the maximum labelled application rate, the application interval and the dissipation of the compound in aquatic systems. Bodies of water of two depths are considered for the risk assessment. A depth of 15 cm is representative of a seasonal water body used by amphibians during the reproduction period. A depth of 80 cm is representative of a permanent water body for all other aquatic organisms. In addition, acute toxicity values are divided by an uncertainty factor of two for aquatic plants and invertebrates and ten for fish species. The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level to withstand, or recover from, a stressor at the level of the population. No uncertainty factor is applied to chronic endpoints.

Freshwater invertebrates: Acute exposure to sulfoxaflor did not affect daphnids, but at high enough concentrations, resulted in mortality of chironomids. The X11719474 transformation product was not acutely toxic to daphnids. Chronic exposure to sulfoxaflor reduced the reproduction rate and delayed the number of days to first brood in daphnids and it resulted in reduced emergence in chironomids.

The screening level risk quotients for acute and chronic exposure of daphnids and chironomids to sulfoxaflor do not exceed the level of concern. Also, the risk quotient for acute exposure of daphnids to the transformation product X11719474 does not exceed the level of concern.

Freshwater fish: Sulfoxaflor was not acutely toxic to rainbow trout, bluegill sunfish and common carp. The X11719474 transformation product was not acutely toxic to rainbow trout. Early life stage exposure to sulfoxaflor resulted in reduced mean fry weight of fathead minnows.

The screening level risk quotients for acute and early life stage exposures of freshwater fish to sulfoxaflor do not exceed the level of concern. Also, the screening level risk quotient for acute exposure of freshwater fish to the X11719474 transformation product does not exceed the level of concern.

Amphibians: To assess the risk to amphibians, fish toxicity endpoints are used as surrogate data to represent aquatic life-stages of amphibians. The difference between fish and amphibian risk assessments is related to the water depth used for the estimated environmental concentrations (water depth of 15 cm for amphibians).

The screening level risk quotients for acute and chronic exposures of amphibians to sulfoxaflor do not exceed the level of concern. The screening level risk quotient for acute exposure of amphibians to the X11719474 transformation product does not exceed the level of concern.

Freshwater algae and vascular plants: Of the three algal species tested in laboratory studies, sulfoxaflor was toxic to blue-green algae and diatoms. No adverse effects were observed in a test with green algae. Sulfoxaflor was not toxic to duckweed.

The screening level risk quotients for freshwater algae and vascular plants exposed to sulfoxaflor do not exceed the level of concern

Marine/estuarine invertebrates: Sulfoxaflor was acutely toxic to the mysid shrimp and the eastern oyster. Exposure to sulfoxaflor for 28 days affected the number of days to first brood of the mysid shrimp.

The screening level risk quotients for acute and chronic exposure of marine/estuarine invertebrates exposed to sulfoxaflor do not exceed the level of concern.

Marine/estuarine fish: Acute exposure to sulfoxaflor resulted in mortality of the sheepshead minnow at high test concentrations. Exposure to sulfoxaflor during early life stages of sheepshead minnows resulted in reductions in mean fry length.

The screening level risk quotients for acute and early life stage exposures of marine/estuarine fish to sulfoxaflor do not exceed the level of concern.

Marine/estuarine algae: In laboratory studies, sulfoxaflor was not acutely toxic to saltwater diatoms.

The screening level risk quotient for marine/estuarine algae exposed to sulfoxaflor does not exceed the level of concern.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1.1 Aphids on Barley and Wheat

Efficacy data from a total of six field trials were provided to demonstrate control of aphids on cereal crops, four conducted against English grain aphid (*Sitobion avenae*), two in Hungary (one on oat and one on barley) and two in Germany (one on oat and one on wheat), and two conducted against Russian wheat aphid (*Diuraphis noxia*) in Colorado (one on wheat and one on barley). The trials against English grain aphid provided support for the application rates of 12.5 to 25 g a.i./ha for control of cereal aphids (other than Russian wheat aphid). Rates close to the lower application rate (12.5 g a.i./ha) provided an acceptable level of control, although sometimes with delayed control, and rates close to the upper application rate (25 g a.i./ha) provided a higher level of control more quickly, without significant further improvement at higher rates. In the case of Russian wheat aphid, however, efficacy of sulfoxaflor was generally inferior to the positive control treatments and only approached acceptable levels of control at the highest application rate tested (25 g a.i./ha). Considering the rate effects generally demonstrated for various aphids on various crops, a higher application rate of 50 g a.i./ha is expected to provide acceptable control of Russian wheat aphid; therefore, application rates of 25 to 50 g a.i./ha can be supported.

5.1.1.2 Aphids on Oilseeds

Efficacy data from a total of four field trials were provided to demonstrate control of aphids on canola, flax seed and similar oilseeds, all conducted against green peach aphid (*Myzus persicae*) on canola (or rapeseed), two in Michigan, one in France and one in the UK. The results of the trials demonstrated high efficacy of sulfoxaflor applied at or near rates of 12.5 to 25 g a.i./ha against green peach aphid on canola/rapeseed and may be considered generally representative of aphids on oilseeds.

5.1.1.3 Lygus Bugs on Oilseeds

Efficacy data from a total of five field trials were provided to demonstrate control of Lygus bugs on canola, flax seed and similar oilseeds, all conducted against *Lygus lineolaris*, two on canola, one in Michigan and one in Mississippi, and three on cotton, one in Mississippi and two in Arkansas. The results of these trials demonstrated control of Lygus bug nymphs by sulfoxaflor at application rates of 50 to 75 g a.i./ha. Rates lower than 50 g a.i./ha were less effective, but in most instances there was little or no difference between 50 and 75 g a.i./ha, and the few small differences that occurred were on cotton. Based on these results, a label claim for control of Lygus bugs on canola (rapeseed), flax seed and similar oilseeds can be supported with an application rate of 50 g a.i./ha. Support for a higher application rate would require further information demonstrating the necessity of that higher rate on canola or similar oilseed crop(s).

5.1.2 Effectiveness of Closer Insecticide

5.1.2.1 Aphids on Brassica and Leafy Vegetables

Efficacy data from a total of four field trials were provided to demonstrate control of aphids on Brassica and leafy vegetable crops. Three trials were conducted against cabbage aphid (*Brevicoryne brassicae*), one on broccoli in California, one on cabbage in the UK, and one on cauliflower in Hungary, in addition, one trial was conducted against lettuce aphid (*Nasonovia ribisnigri*) on leaf lettuce in France. The results of the trials collectively demonstrated efficacy against aphids on Brassica and leafy vegetable crops and provided support for the application rates of 24 to 36 g a.i./ha. With general consistency among trials, 24 g a.i./ha may be adequate in most situations, although 36 g a.i./ha may be required for control in some cases with high pest pressure. Up to six days may be required for the full effect of a treatment to be realized and although control may be maintained up to 20 days or more after a single application, it also may begin to decline by seven days after application, justifying a reapplication interval of seven days.

5.1.2.2 Aphids on Root and Tuber Vegetables

Efficacy data from a total of seven field trials were provided to demonstrate control of aphids on root and tuber vegetables. All trials were conducted on potato, one against potato aphid (*Macrosiphum euphorbiae*) and an unidentified *Aphis* sp. in the UK, two against "*Aphis* sp." in Germany, one against green peach aphid (*Myzus persicae*) and two against potato aphid in Manitoba, and one against green peach aphid in Washington. The results of the trials provided support for the application rates of 12 to 36 g a.i./ha. Rates lower than 12 g a.i./ha generally failed, but 12 g a.i./ha did provide control in some trials and applications of 24 and 36 g a.i./ha were consistently effective. The relatively wide range of application rates allows flexibility to address varying pest pressure or provide sufficient coverage of different root and tuber vegetable crops. The full effect of a treatment was often delayed up to several days, justifying an interval of seven days before reapplication is considered.

5.1.2.3 Aphids on Pome Fruits, Stone Fruits and Tree Nuts

Efficacy data from a total of six field trials were provided to demonstrate control of aphids (excluding woolly apple aphid) on fruit and nut trees, one conducted against rosy apple aphid (*Dysaphis plantaginea*) on apple in Oregon, two conducted against apple aphid (*Aphis pomi*) on apple in Washington and British Columbia, and three conducted against green peach aphid (*Myzus persicae*) on nectarine in Australia and peach in Portugal and Italy. The results of the trials provided support for the application rates of 24 to 48 g a.i./ha and also showed that control of aphids on fruit trees by sulfoxaflor may not be realized until seven days or more after application in some cases, providing support for the reapplication interval of no less than seven days. Considering the combined data for three different aphid species on both pome fruit and stone fruit trees, the label claims for control of aphids on fruit and nut trees can be supported.

5.1.2.4 San Jose Scale on Pome Fruits, Stone Fruits and Tree Nuts

Efficacy data from a total of three field trials were provided to demonstrate control of San Jose scale (*Quadraspidiotus perniciosus*) on fruit and nut trees, two conducted on apple, one in Pennsylvania and one in New York, and one conducted on nectarine in California. The results of the trials indicated that sulfoxaflor may provide control of San Jose scale at an application rate of 50 g a.i./ha in some cases. In other cases, 100 g a.i./ha may be required, but little or no improvement in efficacy was demonstrated at application rates higher than 100 g a.i./ha. Based on these results, application rates of 48 to 96 g a.i./ha can be supported for control of San Jose scale on fruit and nut trees.

5.1.2.5 Woolly Apple Aphid on Pome Fruits

Efficacy data from a total of three field trials were provided to demonstrate suppression of woolly apple aphid (*Eriosoma lanigerum*) on pome fruits, two conducted in New York and one in Washington, all on apple. Treatment with sulfoxaflor generally provided only moderate levels of control of existing woolly apple aphid colonies, consistent with the proposed claim of suppression, and appeared to be more effective in preventing establishment of new colonies. Results were most consistent with an application rate of 50 g a.i./ha, supporting the application rate of 48 g a.i./ha; only in one instance of declining pest pressure did a higher application rate show any indication of better efficacy, which was insufficient to justify the use of the higher rate.

5.1.2.6 Leafhoppers on Grapes

Efficacy data from a total of three field trials were provided to demonstrate control of leafhoppers on grapes. Two trials were conducted against western grape leafhopper (*Erythroneura elegantula*) and one against variegated leafhopper (*Erythroneura variabilis*), all on grapes in California. The results of the trials demonstrated some efficacy of sulfoxaflor against leafhoppers on grapes and indicated that application rates of 48 to 96 g a.i./ha are optimal for this use. However, the level of control provided by sulfoxaflor was limited under higher pest pressure in two of the three trials, so the label claim for leafhoppers on grapes is limited to suppression only.

5.1.3 Aerial Application

Three field trials against potato leafhopper in Manitoba, as well as the two trials against potato aphid in Manitoba, included treatments simulating aerial application. To simulate aerial application in these small scale field trials, treatments were applied in low spray volumes (45 L/ha) and compared to treatments applied in spray volumes typical of ground application (225 L/ha). Although one trial showed significantly lower efficacy with simulated aerial than with ground application in the first assessment, the remaining assessments and all other trials showed no difference in efficacy between simulated aerial and ground application at the same rate, so aerial application can be supported. Two trials against soybean aphid in Minnesota and Wisconsin demonstrated equivalent efficacy of Transform WG Insecticide and Closer Insecticide when applied at the same rate of active ingredient, so aerial application can be supported for both products.

5.1.4 Acceptable Efficacy Claims

Acceptable efficacy claims for Transform WG Insecticide are control of cereal aphids and Russian wheat aphid on barley and wheat, as well as aphids and Lygus bugs on canola (rapeseed), flax seed and similar oilseeds (Appendix I, Table 24). Acceptable efficacy claims for Closer Insecticide are control of aphids on Brassica vegetables, leafy vegetables, root and tuber vegetables; suppression of leafhoppers on grapes; control of green apple aphid, rosy apple aphid and San Jose scale and suppression of woolly apple aphid on pome fruits; control of green peach aphid, mealy plum aphid and San Jose scale on stone fruits; and control of aphids and San Jose scale on tree nuts (Appendix I, Table 25).

5.2 Non-Safety Adverse Effects

Assessments of phytotoxicity were reported in 26 of the submitted efficacy trials, including two on cabbage, one on cauliflower, one on lettuce, six on potato, four on apple, one on nectarine, two on peach, one on grape, two on wheat, one on oat, two on canola, one on rapeseed and two on cotton. No evidence of phytotoxicity was detected in any of these trials.

5.3 Consideration of Benefits

5.3.1 Social and Economic Impact

At the time of registration, no high priorities had been identified for sulfoxaflor in the Canadian Grower Priority Database, but the supported use pattern for sulfoxaflor included at least 27 specific uses (crop-pest combinations) identified in that database as high priorities for other active ingredients. At the 2012 Canadian Minor Use Pesticide Priority Setting Workshop, two specific uses (aphids on nectarine and Lygus bugs on canola) for which sulfoxaflor was identified as a potential solution, and at least 20 additional specific uses (mostly aphids on various crops) for which sulfoxaflor was not identified as a potential solution, were considered priorities by one or more provinces. Although not always specifically identified as a potential solution, sulfoxaflor may help to address these priority pest issues.

5.3.2 Survey of Alternatives

Alternative insecticides for supported uses of sulfoxaflor include active ingredients in IRAC mode-of-action groups 1A (three carbamates), 1B (various organophosphates), 2A (endosulfan), 3A (four pyrethroids), 4A (four neonicotinoids), 9B (pymetrozine), 9C (flonicamid) and 23 (spirotetramat) as well as unclassified active ingredients lime sulfur, mineral oil and potassium salts of fatty acids. Many of these alternatives are in older classes of chemistry, some are currently under re-evaluation (carbamates, organophosphates, pyrethroids and neonicotinoids) and a few are being phased out (some organophosphates and endosulfan). Current availability of alternatives varies depending on the pest and the crop. For aphids on vegetable and tree fruit crops there are 12 or more alternatives registered, representing most or all of the different mode-of-action groups above; however, for the remaining uses there are seven or fewer alternatives registered, representing four or fewer mode-of-action groups. Uses with the fewest alternatives include:

- Aphids on barley (organophosphates only)
- Aphids on oilseeds (dimethoate and potassium salts of fatty acids)
- Aphids on wheat (organophosphates and potassium salts of fatty acids)
- Woolly apple aphid on pome fruits (carbaryl, organophosphates and lambda-cyhalothrin)
- San Jose scale on tree nuts (spirotetramat and potassium salts of fatty acids)
- Lygus bugs on oilseeds (chlorpyrifos and pyrethroids)

5.3.3 Compatibility with Current Management Practices Including Integrated Pest Management

Application of Transform WG Insecticide or Closer Insecticide using conventional ground application equipment, or by aerial application equipment, on potato, barley, wheat and oilseeds to control or suppress sap-feeding insect pests on various field vegetable, cereal grain, oilseed, fruit and nut crops is compatible with current management practices. However, sulfoxaflor may have adverse effects on predatory and parasitic arthropods (see Section 4.2.1) that are beneficial to integrated pest management. Canadian product labels for Transform WG Insecticide and Closer Insecticide limit applications of sulfoxaflor to a maximum of two per growing season, which will help to minimize adverse effects on beneficial arthropods.

5.3.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of insecticides having the same mode of action increases the probability of selecting biotypes (groups of insects within a species that have biological traits not common to the species as a whole) with less susceptibility to insecticides with the same mode of action. Sulfoxaflor has a novel mode of action and insects resistant to various other classes of insecticides, including neonicotinoids, have been shown to lack cross-resistance to sulfoxaflor. Furthermore, structural differences render the compound stable in the presence of monooxygenases that degrade a variety of neonicotinoids and are associated with most known cases of neonicotinoid resistance (Zhu *et al.* 2010). To help minimize the potential for the development of resistance to sulfoxaflor, Canadian product labels stipulate a maximum of two applications per growing season and include the recommended statements for resistance management as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.3.5 Contribution to Risk Reduction

For many uses of sulfoxaflor, a majority of the available alternatives are active ingredients belonging to older chemical classes, some of which are undergoing re-evaluation. Sulfoxaflor provides a contribution to the range of alternatives available to replace older compounds that are phased out.

5.4 Supported Uses

Supported uses of Transform WG Insecticide are for control of cereal aphids and Russian wheat aphid on barley and wheat and aphids and Lygus bugs on canola (rapeseed), flax seed and similar oilseeds (Appendix I, Table 24). Supported uses of Closer Insecticide are for control of aphids on Brassica vegetables, leafy vegetables and root and tuber vegetables; suppression of leafhoppers on grapes; control of green apple aphid, rosy apple aphid and San Jose scale and suppression of woolly apple aphid on pome fruits; control of green peach aphid, mealy plum aphid and San Jose scale on stone fruits; and control of aphids and San Jose scale on tree nuts (Appendix I, Table 25).

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, 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, sulfoxaflor and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Sulfoxaflor does not meet Track 1 criteria, and is not considered a Track 1 substance. See Appendix 1, Table 27 for comparison with Track 1 criteria.

- Transformation products of sulfoxaflor are not Track 1 substances based on a log K_{ow} of less than 0.3 which is below the Track 1 criterion for bioaccumulation.

Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusion:

---

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

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

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

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

- Technical grade sulfoxaflor and the end-use products Transform WG Insecticide and Closer Insecticide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[9]

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for sulfoxaflor was adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies with adult laboratory animals, the primary targets were the liver and testes. There was evidence of carcinogenicity in rats and mice after longer-term dosing. Liver tumours observed in rats and mice were determined to be not relevant to humans. In male rats, equivocal increases in preputial gland tumours were observed, as were increases in bilateral Leydig cell tumours but only at the highest dose tested. There was evidence of increased susceptibility of the young in reproductive and developmental toxicity studies, as reduced neonatal survival, which occurred in the absence of maternal toxicity. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders, and applicators handling Transform WG Insecticide and Closer Insecticide, and workers entering treated cereal, oilseed, vegetable, fruit and nut (including pistachio) orchards, and grape vineyards, are not expected to be exposed to levels of sulfoxaflor that will result in an unacceptable risk when Transform WG Insecticide and Closer Insecticide are used according to label directions. The personal protective equipment and the restricted entry interval on the product labels are adequate to protect workers.

Exposures to the general population entering and participating in pick-your-own activities are not expected to result in unacceptable risk when Closer Insecticide is used according to label directions.

Residential exposure to individuals contacting treated trees is not expected to result in unacceptable risk when Closer Insecticide is used according to label directions.

The nature of the residue in plants and animals is adequately understood. The residue definition for enforcement is sulfoxaflor. The use of sulfoxaflor on various fruits, vegetables, oilseeds, cereal grains, legumes, and tree nuts does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health.

---

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

7.2 Environmental Risk

Sulfoxaflor may pose a risk to certain beneficial arthropods and to bees. However, these risks are considered to be acceptable when the product is used according to label instructions. Risk to other non-target organisms is not expected when sulfoxaflor is used according to label directions.

7.3 Value

Transform WG Insecticide has value for the control of aphids and plant bugs on cereal grains and oilseeds; Closer Insecticide has value for the control or suppression of aphids, leafhoppers and scale insects on field vegetable, fruit and nut crops. Some of these uses have been identified as priorities for Canadian growers. The novel mode of action of sulfoxaflor has value for insecticide resistance management.

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 Isoclast Active, Transform WG Insecticide and Closer Insecticide, containing the technical grade active ingredient sulfoxaflor, to control or suppress aphids, leafhoppers, San Jose scale and Lygus bug on a wide range of field vegetable, cereal grain, oilseed, fruit and nut crops.

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

♂	male
♀	female
µg	micrograms
µM	micromolar
ADI	acceptable daily intake
AFC	antibody forming cell
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AnR	androgen receptor
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agriculture Re-entry Task Force
AST	aspartate aminotransferase
atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
BQ	benzylquinoline
BrdU	bromodeoxyuridine
BROD	pentoxyresorufin-O-dealkylase
BUN	blood urea nitrogen
bw	body weight
bwg	bodyweight gain
°C	degrees Celsius
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CDN	Canadian
CEPA	*Canadian Environmental Protection Act*
CG	crop group
cm	centimetres
d	day(s)
DAA	day(s) after application
DAT	days after treatment
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue
DNT	developmental neurotoxicity
DOPAC	dihydroxyphenylacetic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
EbC_{50}	EC_{50} in terms of algal biomass
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population

EDE	estimated dietary exposure
EEC	Estimated environmental concentration
ER	estrogen receptor
ER_{25}	effective rate for 25% of the population
ER_{50}	effective rate on 25% of the population
ErC_{50}	EC_{50} in terms of reduction of growth rate
EROD	ethoxyresorufin-O-dealkylase
EU	European Union
EyC_{50}	EC_{50} in terms of reduction of yield
F_1	first generation
F_2	second generation
fc	food consumption
FIR	food ingestion rate
g	gram(s)
GAP	Good Agricultural Practices (registered)
GD	gestation day
GGT	gamma glutamyl transferase
GnRH	gonadotropin-releasing hormone
GUS	groundwater ubiquity scores
h	hour(s)
ha	hectare(s)
HCT	hematocrit
HDPE	high-density polyethylene
HGB	hemoglobin
HPLC	high performance liquid chromatography
HVA	homovanillic acid
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose 50%
LH	luteinizing hormone
LHR	luteinizing hormone receptor
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	level of detection
LOEC	low observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)

M	molar
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
mL	millilitre
mM	millimolar
MOA	mode of action
MOE	margin of exposure
mol	mole
MRBD	Maximum Reasonably Balanced Diet
MRL	maximum residue limit
mRNA	messenger ribonucleic acid
MS/MS	tandem mass spectrometry
N/A	not applicable
nAChR	nicotinic acetylcholine receptor
NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NAFTA	North American Free Trade Agreement
nm	nanometre
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZ	Northern zone
NZW	New Zealand white
P	parental generation
Pa	pascals
PBI	plantback interval
pH	potential of hydrogen
PHED	Pesticide Handlers' Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post-natal day
ppm	parts per million
PROD	pentoxyresorufin-O-dealkylase
PXR	pregnane X receptor
PYO	Pick-Your-Own
RBC	red blood cell
rel	relative
RQ	risk quotient
RT_{25}	residual time needed to bring mortality down to 25%
SC	soluble concentrate
SPE	solid phase extraction
StAR	steroidogenic acute regulatory protein
STMdR	supervised trial median residue
STMR	supervised trial mean residue
SZ	Southern zone

$t_{1/2}$	half-life
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UV	ultraviolet
w	week(s)
WDG	water dispersible granular
WG	wettable granule
wt	weight

Appendix I Tables and Figures

Table 1 Methods for Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Soil	091185	Sulfoxaflor	HPLC-MS/MS	0.001 mg/kg	Silt loam, sandy loam, clay loam and loam	1941250
		X11519540				
		X11579457				
		X11719474				
Water	091186	Sulfoxaflor	HPLC-MS/MS	0.05 µg/L (with SPE) 0.25 µg/L (without SPE)	Drinking (tap), ground (well) and surface (pond) water	1941253
		X11519540				
		X11579457				
		X11719474				
Plant	091116, 101097, 091031, CEMS-4295	Sulfoxaflor	LC/MS/MS	0.010 ppm for dry crops, wet crops, acidic crops, oily crops		1941241, 1941242, 1941243, 1941244
Animal	091188, 101098, CEMS-4567, CEMS-4568	Sulfoxaflor	LC/MS/MS	0.010 ppm poultry and bovine tissue, milk, and eggs		1941245, 2029414, 1941247, 1941246, 1941258

Table 2 Toxicity Profile of Isoclast Active

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

Study Type / Animal / PMRA #	Study Results
Acute Oral Toxicity CD1 mouse PMRA #1941263	LD_{50} (♂) = 750 mg/kg bw Moderate toxicity
Acute Oral Toxicity Fischer 344 rat PMRA #1941262	LD_{50} (♂) = 1405 mg/kg bw LD_{50} (♀) = 1000 mg/kg bw Slight toxicity
Acute Dermal Toxicity Fischer 344 rat PMRA #1941264	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Inhalation Toxicity Fischer 344 rat PMRA #1941265	LC_{50} > 2.09 mg/L Low toxicity
Dermal Irritation NZW rabbit PMRA #1941266	MAS = 0.6 MIS = 2.0 observed at 1 hour Minimally irritating
Eye Irritation NZW rabbit PMRA #1941267	MAS = 3.4 MIS = 12 observed at 1 hour Minimally irritating
Dermal Sensitization (LLNA) CBA/J mouse PMRA #1941268	Not a skin sensitizer
28-Day Dermal Fischer 344 rat PMRA #1941279	NOAEL = 1000 mg/kg bw/day LOAEL was not established as no adverse effects were observed. Non-adverse effects noted at1000 mg/kg bw/day included ↑ cholesterol, ↑ liver wt, liver hypertrophy with altered tinctorial properties (♂).

90-Day Oral (gavage) Beagle dog PMRA #1941278	NOAEL = 6 mg/kg bw/day LOAEL = 10 mg/kg bw/day, based on ↓ bw, ↓ fc.
12-Month Oral (gavage) Beagle dog PMRA #1999110	NOAEL = 6 mg/kg bw/day LOAEL was not established as no treatment-related effects were observed.
28-Day Dietary CD1 mouse PMRA #1941272	NOAEL = 44/53 mg/kg bw/day (♂/♀) LOAEL = 230/273 mg/kg bw/day, based on ↓ bw & bwg, ↓ fc, ↑ liver wt, ↑ ALT and AST, hepatocellular hypertrophy with altered tinctorial properties (♂ & ♀); necrosis of liver, liver histopathology (mitotic cells, vacuolization/fatty change), ↓ kidney wt (♂). Effects observed at next highest dose (524/638 mg/kg bw/day) included ↑ ALP, ↑ triglycerides (♂ & ♀); ↑ adrenal wt, adrenal hypertrophy (♂); liver necrosis (♀).
90-Day Dietary CD1 mouse PMRA #1941277	NOAEL = 6.4/7.0 mg/kg bw/day (♂/♀) LOAEL = 48/52 mg/kg bw/day, based on ↓ fc , ↓ bwg, ↑ liver wt, hepatocyte hypertrophy with altered tinctorial properties, centrilobular hepatocyte single cell necrosis (♂ & ♀); ↓ bw, ↓ spleen wt, aggregates of macrophages in liver, hepatocyte vacuolization consistent with fatty change (♂). Effects observed at the next highest dose (95/101 mg/kg bw/day) included ↑ cholesterol, ↑ total protein, ↑ potassium, ↑ atrophy of mesenteric adipose tissue (♂ & ♀); ↓ reticulocytes, ↓ AFC/10^6 splenocytes (♂); ↓ bw, ↑aggregates of macrophages in liver (♀). The plasma half-life of elimination was 9 hours in ♂ and 8 hours in ♀. The area under the curve for 24 hours was lower in ♀ than in ♂, indicating ↑ elimination for ♀. Plasma concentrations increased proportionally with dose.
28-Day Dietary Fischer 344 rat PMRA #1941270	
90-Day Dietary Fischer 344 rat PMRA #1941276	

18-Month Dietary CD1 mouse PMRA #1941285	NOAEL (♂) = 10 mg/kg bw/day NOAEL (♀) = 34 mg/kg bw/day LOAEL (♂) = 80 mg/kg bw/day, based on ↑ liver wt, liver nodules, liver hypertrophy, liver necrosis, fatty liver, liver foci (eosinophilic and vacuolated), dermal effects (dermatitis, chronic inflammation, epidermal ulceration, acanthosis) with associated reactive plasmacytosis of local submandibular lymph nodes. LOAEL (♀) = 176 mg/kg bw/day, based on ↑ liver wt, liver nodules, liver hypertrophy, liver necrosis, fatty liver, liver foci (eosinophilic and vacuolated). Neoplastic lesions: ↑ incidence of hepatocellular adenomas and carcinomas in ♂; ↑ incidence of hepatocellular carcinomas in ♀. Toxicokinetic analysis indicated that the plasma and urine concentrations of sulfoxaflor increased proportionally with dose. Evidence of carcinogenicity
Two-Year Dietary Fischer 344 rat PMRA #1941284	NOAEL (♂) = 1.04 mg/kg bw/day NOAEL (♀) = 5.13 mg/kg bw/day LOAEL (♂) = 4.24 mg/kg bw/day, based ↑ testes wt ↓ epididymidal wt,↑ unilateral testes interstitial cell adenoma, ↑ bilateral atrophy of seminiferous tubule, ↑ incidence of decreased spermatic elements in epididymides (♂). Effects observed at next highest dose (21 mg/kg bw/day) in ♂ included ↑ cholesterol, absence of bilirubin in urine, hepatocellular hypertrophy, hepatocyte vacuolization (consistent with fatty change), necrosis of centrilobular hepatocytes, aggregates of liver macrophages, ↑ incidence of decreased secretory material (in coagulating gland, prostate and seminal vesicle). LOAEL (♀) = 39 mg/kg bw/day, based on ↑ cholesterol, absence of bilirubin in urine, hepatocellular hypertrophy, hepatocyte vacuolization (consistent with fatty change), necrosis of centrilobular hepatocytes, aggregates of liver macrophages ↓ basophilic foci of altered hepatocytes. Neoplastic lesions: ↑ incidence of preputial gland carcinomas, interstitial (Leydig) cell adenomas, and hepatocellular adenomas in ♂. Toxicokinetic analysis indicated that the plasma and urine concentrations of sulfoxaflor increased proportionally with dose. Evidence of carcinogenicity
Range-Finding Reproductive Toxicity (Dietary) Sprague-Dawley rat PMRA #1941291	A NOAEL was not established as this was a dose range-finding study. Parental effects noted at 41/39 mg/kg bw/day (♂/♀) included ↑ liver wt, hepatocellular hypertrophy with altered tinctorial properties (♂); ↓ bwg first week of gestation (♀). Parental effects noted at 79/78 mg/kg bw/day (♂/♀) included ↓ fc (♂); ↓ fc during gestation, hepatocellular hypertrophy with altered tinctorial properties (♀). Offspring effects noted at 41/39 mg/kg bw/day included ↑ pup deaths at PND 4, ↓ pup bw (PND 1 only). Offspring effects noted at 79/78 mg/kg bw/day included ↓ bw, complete litter losses. Evidence of sensitivity of the young

Two-Generation Reproductive Toxicity (Dietary) Sprague-Dawley Rat PMRA #1941292	<u>Parental Toxicity</u> NOAEL (♂) = 6.1 mg/kg bw/day NOAEL (♀) = 30 mg/kg bw/day LOAEL (♂) = 25 mg/kg bw/day, based on ↑ liver wt, centrilobular vacuolization of the liver (P generation only), centrilobular hepatocyte hypertrophy with altered tinctorial properties, centrilobular necrosis of hepatocytes (♂). LOAEL (♀) was not established as no treatment-related effects were observed. <u>Reproductive Toxicity</u> NOAEL = 6.1/7.8 mg/kg bw/day (♂/♀) LOAEL = 25/30 mg/kg bw/day, based on ↑ post-implantation loss (F_1 parents), ↑ stillbirths (F_2 offspring), ↓ percentage of pups delivered alive at birth (F_2 pups), delayed preputial separation (F_1). <u>Offspring Toxicity</u> NOAEL = 6.1/7.8 mg/kg bw/day (♂/♀) LOAEL = 25/30 mg/kg bw/day, based on ↑ pup deaths PND 0-4 (F_1). Toxicokinetic analyses on PND 4 indicated that the plasma concentrations of sulfoxaflor increased proportionally with dose. Plasma concentrations of sulfoxaflor in pups were, on average, 32% of the levels measured in dams Evidence of sensitivity of the young
Range-Finding Developmental Toxicity (Dietary) Sprague-Dawley rat PMRA #1941293	A NOAEL was not established as this was a dose range-finding study. Maternal effects noted at 35 mg/kg bw/day included ↓ fc. Maternal effects noted at 68 mg/kg bw/day included ↓ bw & bwg, ↑ rel liver wt. All maternal animals were sacrificed on GD 13 at 87 and 94 mg/kg bw/day due to excessive toxicity.
Developmental Toxicity (Dietary) Sprague-Dawley rat PMRA #1941294	<u>Maternal Toxicity</u> NOAEL = 11.5 mg/kg bw/day LOAEL = 70 mg/kg bw/day, based on ↓ bw & bwg, ↓ fc, ↓ gravid uterine wt. <u>Developmental Toxicity</u> NOAEL = 11.5 mg/kg bw/day LOAEL = 70 mg/kg bw/day, based on ↓ fetal bw, ↑ resorptions, ↑ post-implantation loss, ↓ viable fetuses/litter, ↑ incidence of variations (forelimb flexure, hindlimb rotation, convoluted ureter, hydroureter, bent clavicle, fused sternebrae). Toxicokinetic analyses on GD 21 revealed that fetal plasma levels of sulfoxaflor were 76-85% of those in the dams. Evidence of sensitivity of the young
Range-Finding Developmental Toxicity (Gavage) NZW rabbit PMRA #1941295	A NOAEL was not established as this was a dose range-finding study. Maternal effects noted at 15 mg/kg bw/day included bw loss, ↓ bwg, ↓ fc. At higher doses of 20 and 25 mg/kg bw/day, maternal animals were sacrificed due to severe inanition on GD 16 and 13, respectively. Toxicokinetic analyses on GD 27 revealed the half-life of elimination from plasma to be 14 hours and that plasma concentrations of sulfoxaflor increased proportionally with dose. The maximum plasma concentration of sulfoxaflor was reached 2-4 hours following dosing.

Range-Finding Developmental Toxicity (Dietary) NZW rabbit PMRA #1941296	A NOAEL was not established as this was a dose range-finding study. Maternal effects noted at 22 mg/kg bw/day included ↓ bwg. Maternal effects noted at 37 mg/kg bw/day included inanition, ↓ feces, cold to touch, bw loss, ↓ bwg, ↓ fc (1 doe was sacrificed at this dose). Toxicokinetic analyses on GD 27 indicated that plasma concentrations of sulfoxaflor increased proportionally with dose.
Developmental Toxicity (Dietary) NZW rabbit PMRA #1941297	<u>Maternal Toxicity</u> NOAEL = 6.6 mg/kg bw/day LOAEL = 32 mg/kg bw/day, based on ↓ bwg, ↓ fc, ↓ feces. <u>Developmental Toxicity</u> NOAEL = 32 mg/kg bw/day LOAEL was not established as no treatment-related effects were observed Toxicokinetic analyses on GD 21 indicated similar plasma concentrations in dams and fetuses. No evidence of sensitivity of the young.
Acute Neurotoxicity (Gavage) Fischer 344 rat PMRA #1941305	NOAEL = 25 mg/kg bw LOAEL = 75 mg/kg bw, based on ↓ motor activity. Effects observed at the next highest dose (750 mg/kg bw) included ↓ feces, red perioral soiling, ↓ rectal temperature, lacrimation, salivation, ↓ pupil size, ↓ response to touch, ↓ level of open-field activity, unable to walk, muscle tremor, twitches, convulsions, splayed hindlimbs, perineal urine soiling (♂ & ♀); ↓ bw & bwg, slight incoordination of gait (♂); 1 death (day1), perineal urine soiling, ↑urination (♀).
Developmental Neurotoxicity (Dietary) Sprague-Dawley rat PMRA#1941306	<u>Maternal Toxicity</u> NOAEL = 29 mg/kg bw/day LOAEL was not established as no treatment-related effects were observed <u>Developmental Toxicity</u> NOAEL = 1.9 mg/kg bw/day LOAEL = 7.4 mg/kg bw/day, based on ↑ pup deaths. Developmental effects noted at the next highest dose (29 mg/kg bw/day) included malrotation of left forelimb, ↓ bw, delay in attainment of surface righting response (♂ & ♀); ↓ brain weight & brain length PND 72 (♂); ↑ brain length PND 72 (♀). Evidence of sensitivity of the young
Special Study Critical window for developmental abnormalities and neonatal survival (Phase I) (Dietary) Sprague-Dawley rat PMRA #1941301	No treatment-related effect on development or survival when sulfoxaflor was administered from GD 6 to 16 at 79 mg/kg bw/day. Reduced survival (PND 1-4) and abnormalities (forelimb flexure, hindlimb rotation) observed when sulfoxaflor was administered from GD 16 to parturition at 39 mg/kg bw/day. Toxicokinetic analyses indicated that maternal blood concentrations of sulfoxaflor were similar on GD 16 in pregnant rats dosed at 79 mg/kg bw/day from GD 6 to 16 and on GD 21 in pregnant rats dosed at 39 mg/kg bw/day from GD 16 to parturition.

Special Study Critical window for developmental abnormalities and neonatal survival (Phase II) (Dietary) Sprague-Dawley rat PMRA #1941302	No treatment-related effect on development or survival when sulfoxaflor was administered from GD 16 to 18 at 64 mg/kg bw/day, or from GD 18 to 20 at 42 mg/kg bw/day. Reduced survival (PND 2-4) and abnormalities (hindlimb rotation) observed when sulfoxaflor was administered from GD 20 to 22 at 36 mg/kg bw/day. Results demonstrate that GD 20-22 was the critical window for exposure resulting in reduced pup survival and developmental abnormalities. Toxicokinetic analyses revealed that maternal blood concentration ranged from 16 to 33 µg/g on GD 18 in dams dosed at 64 mg/kg bw/day from GD 16 to 18, from 23 to 30 µg/g on GD 20 in dams dosed at 42 mg/kg bw/day from GD 18 to 20, and from 5 to 7 µg/g on LD 0 in dams dosed at 36 mg/kg bw/day from GD 20 to 22.
Special Study Cross-fostering study Sprague-Dawley rat PMRA #1941298	There was no effect on pup survival when control pups (not exposed to sulfoxaflor in utero) were cross-fostered with dams exposed to sulfoxaflor during lactation. Reduced survival was observed for pups born from dams exposed to sulfoxaflor prior to birth that were cross-fostered with either control or sulfoxaflor-exposed dams. Some of these pups were cold to touch, had bluish skin, were autolyzed and cannibalized, and had stomach void of milk. The results of this study indicate that effect on pup survival was due to in utero exposure and not as a result of lactational exposure Toxicokinetic analyses indicated that plasma levels of sulfoxaflor were similar among dams, fetuses and pups.
Special Study Rabbit neonatal survival NZW rabbit PMRA #1941299	Maternal effects noted at 29 mg/kg bw/day included bw loss, ↓ bwg, ↓ fc, ↓ feces. No developmental effects or effects on neonatal survival were observed at 29 mg/kg bw/day.
Special Study Effects on the phrenic nerve – hemidiaphragm in the newborn rat Sprague-Dawley rat PMRA#1941303	Sulfoxaflor produced a concentration-dependent contracture of the phrenic nerve-hemidiaphragm (100 µM did not produce much contraction, while a concentration of 1 mM was required). A concentration of 1 mM sulfoxaflor produced contracture of diaphragm and a decrease in muscle twitch response, similar in magnitude to that observed with 100 µM acetylcholine. Tubocurarine (10 µM) blocked about half of the contracture when co-applied with sulfoxaflor (due to rate-limiting diffusion of the antagonist into the tissue). Pre-application of tubocurarine (10 µM) effectively blocked muscle twitches and antagonized responses to 100 µM and 1 mM sulfoxaflor, demonstrating that sulfoxaflor acts via the nicotinic acetylcholine receptor and not via a post-receptor mechanism. Muscle contracture was sustained and muscle twitches reduced in presence of prolonged application of 1 mM sulfoxaflor (suggesting little desensitization) but normal function resumed upon removal of sulfoxaflor.

Special Study Histopathological evaluation of fetal lung samples Sprague-Dawley rat PMRA # 1941304	Histopathologic examinations were conducted on fetuses to determine if neonatal death was mediated by histopathologic changes in lung tissue. No sulfoxaflor-induced lesions were noted in the trachea, bronchi, bronchioles or alveoli in any of the treated fetuses. There was no treatment-related increase in collagen deposition around airways or alveolar walls.
Special Study Characterization of the agonist effects on mammalian muscle nAChR Sprague-Dawley rat NZW rabbit Human recombinant nAChR PMRA #1941300	Due to high levels of non-specific binding, it was not possible to definitively demonstrate whether sulfoxaflor bound specifically to the tissue preparations. A dose-dependent displacement of [^{3}H]-epibatidine was observed with increasing concentrations of sulfoxaflor (0.3µM to 30 mM) for all three tissue preparations; the data fit into a single binding site model for humans and rabbits, and into a two-site model for rats (two binding sites with different affinities). Sulfoxaflor produced agonist-evoked response with the rat fetal nAChR only. No significant agonist effects were observed with the sulfoxaflor metabolite X11719474 and the rat fetal nAChR. The results of this study demonstrated sulfoxaflor is an agonist of the rat fetal muscle nAChR, but has no agonist activity on human fetal, rat adult, or human adult muscle nAChR.
Special Study Screening for estrogen and androgen receptor binding PMRA #2060409	Sulfoxaflor was a potential binder to the androgen receptor; relative binding affinity of sulfoxaflor compared to testosterone was weak with a mean value of 0.0014. Sulfoxaflor did not bind to the estrogen receptor.
Special Study Screening for estrogen and androgen transactivation PMRA #2060409	Sulfoxaflor was considered negative for agonism and antagonism.
Special Study Screening for androgen receptor aromatase inhibition PMRA #2060409	Sulfoxaflor did not inhibit aromatase (Cyp19) activity.
Special Study Leydig cell MOA study Sprague-Dawley rat, Fischer 344 rat PMRA #1999148	Fischer 344 rat: ↑ luteinizing hormone (high-dose only) and ↓ prolactin (high-dose only) and ↑ testosterone at week 4 (all doses), ↓ prolactin and luteinizing hormone gene expression at 4 weeks (high-dose only) and no effect at 8 weeks; no changes in StAR, Cyp11a1, Cyp17a1, HSD3b, SDR5a1. Sprague-Dawley rat: ↑ luteinizing hormone (high-dose only) and testosterone at 2 weeks (all doses), ↓ prolactin at 4 weeks (high-dose only), ↑ luteinizing hormone at 8 weeks (all doses); gene expression not assessed. No difference in biliary excretion of testosterone between rat strains.

Special Study Microdialysis assay Sprague-Dawley rat PMRA #2109857	Increases in dopamine efflux in extracellular fluid of hypothalamus after infusion with 400 µM (15% over baseline) and 2 mM (25% over baseline). Maximal rise of 39% over baseline at 40 min after infusion onset with 2 mM. No increase in dopamine metabolites (DOPAC or HVA) in the hypothalamus. Infusion of potassium ions into hypothalamus resulted in increased dopamine efflux (61% over baseline), no change in DOPAC, and a slight decrease in HVA (79% of baseline).
Special Study Induction profile and gene expression in mouse liver C57BL/6J mouse PMRA #1941289	≥160 mg/kg bw/day: ↑ liver wt, ↓ fc, ↑ PROD, ↑ BROD, ↑ BQ debenzylation, ↑ total P450, ↑ Cyp2b10 mRNA expression, ↑ Cyp2b10 proteins 310 mg/kg bw/day: ↓ bw & bwg, ↑ ALT, ↑ Cyp3a11 proteins Gene expression analysis: ↑ Cyp2b10 & Cyp3a11 mRNA expression Western blotting: demonstrated induction of Cyp2b10 and Cyp3a11 The data suggested that sulfoxaflor exerts enzyme induction properties via CAR and possibly PXR.
Special Study Gene expression and cell proliferation analyses (dietary) Fischer 344 rat CD1 mouse PMRA #1941286	Liver gene expression: ↑ Cyp2b10, ↑ Cyp3a11, ↑ Alas1, ↑ NADPH-Cyp-Reductase , ↑ Dhcr7, ↑ Sqle1, ↓ Cyp4a10, ↓ Slco1b2 Ki-67 immunostaining in mouse: ↑ hepatic proliferation in centrilobular and mid-zonal regions at 418 mg/kg bw/day for 7 days; no significant ↑ hepatic proliferation at 345 mg/kg bw/day for 3 days. Ki-67 immunostaining in rat: ↑hepatic proliferation in centrilobular regions at 155/170 mg/kg bw/day. Sulfoxaflor shared similar gene expression with six of seven phenobarbital-marker genes examined (Cyp2b10, Cyp3a11, Alas1, NADPH-Cyp-Reductase, Dhcr7, Sqle1, Slcolb2). Lack of induction of Cyp4a10 and Slco1b2 indicated that sulfoxaflor does not act as a peroxisome proliferator.
Special Study Investigating liver weight effects in mice (dietary) CD1 mouse PMRA #1941288	≥ 89 mg/kg bw/day (♂): mitotic alteration, hepatocyte necrosis, Cyp2b10 induction, ↑ EROD, ↑ PROD, ↑ BROD, centrilobular hepatocellular proliferation 128 mg/kg bw/day (♂): ↑ liver wt, hypertrophy with altered tinctorial properties, slight fatty change in liver, Cyp3a11 induction ≥ 211 mg/kg bw/day (♀): ↓ fc, ↑ triglycerides, ↑ liver wt, hypertrophy with altered tinctorial properties, mitotic alteration, hepatocyte necrosis, Cyp2b10 induction, Cyp3a11 induction ,↑ EROD, ↑ PROD, ↑ BROD, centrilobular & mid-zonal hepatocellular proliferation
Special Study Targeted gene expression, cell proliferation and cytochrome P450 activity (dietary) Fischer 344 rat PMRA 1941287	<u>Day 3</u> ≥8.8/7.8 mg/kg bw/day (♂/♀): ↑ Cyp2b1, ↑ EROD (♂); ↑ Cyp2b2 (♀) ≥60/51 mg/kg bw/day (♂/♀): ↑ cholesterol, ↑ Cyp1a1 (♂); ↓ fc, ↑ Cyp3a3, ↑ Alas1, ↑ NADPH, ↑ PROD, ↑ BROD (♀) 99/83 mg/kg bw/day (♂/♀): ↓ bw, ↓ fc, ↑ Cyp3a3, ↑ Alas1, ↑ NADPH, ↑ PROD, ↑ BROD (♂ & ♀); ↓ bwg, ↑ rel liver wt, ↑ Cyp2b2, ↑ EROD, ↑ Dhcr7 (♂); bw loss, ↑Cyp2b1, ↑Cyp1a1 (♀) <u>Day 7</u> ≥8.0/7.7 mg/kg bw/day (♂/♀): ↑ Cyp2b1, ↑ Cyp2b2 (♂)

	≥59/53 mg/kg bw/day (♂/♀): ↑ Cyp3a3, ↑ Alas1, ↑ NADPH, ↑ PROD, ↑ BROD (♂ & ♀); ↑ cholesterol, ↑ liver wt, centrilobular and mid-zonal hepatocellular proliferation, ↑ Cyp1a1 (♂); ↑ Cyp2b1, ↑ Cyp2b2 (♀) 102/94 mg/kg bw/day (♂/♀): ↓ bw & bwg ↓ fc (♂ & ♀); very slight centrilobular hypertrophy & vacuolation , ↑ Dhcr7, ↑ Sqle1 (♂); ↑ liver wt, ↑ cholesterol, centrilobular hepatocellular proliferation (♀) The results of this study demonstrated that sulfoxaflor is not likely an aryl hydrocarbon receptor or a peroxisome proliferation agonist.
Special Study Investigation into mode of action for liver effects using dual CAR-PXR knockout and humanized mice (dietary) C57BL/6J wild type mice C57BL/6J mice null for PXR and CAR (PXRKO/CARKO) C57BL/6J mice "humanized" for PXR and CAR (hPXR/hCAR) PMRA #1941290	<u>C57BL/6J wild type mice</u> 116 mg/kg bw/day: ↑ liver wt, ↑ BrdU S-phase labeling, very slight to slight centrilobular/midzonal hepatocellular hypertrophy with altered tinctorial properties, very slight hepatocyte mitotic alteration, ↑ PROD, ↑ BROD, ↑ BQ debenzylation, ↑ total P450, ↑ Cyp2b10 mRNA, ↑ Cyp3a11 mRNA, induction of Cyp2b10 proteins, induction of Cyp3a11 proteins <u>PXRKO/CARKO mice</u> 120 mg/kg bw/day: ↑ BROD, ↓ Cyp3a11 mRNA <u>hPXR/hCAR mice</u> 99 mg/kg bw/day: ↑ liver wt, very slight to slight centrilobular/midzonal hepatocellular hypertrophy with altered tinctorial properties, ↑ PROD, ↑ BROD ↑ BQ debenzylation, ↑ total P450, slight ↑ Cyp2b10 mRNA, ↑ Cyp3a11 mRNA, induction of Cyp2b10 proteins, induction of Cyp3a11 proteins Sulfoxaflor exhibited markedly more activity towards the mouse CAR than the human CAR and relatively weak activity towards the mouse and human PXR. Hence, the difference in hepatic response between wild type and humanized mice in this study was considered to be mediated via CAR.
In vitro Bacterial Gene Mutation Assay (S. typhimurium strains TA98, TA100, TA1535, TA1537; E. coli strain WP2uvrA) PMRA #1941280	Negative
In vitro Mammalian Gene Mutation Assay (primary rat lymphocytes) PMRA #1941281	Negative
In vitro Mammalian Gene Mutation Assay (Chinese hamster ovary cells) PMRA #1941282	Negative
In vivo Mammalian Cytogenetics – Erythrocyte Micronucleus Assay CD1 mouse PMRA #1941283	Negative

Toxicokinetics Fischer 344 rat CD1 mouse PMRA #1941259, 1941260, 1941261	Rapid and almost complete absorption and elimination without detectable metabolism. Most (rat: 87-98%; mouse: 80-85%) of the elimination was via the urine. The half-life of elimination from plasma was 9 hours in ♂ rats and 7 hours in ♀ rats. Widely distributed to tissues. Radioactivity detected mainly in portal of entry (gastrointestinal tract, liver) and excretion (kidney, urinary bladder) tissues. No metabolites detected in tissue or plasma. No tissue accumulation, ≤1.2% of administered radioactivity remained in tissues after 7 days. Results did not provide indication of potential for bioaccumulation.

Table 3 Toxicity Profile of Sulfoxaflor Metabolites

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

Study Type / Animal / PMRA #	Study Results
METABOLITE X11719474	
Acute Oral Toxicity Fischer 344 rat PMRA #1941309	LD_{50} (♀) > 5000 mg/kg bw Low toxicity
Dermal Sensitization (LLNA) CBA/J mouse PMRA #1941311	Not a skin sensitizer
28-Day Dietary Fischer 344 rat PMRA #1941313	NOAEL = 244/248 mg/kg bw/day LOAEL = 662/734 mg/kg bw/day (♂/♀), based on liver hypertrophy, ↓ bw & bwg, ↑ cholesterol, ↑ liver wt. Toxicokinetics analysis indicated that the systemic bioavailability of metabolite X11719474 was 33-43% higher in ♂ rats when compared to ♀ rats.
90-Day Oral (Gavage) Beagle dog PMRA #1941316	NOAEL = 50 mg/kg bw/day LOAEL was not established as no adverse effects were observed

90-Day Dietary Fischer 344 rat PMRA #1941314	NOAEL = 65/72 mg/kg bw/day LOAEL = 327/352 mg/kg bw/day (♂/♀), based on liver hypertrophy with altered tinctorial properties, ↑ cholesterol, ↑ liver wt, thyroid wt (♂ & ♀); hepatocyte necrosis, multifocal hepatocyte vacuolization (♂). Toxicokinetic analyses indicated that minimal metabolism occurred prior to excretion, and bioavailability was similar for both sexes.
Reproduction Screening Study (Dietary) Sprague-Dawley rat PMRA #1941321	<u>Parental Toxicity</u> NOAEL (♂) = 162 mg/kg bw/day NOAEL (♀) = 82 mg/kg bw/day LOAEL (♂) = 396 mg/kg bw/day, based on hepatocellular hypertrophy. LOAEL (♀) = 167 mg/kg bw/day, based on ↓ bw & bwg. <u>Reproductive Toxicity</u> NOAEL = 396/451 mg/kg bw/day LOAEL was not established as no treatment-related findings were observed. <u>Offspring Toxicity</u> NOAEL = 396/451 mg/kg bw/day LOAEL was not established as no treatment-related findings were observed.
Developmental Toxicity (Dietary) Sprague-Dawley rat PMRA #1941322	<u>Maternal Toxicity</u> NOAEL = 152 mg/kg bw/day LOAEL = 368 mg/kg bw/day, based on ↓ bw & bwg. <u>Developmental Toxicity</u> NOAEL = 368 mg/kg bw/day LOAEL = 368 mg/kg bw/day, based on slightly ↑ incidence of wavy ribs (malformation). Toxicokinetic analyses indicated that the mean concentration of X11719474 in dam and fetal plasma on GD 21 increased proportionally with dose and that fetal blood concentrations were 113-123% of those in the dam. Evidence of sensitivity of the young
Special Study Targeted gene expression, cell proliferation, and cytochrome P450 activity Fischer 344 rat PMRA #1941320	Effects noted at 583 mg/kg bw/day included ↓ bwg, ↑ liver wt, very slight centrilobular & midzonal hypertrophy, ↑ Cyp2b1, ↑ Cyp2b26, ↑ Cyp3a3, ↑ PROD, hepatocellular proliferation in centrilobular, mid-zonal & periportal areas. The results of this study suggested that metabolite X11719474, like the parent sulfoxaflor, may be an agonist ligand for CAR.
In vitro Bacterial Gene Mutation Assay (*S. typhimurium* strains TA98, TA100, TA1535, TA1537; *E. coli* strain WP2uvrA) PMRA #1941317	Negative
In vitro Mammalian Gene Mutation Assay (primary rat lymphocytes) PMRA #1941318	Negative

In vitro Mammalian Gene Mutation Assay (Chinese hamster ovary cells) PMRA #1941319	Negative
Toxicokinetics Fischer 344 rat PMRA #2099400	Rapid and almost complete absorption and elimination without detectable metabolism. Most (>90%) of the elimination was via the urine.
METABOLITE X11519540	
Acute Oral Toxicity Fischer 344 rat PMRA #1941333	LD_{50} (♀) = 566 mg/kg bw Moderate toxicity
28-Day Dietary Fischer 344 rat PMRA #1999147	NOAEL was not established as effects were noted at the lowest dose tested LOAEL = 7.7/8.5 mg/kg bw/day (♂/♀), based on ↑ adrenal wt, liver hypertrophy (♂ & ♀); adrenal cortex vacuolization (♂) Effects noted at 23/25 mg/kg bw/day included ↑ protein, ↑ albumin, ↑ cholesterol, ↓ glucose, ↑ calcium , ↑ platelets, adrenal zona fasciculata hypertrophy, hepatocyte necrosis (♂ & ♀); ↑ ALT, ↓ ALP, kidney tubule degeneration, thyroid follicular cell hypertrophy (♂); adrenal cortex vacuolization (♀) Effects noted at 74/77 mg/kg bw/day included ↓ bw & bwg, ↓ fc, ↓ RBC, ↓ HGB, ↓ HCT, ↑ BUN, ↑ globulin, ↓ urinary pH (♂ & ♀); ↑ liver wt, ↑adrenal wt, atrophy of mesenteric adipose tissue, thyroid gland follicular cell diffuse hypertrophy; ↑ AST, bone marrow erythroid cell hyperplasia slight, salivary gland hypertrophy (♂); ↑ GGT, ↓ uterine size (♀) Effects noted at 140/152 mg/kg bw/day included ↑ GGT, ↑ urinary protein concentration, spleen extramedullary bone marrow erythroid cell hyperplasia slight (♂); ↓vagina size, diffuse salivary gland hypertrophy (♀) Toxicokinetics analysis indicated that amount of X11519540 eliminated within 24 hours of dosing decreased with increasing dose. Gene expression results suggest that X11519540 may stimulate gene expression consistent with CAR activation similar to the parent compound
In vitro Bacterial Gene Mutation Assay (*S. typhimurium* strains TA98, TA100, TA1535, TA1537; *E. coli* strain WP2uvrA) PMRA #1941334	Negative
In vitro Mammalian Gene Mutation Assay (primary rat lymphocytes) PMRA #1999141	Negative

In vitro Mammalian Gene Mutation Assay (Chinese hamster ovary cells) PMRA #1999140	Negative
METABOLITE X11596066	
Acute Oral Toxicity Fischer 344 rat PMRA #1941329	LD_{50} (♀) >2000 mg/kg bw Low toxicity
In vitro Bacterial Gene Mutation Assay(*S. typhimurium* strains TA98, TA100, TA1535, TA1537; *E. coli* strain WP2uvrA) PMRA #1941330	Negative
METABOLITE X11721061	
Acute Oral Toxicity Fischer 344 rat PMRA #1941323	Female LD_{50} (♀) = 2000 mg/kg bw Low toxicity
28-Day Dietary Fischer 344 rat PMRA #1941325	NOAEL = 236/244 mg/kg bw/day (♂/♀) LOAEL = 622/649 mg/kg bw/day, based on ↓ fc (♂ & ♀); ↑ liver wt, ↑cholesterol (♂)
In vitro Bacterial Gene Mutation Assay(*S. typhimurium* strains TA98, TA100, TA1535, TA1537; *E. coli* strain WP2uvrA) PMRA #1941326	Negative
In vitro Mammalian Gene Mutation Assay (Chinese hamster ovary cells) PMRA #1941328	Negative
In vitro Mammalian Gene Mutation Assay (primary rat lymphocytes) PMRA #1941327	Negative
METABOLITE X1157947	
Acute Oral Toxicity Fischer 344 rat PMRA #1941331	LD_{50} (♀) >2000 mg/kg bw Low toxicity

In vitro Bacterial Gene Mutation Assay (*S. typhimurium* strains TA98, TA100, TA1535, TA1537; *E. coli* strain WP2uvrA) PMRA #1941332	Negative
In vitro Mammalian Gene Mutation Assay (primary rat lymphocytes) PMRA #1999138	Negative
In vitro Mammalian Gene Mutation Assay (Chinese hamster ovary cells) PMRA #1999139	Negative

Table 4 Toxicity Profile of Transform WG Insecticide and Closer Insecticide
(Effects are known or assumed to occur in both sexes unless otherwise noted)

Study Type / Animal / PMRA #	Study Results
Transform WG Insecticide	
Acute Oral Toxicity Fischer 344 rat PMRA #1941093	LD_{50} > 2000 mg/kg bw Low toxicity
Acute Dermal Toxicity Fischer 344 rat PMRA #1941094	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Inhalation Toxicity (nose only) Fischer 344 rat PMRA #1941095	LC_{50} > 5.35 mg/L Low toxicity
Dermal Irritation NZW rabbit PMRA #1941096	MAS = 0.4 MIS = 1.0 observed at 1 hour Minimally irritating
Eye Irritation NZW rabbit PMRA #1941097	MAS = 7.4, MIS = 27 at 1 hour, irritation persisted to day 7 in one animal Moderately irritating
Dermal Sensitization (LLNA)	Not a skin sensitizer

CBA/J mouse PMRA #1941098	
Closer Insecticide	
Acute Oral Toxicity Fischer 344 rat PMRA #1941141	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Dermal Toxicity Fischer 344 rat PMRA #1941142	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Inhalation Toxicity PMRA #1941143, 2024787	Respirable particles could not be generated Considered to be of low toxicity
Dermal Irritation NZW rabbit PMRA #1941144	MAS = 0 MIS = 0.3 observed at 1 hour Non-irritating
Eye Irritation NZW rabbit PMRA #1941145	MAS = 1.9 MIS = 10 observed at 1 hour Minimally irritating
Dermal Sensitization (LLNA) CBA/J mouse PMRA #1941146	Not a skin sensitizer

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Sulfoxaflor

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or Target MOE[1]
Acute dietary – general population	Acute oral neurotoxicity study in the rat	NOAEL = 25 mg/kg bw Reduced motor activity	100
	ARfD (general population) = 0.25 mg/kg bw		
Acute dietary – females 13-49 years of age	Developmental neurotoxicity study in the rat	NOAEL = 1.9 mg/kg bw Decreased neonatal survival	300[2]
	ARfD (females 13-49 years) = 0.006 mg/kg bw		

Chronic dietary – general population	Two-year chronic dietary study in the rat	NOAEL = 1.04 mg/kg bw/day Decreased food consumption, increased liver and testes weights, decreased epididymidal weight, bilateral atrophy of the seminiferous tubule, decreased spermatic elements	100
	ADI (general population) = 0.01 mg/kg bw/day		
Chronic dietary – females 13-49 years of age	Developmental neurotoxicity study in the rat	NOAEL = 1.9 mg/kg bw/day Decreased neonatal survival	300[2]
	ADI (females 13-49 years) = 0.006 mg/kg bw/day		
Short- to long-term dermal[3] and inhalation[4]	Developmental neurotoxicity study in the rat	NOAEL = 1.9 mg/kg bw/day Decreased neonatal survival	300[2]
Aggregate ("pick your own")	Developmental neurotoxicity study in the rat	NOAEL = 1.9 mg/kg bw/day Decreased neonatal survival	300[2]
Cancer	Evidence of liver tumours in rats and mice (not relevant to humans) and Leydig cell tumours in rats (low level of concern to humans). Equivocal increase in preputial gland carcinomas in rats. Endpoints selected for non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of sulfoxaflor.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.
[2] For endpoints based on the finding of reduced neonatal survival in rats, the standard 10-fold uncertainty factor for interspecies extrapolation was reduced to 3-fold. This was based on available evidence indicating that humans may be less sensitive than rats to sulfoxaflor-mediated toxicity stemming from interaction with the nicotinic acetylcholine receptor in muscle, which likely plays a role in the neonatal mortality observed in rats.
[3] Since an oral NOAEL was selected, a dermal absorption factor of 4% was used in a route-to-route extrapolation.
[4] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to route extrapolation.

Table 6 Mixer/Loader/Applicator Exposure Estimates and MOE for Transform WG Insecticide

Mixer, Loader, and Applicator	Crop	Mixer/Loader unit exposure [A] (µg/kg a.i.)		Amount of active handled per day (kg a.i. /day)	Applicator Equipment	Applicator unit exposure [A] (µg/ kg a.i.)		Combined Mixer/Loader and Applicator Exposure [B] (mg/kg bw /day)	MOE [C]
		Dermal	Inhalation			Dermal	Inhalation		
Farmer	wheat, barley, canola	163.77	1.02	5.35	groundboom, open-cab	32.98	0.96	0.000753	2520
Custom applicator		163.77	1.02	18	groundboom, open-cab	32.98	0.96	0.00253	751
Farmer, and Custom applicator	wheat, barley, canola	91.94	1.02	20	aerial; fixed or rotary wing aircraft	N/A		0.00134	1420

		N/A	20		9.66	0.07	0.000130	14600

A. Unit exposures from Canadian PHED tables (2006)
B. Exposure Estimate = PHED Unit Exposure (µg/kg a.i. handled) × Amount of a.i. handled ((kg a.i./day) × Absorption Factor × 0.001(mg/µg)
bw (70kg)

Where, Absorption Factor = 4% for dermal route; 100% for inhalation route
Combined Mixer/Loader and Applicator is the sum of exposures from the dermal and inhalation routes

C. MOE = NOAEL (mg/kg bw/d)
Exposure estimate (mg/kg bw/day)

Where, NOAEL = 1.9 mg/kg bw/day; target MOE = 300

Table 7 Mixer/Loader/Applicator Exposure Estimates and MOE for Closer Insecticide

Mixer, Loader, and Applicator	Crop	Mixer/Loader unit exposure [A] (µg/kg a.i.)		Amount of active handled per day (kg a.i./day)	Applicator Equipment	Applicator unit exposure [A] (µg/ kg a.i.)		Combined Mixer/Loader and Applicator Exposure [B] (mg/kg bw/day)	MOE [C]
		Dermal	Inhalation			Dermal	Inhalation		
Farmer	root and tuber (CG1, including potato)	51.14	1.6	3.852	groundboom, open-cab	32.98	0.96	0.000326	5830
Custom applicator	root and tuber (CG1, including potato)	51.14	1.6	12.96	groundboom, open-cab	32.98	0.96	0.0011	1730
Farmer, and Custom applicator	potato	51.14	1.6	14.4	mixing and loading for aerial application	N/A	N/A	0.000750	2530
	potato	N/A	N/A	14.4	fixed or rotary wing aircraft	9.66	0.07	0.0000939	20200
	pome, stone fruits, nut trees, grapes	51.14	1.6	1.92	airblast, open cab	828.22	5.8	0.00117	1630
	brassica and leafy vegetables	51.14	1.6	0.936	groundboom, open-cab	32.98	0.96	0.0000792	24000

A. Exposure Estimate = PHED Unit Exposure (µg a.i./kg a.i. handled) × Amount of a.i. handled ((kg a.i./day) × Absorption Factor × 0.001(mg/µg)
bw (70kg)

Where, Absorption Factor = 4% for dermal route; 100% for inhalation route
Combined Mixer/Loader and Applicator is the sum of exposures from the dermal and inhalation routes

B. MOE = NOAEL (mg/kg bw/d)

Exposure estimate (mg/kg bw/day)

Where, NOAEL = 1.9 mg/kg bw/day; target MOE = 300

Table 8 Postapplication Estimates of Dermal Exposure for worker entry into crops treated with Transform WG Insecticide

Crop	Dislodgeable foliar residue [A] ($\mu g/cm^2$)	Tasks with maximum transfer coefficients [B]	Dermal Exposure [C] (mg/kg bw/day)	Margin of Exposure [D]
Wheat, barley, canola	0.119	scouting, irrigation	0.000598	3180

A. Dislodgeable foliar residue at 0 days after last application
B. From Agricultural Re-entry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.
C. Dermal Exposure = Dislodgeable foliar residue × task-specific transfer coefficient (cm^2/hour) × 8 hours worked/day × 4% dermal absorption × 0.001 mg/µg / 70 kg body weight;
D. Margin of Exposure (MOE) = NOAEL/ Dermal Exposure; NOAEL is 1.9 mg/kg bw/day; target MOE is 300

Table 9 Postapplication Estimates of Dermal Exposure for worker entry into crops treated with Closer Insecticide

Crop	Dislodgeable foliar residue [A] ($\mu g/cm^2$)	Tasks with maximum transfer coefficients [B]	Dermal Exposure [C] (mg/kg bw/day)	Margin of Exposure [D]
root and tuber (CG1, including potato)	0.1064	Irrigation	0.000535	3550
pome and stone fruits, and nut trees (including pistachio)	0.2838	Thinning	0.00389	488
leafy vegetables	0.1064	Hand harvest, tying, pinching, pruning, training, irrigation	0.000535	3550
brassica vegetables	0.115	Hand harvesting	0.00271	702
grapes	0.0710	Cane turning and girdling	0.00626	303

A. Dislodgeable foliar residue at 0 days after last application
B. From Agricultural Re-entry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.
C. Dermal Exposure = Dislodgeable foliar residue × task-specific transfer coefficient (cm^2/hour) × 8 hours worked/day × 4% dermal absorption × 0.001 mg/µg / 70 kg body weight;
D. Margin of Exposure (MOE) = NOAEL/ Dermal Exposure; NOAEL is 1.9 mg/kg bw/day; target MOE is

Table 10 Acute aggregate (dermal and dietary) pick-your-own assessment of peaches (representing pome fruit, stone fruit, and strawberry) for females 13-49 years of age.

Sub-population (age range)	Acute Dermal [A] Margin of Exposure	Acute Dietary [B] Margin of Exposure	Total Aggregate Margin of Exposure [C, D] (target = 300)
Females (13-49 yrs)	8164	1324	1139

A. Dermal exposure risk estimate from Equation 6;
B. From the Dietary Exposure Assessment, 95th percentile user-only, maximum residue value, fresh commodity-only, commodity-specific (peaches) value presented as a one-day exposure (mg/kg bw/day); females 13-49 yrs of age;
C. The oral NOAEL of 1.9 mg/kg bw/day, from the rat oral developmental study, was determined to be most protective of the acute dietary and

acute-term dermal exposures. The target Margin of Exposure is 300.
D. Aggregated Margin of Exposure calculated according to Science Policy Notice SPN2003-04.

Table 11 Residential Intermediate-term Aggregate Assessment for Treated Fruit Trees

Sub-Population (age range)	Dislodgeable foliar residue [A] ($\mu g/cm^2$)	Transfer coefficient [B]	Dermal Margin of Exposure [C]	Chronic (dietary + drinking water) Margin of Exposure [D]	Aggregated Margin of Exposure [E, F]
Females (13-49 yrs)	0.2838	Hand harvesting	11700	983	907

A. Dislodgeable foliar residue based on contacting treated trees on day 0 after the 2nd application;
B. Transfer coefficient for hand harvesting orchard trees represents dermal contact activities with treated fruit trees in a residential scenario; value from Agricultural Re-entry Task Force (ARTF). 2008. Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients.
C. Dermal Exposure = (Dislodgeable foliar residue × Transfer coefficient × Exposure time × Dermal absorption × 0.001mg/µg)/Body weight;
D. From dietary exposure assessment;
E. Margin of Exposure (MOE) = NOAEL/Exposure; NOAEL of 1.9 mg/kg bw/day, from the DNT study, was determined to be most appropriate for short- to intermediate-term dermal exposures; target MOE = 300;
F. MOE calculated according to Science Policy Notice SPN2003-04.

Table 12 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN RICE			**PMRA # 1941343**
Radiolabel Position	^{14}C- Sulfoxaflor		
Test Site	Outdoors		
Treatment	Foliar		
Rate	578 g a.i./ha (227, 205, 145 g a.i./ha)		
End-use product	GF-2032 SC formulation		
Preharvest interval	14 days after first application for immature plants; 14 days after final application for mature rice		
Matrix	**PHI (days)**	**TRR (ppm)**	
Immature plants	14 (after 1st treatment)	2.841	
Mature rice straw	14 (after last treatment)	5.627	
Mature rice hulls	14 (after last treatment)	3.669	
Mature white rice	14 (after last treatment)	0.243	
Matrix	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Immature plants	Sulfoxaflor		X11719474, glucose conjugate of X11721061, X11721061
Mature straw	Sulfoxaflor		X11719474, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061
Mature hulls	Sulfoxaflor		X11719474, glucose conjugate of X11721061, X11721061
Mature white rice	Sulfoxaflor		X11719474, glucose conjugate of X11721061, X11721061
NATURE OF THE RESIDUE IN PEAS			**PMRA # 1941341**
Radiolabel Position	^{14}C- Sulfoxaflor		
Test Site	Outdoors		
Treatment	Foliar		
Rate	601 g a.i./ha (197, 201, 203 g a.i./ha)		

End-use product	GF-2032 SC formulation		
Preharvest interval	14 days after first and second applications for immature plants; 14 days after final application for mature pods and vines		
Matrix	**PHI (days)**	**TRR (ppm)**	
Immature plants	14 (after 1st treatment)	0.348	
	14 (after 2nd treatment)	0.592	
Mature pods	14 (after last treatment)	1.046	
Mature vines	14 (after last treatment)	5.478	
Matrix	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Immature plants (14 days after 1st and 2nd treatments)	Sulfoxaflor, X11719474, glucose conjugate of X11721061		glucose plus malonyl conjugate of X11721061, X11721061
Mature pods	Sulfoxaflor, X11719474, glucose conjugate of X11721061		glucose plus malonyl conjugate of X11721061, X11721061
Mature vines	Sulfoxaflor, X11719474		glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061
NATURE OF THE RESIDUE IN LETTUCE			**PMRA # 1941342**
Radiolabel Position	^{14}C- Sulfoxaflor		
Test Site	Outdoors		
Treatment	Foliar		
Rate	599 g a.i./ha (195, 199, 205 g a.i./ha)		
End-use product	GF-2032 SC formulation		
Preharvest interval	14 days after first application for immature plants; 7 days after final application for mature lettuce		
Matrix	**PHI (days)**	**TRR (ppm)**	
Immature plants	14 (after 1st treatment)	0.182	
Mature lettuce	7 (after last treatment)	4.393	
Matrix	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Immature plants (14 days after 1st)	Sulfoxaflor, X11719474,		Glucose plus malonyl conjugate of X11721061, glucose conjugate of X11721061, X11721061, X11579457
Mature lettuce	Sulfoxaflor, X11719474,		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
NATURE OF THE RESIDUE IN TOMATO			**PMRA # 1941340**
Radiolabel Position	^{14}C- Sulfoxaflor		
Test Site	Outdoors		
Treatment	Foliar		
Rate	618 g a.i./ha (213, 202, 129, 74 g a.i./ha)		
End-use product	GF-2032 SC formulation		
Preharvest interval	14 days after 1st and 2nd applications for immature plants; 1, 7, 14 days after final application for ripe tomatoes; 14 days for mature vines		
Matrix	**PHI (days)**	**TRR (ppm)**	
Immature plants	14 (after 1st treatment)	0.578	
	14 (after 2nd application)	0.799	
Ripe tomatoes	1	0.038	
	7	0.033	
	14	0.030	
Mature vines	14	1.344	
Matrix	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**

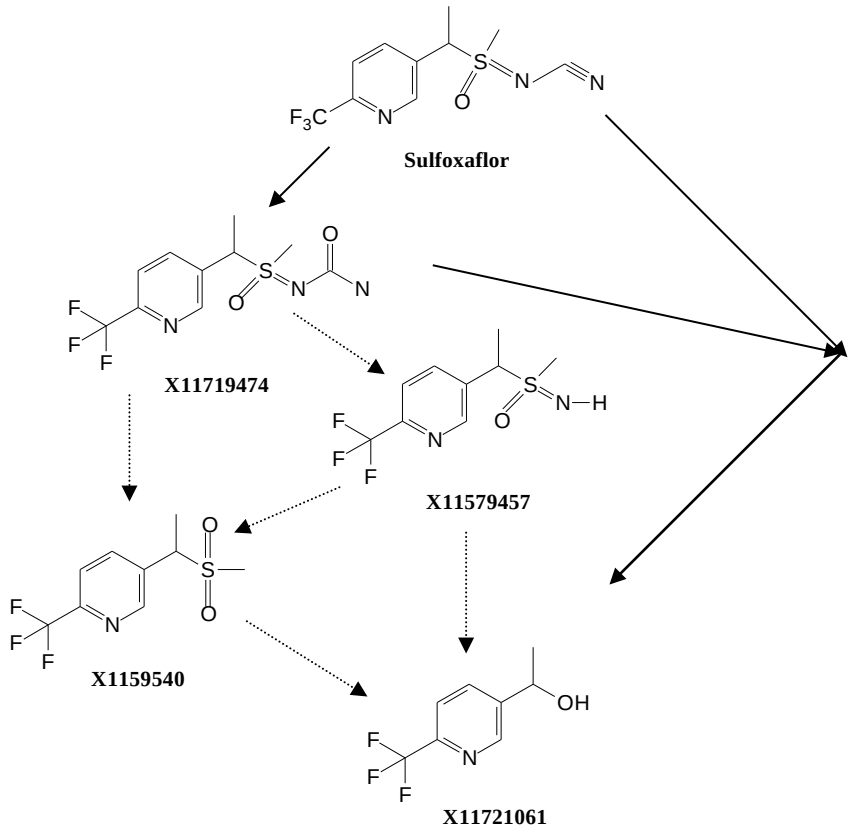
Immature plants (14 days after 1st)	Sulfoxaflor, X11719474, glucose plus malonyl conjugate of X11721061	Glucose conjugate of X11721061, X11721061
Immature plants (14 days after 2nd)	Sulfoxaflor, X11719474	Glucose conjugate of X11721061, X11721061, glucose plus malonyl conjugate of X11721061
Ripe tomatoes (1, 7, and 14 day PHI's)	Sulfoxaflor, X11719474, glucose plus malonyl conjugate of X11721061	Glucose conjugate of X11721061
Mature vines	Sulfoxaflor, X11719474	Glucose conjugate of X11721061, X11721061, glucose plus malonyl conjugate of X11721061

CONFINED ACCUMULATION IN ROTATIONAL CROPS – RADISH, LETTUCE, WHEAT	**PMRA # 2035844**
Radiolabel Position	^{14}C- Sulfoxaflor
Test site	Outdoors
Formulation used for trial	-
Application rate and timing	600 g a.i./ha; Planting of rotational crops at 30, 120, 365 day plant-back intervals (PBI's)

Metabolites Identified			
Matrix	**PBI (days)**	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Immature radish tops	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11579457, X11519540
	365		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
Mature radish tops	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11579457, X11519540
	365		Sulfoxaflor, glucose conjugate of X11721061, X11721061, X11579457, X11519540
Mature radish roots	30	X11719474	Glucose plus malonyl conjugate of X11721061, X11579457, X11519540
	120		X11579457
	365		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11579457, X11519540
Immature lettuce	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11579457, X11519540
	365		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540

Mature lettuce	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	365		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
Wheat Forage	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	365		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
Wheat Hay	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	365		Glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
Wheat straw	30	X11719474	Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	120		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
	365		Sulfoxaflor, glucose conjugate of X11721061, glucose plus malonyl conjugate of X11721061, X11721061, X11579457, X11519540
Wheat grain	30	X11719474	-
	120		-
	365		X11579457

Proposed metabolic scheme in primary crops and in rotational crops



glucose conjugate of X11721061

glucose plus malonyl conjugate of X11721061

Natural incorporation

Metabolism of sulfoxaflor proceeds through oxidation of the cyano-carbon to X11719474. Potential pathways could proceed from either sulfoxaflor or X11719474 or both directly to X11721061. It was postulated that rearrangement and loss of isocyanate of X11719474 could give rise to X11579457, which is oxidized to X11519540, with final loss of sulfone group to produce X11711061. X11721061 is then conjugated with glucose, which in turn may be conjugated with a malonyl group.

NATURE OF THE RESIDUE IN LAYING HEN	**PMRA # 1941344**

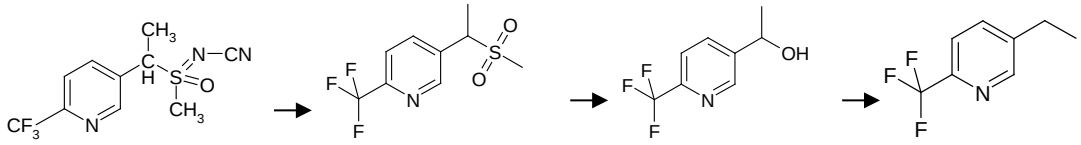
Hens were fed a nominal dose of 10 mg/kg feed/day of **^{14}C- Sulfoxaflor** for 7 days. Eggs were collected twice per day, and liver, muscle (breast and leg), fat, and skin with subcutaneous fat were collected at sacrifice.

Matrices	**% of Administered Dose**
Excreta	37.1
Cage rinse	5.5
Muscle-breast	0.13
Muscle-leg	0.14
Fat	0.011
Skin with subcutaneous fat	0.047

Liver		0.065
Eggs		0.14
Matrix	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Excreta	Sulfoxaflor	-
Muscle-breast	Sulfoxaflor	X11519540
Muscle-leg	Sulfoxaflor	X11519540
Fat	Sulfoxaflor	X11519540
Skin with subcutaneous fat	Sulfoxaflor	-
Liver	Sulfoxaflor	X11519540, X11596066
Eggs	Sulfoxaflor	X11519540
NATURE OF THE RESIDUE IN LACTATING GOAT		**PMRA # 1941346**
One lactating goat was fed a nominal dose of 10 mg/kg feed/day of **^{14}C- Sulfoxaflor** for 5 days. Milk was collected twice a day, and muscle (loin and flank), liver, kidney, fat (subcutaneous, omental, renal), and the gastrointestinal tract were collected at sacrifice.		
Matrices		**% of Administered Dose**
Urine		41.00
Feces		13.28
Cage wash		0.35
Muscle-loin		0.24
Muscle-flank		0.11
Fat-subcutaneous		0.08
Fat-omental		0.13
Fat-renal		0.14
Kidney		0.09
Liver		0.55
Stomach		0.94
Gastrointestinal-tract contents		12.16
Small intestine		0.19
Large intestine		0.24
Milk		3.69
Matrix	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Milk	Sulfoxaflor	X11519540
Muscle-Loin	Sulfoxaflor	-
Muscle-flank	Sulfoxaflor	-
Liver	Sulfoxaflor, X11596066	X11721061, X11519540
Kidney	Sulfoxaflor	X11519540
Fat-subcutaneous	Sulfoxaflor	X11519540
Fat-omental	Sulfoxaflor	-
Fat-renal	Sulfoxaflor	X11519540
Urine	Sulfoxaflor	X11721061
Feces	Sulfoxaflor	-
NATURE OF THE RESIDUE IN LAYING HEN		**PMRA # 1941345**
Hens were fed a nominal dose of 10 mg/kg feed/day of **^{14}C- X11719474** for 7 days. Eggs were collected twice per day, and liver, muscle (breast and leg), fat, and skin with subcutaneous fat were collected at sacrifice.		
Matrices		**% of Administered Dose**
Excreta		92
Muscle-breast		0.565
Muscle-leg		0.570
Fat		0.016

Skin with subcutaneous fat		0.129
Liver		0.116
Eggs		0.95
Matrix	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Muscle-breast	X11719474	-
Muscle-leg	X11719474	-
Fat	X11719474	-
Skin with subcutaneous fat	X11719474	-
Liver	X11719474	-
Eggs	X11719474	-
NATURE OF THE RESIDUE IN LACTATING GOAT		**PMRA # 1941347**
One lactating goat was fed a nominal dose of 10 mg/kg feed/day of **^{14}C- X11719474** for 5 days. Milk was collected twice a day, and muscle (loin and flank), liver, kidney, fat (subcutaneous, omental, renal), and the gastrointestinal tract were collected at sacrifice.		
Matrices		**% of Administered Dose**
Urine		34.76
Feces		4.42
Cage wash		2.77
Muscle-loin		0.17
Muscle-flank		0.11
Fat-subcutaneous		0.01
Fat-omental		0.03
Fat-renal		0.01
Kidney		0.06
Liver		0.26
Gastrointestinal-tract		1.98
Gastrointestinal-contents		12.94
Milk		1.14
Matrix	**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Milk	X11719474	-
Muscle-Loin	X11719474	-
Muscle-flank	X11719474	-
Liver	X11719474	-
Kidney	X11719474	-
Fat-subcutaneous	X11719474	-
Fat-omental	X11719474	-
Fat-renal	X11719474	-
Urine	X11719474	-

Proposed Metabolic Scheme for Sulfoxaflor in Livestock



XDE-208 X11519540 X11721061 X11596066

The major plant metabolite, X11719474 is not metabolized in livestock.

STORAGE STABILITY	**PMRA # 1999149, 1941338, 1941339**

Untreated crop samples (dry, high water content, high fat content, and high acid content) were spiked separately with sulfoxaflor, X11719474, and X11721061 each at 0.10 ppm and stored frozen at -20°C for 680 days. Samples were analyzed at storage intervals of 0, 30, 60, 182, 288, 375, 548, and 680 days. The results indicate that sulfoxaflor, X11719474, and X11721061 are stable in/on orange whole fruit, peach whole fruit, wheat grain, and soybean seed at -20°C for 680 days.

Control samples of poultry commodities were separately spiked with sulfoxaflor, X11719474, and X11721061 each at 0.10 ppm and stored at -18°C for 64 days. Samples were analyzed at storage intervals of 0, 21, 44, and 64 days. Results show that sulfoxaflor, X11719474, and X11721061 are stable in/on poultry muscle, liver, fat, and eggs stored at -18°C for 64 days.

Control samples of ruminant commodities were separately spiked with sulfoxaflor, X11719474, and X11721061 each at 0.10 ppm and stored at -18°C for 56 days. Samples were analyzed at storage intervals of 0, 21, 44, and 56 days. Results show that sulfoxaflor, X11719474, and X11721061 are stable at -18°C in/on milk, skim milk, cream, muscle, liver, kidney, and fat for 56 days.

The results detailed above fully support the crop field trials and the livestock feeding studies for sulfoxaflor.

RESIDUE STUDIES

As part of this Global Joint Review, crop trials from the US, the EU (Northern Zone (NZ) and Southern Zone (SZ)), Australia, New Zealand, Brazil, and Canada for various fruits, vegetables, oilseeds, cereal grains, tree nuts, and legumes were submitted.

Where NAFTA trials were submitted, the location of trials did not meet the guideline requirements, but since other trials were submitted from international regions, the number of trials was exceeded.

For the residue decline trials, residues of sulfoxaflor generally declined with increasing PHI.

ROOT AND TUBER VEGETABLES, CG 1 (CDN GAP: 72 g a.i./ha, 7 day PHI)		**PMRA # 1941424, 1941423, 1999130, 1999131, 1941371, 1941372, 1941434, 1941433**
Potato trials:	**6 NAFTA (Regions 1, 2, 5, 9, 10, and 11); 8 EU (4NZ, 4SZ); 3 residue decline studies**	
Radish trials:	**6 NAFTA (Regions 1, 3, 5, and 10); 1 residue decline trial**	
Carrot trials:	**4 NAFTA (Regions 3, 5, 6, and 10); 8 EU (4NZ, 4SZ); 3 residue decline**	
Sugar beet trials:	**5 NAFTA (Regions 5, 7, 9, 10, and 11); 8 EU (4NZ, 4 SZ); 3 residue decline**	

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Potatoes	399-420	6-8	36	<0.010	<0.010	<0.010	<0.010	<0.010	-
Radish	404-407	7	18	<0.010	0.016	0.012	0.010	0.011	0.002
Carrots	401-423	7	24	<0.010	0.032	0.031	0.010	0.015	0.008
Sugar beets	394-420	7	26	<0.010	0.025	0.023	0.010	0.011	0.004

LEAVES OF ROOT AND TUBER VEGETABLES, CG 2 (CDN GAP: 72 g a.i./ha, 7 day PHI)									**PMRA # 1999131, 1941371, 1941434, 1941433**
Carrot top trials:	**4 NAFTA (Regions 3, 5, 6, and 10); 8 EU (4NZ, 4SZ); 3 residue decline**								
Radish top trials:	**6 NAFTA (Regions 1, 3, 5, and 10); 1 residue decline trial**								
Sugarbeet top trials:	**5 NAFTA (Regions 5, 7, 9, 10, and 11); 8 EU (4NZ, 4SZ); 3 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Carrot tops	401-423	7	8	0.311	2.228	2.041	0.515	0.850	0.750
Radish tops	404-407	7	18	0.183	0.506	0.478	0.266	0.321	0.108
Sugarbeet tops	394-420	7	25	0.141	1.685	1.615	0.716	0.744	0.452
BULB VEGETABLES, CG 3 (US GAP: 298 g a.i./ha, 7 day PHI)									**PMRA # 1941405, 1941406**
Green onion trials:	**6 NAFTA (Regions 1, 2, 5, 6, 10, and 12); 1 residue decline**								
Dry onion trials:	**6 NAFTA (Regions 1, 6, 8, 10, 11); 1 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Green onions	404-410	7-8	12	<0.010	0.440	0.387	0.105	0.132	0.130
Dry onions	400-409	7	12	<0.010	<0.010	<0.010	<0.010	<0.010	-
LEAFY VEGETABLES, EXCEPT BRASSICA, CG 4 (CDN GAP: 72 g a.i./ha, 3 day PHI)									**PMRA # 1941375, 1941392, 1941394, 1999120, 1941393, 1941396, 1941398, 1999121, 1941397, 1941429, 141428**
Celery trials:	**6 NAFTA (Regions 3, 5, and 10); 1 residue decline**								
Head lettuce trials:	**4 NAFTA (Regions 2 and 10); 4 Australia; 6 EU (3 NZ; 3 SZ); 5 residue decline**								
Leaf lettuce trials:	**8 NAFTA (Regions 1, 2, 3, and 10); 4 Australia; 6 EU (3 NZ; 3 SZ); 5 residue decline**								
Spinach trials:	**6 NAFTA (Regions 1, 2, 6, 9, and 10); 1 Australia; 2 residue decline**								
Swiss chard trials:	**1 Australia; no residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Celery	404-405	2-3	24	0.058	0.804	0.771	0.143	0.229	0.235
Head lettuce	369-436	2-3	27	<0.010	0.528	0.494	0.040	0.148	0.177
Leaf lettuce	384-424	2-3	42	0.050	3.068	2.744	0.546	0.722	0.615
Spinach	404-418	3	14	0.039	3.256	2.863	1.038	1.145	0.975
Swiss Chard	385	3	2	0.53	0.66	-	-	0.60	-

BRASSICA (COLE) LEAFY VEGETABLES, CG 5 (CDN GAP: 72 g a.i./ha, 3 day PHI)		**PMRA # 1941361, 1941364, 1941360, 1999111, 1941362, 1941363, 1941364, 1999124, 1999113, 1941373, 1941374**
Broccoli trials:	**6 NAFTA (Regions 6, 10, and 12); 2 Australia; 7 EU (3 NZ; 4 SZ); 6 residue decline**	
Cabbage trials:	**6 NAFTA (Regions 6, 10, and 12); 2 Australia; 6 EU (4 NZ; 2 SZ); 4 residue decline**	
Mustard green trials:	**8 NAFTA (Regions 2, 3, 4, 5, 6, and 10); 1 residue decline**	
Cauliflower trials:	**2 Australia; 8 EU (3 NZ; 5 SZ); 5 residue decline**	

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Broccoli	390-426	3	29	<0.010	1.600	1.584	0.070	0.201	0.395
Cabbage	383-430	3	28	<0.010	0.400	0.377	0.058	0.092	0.103
Mustard greens	404	2-4	16	0.278	1.167	0.899	0.667	0.680	0.234
Cauliflower	360-419	3-4	20	<0.010	0.070	0.055	0.014	0.020	0.015

FRUITING VEGETABLES, CG 8-09 (US GAP: 298 g a.i./ha, 1 day PHI)		**PMRA # 1941439, 1941436, 1941438, 1941435, 1999132, 1999133, 1999134, 1941437, 1999135, 1941421, 1999129, 1941420, 1999128, 1999127**
Tomato trials:	**7 NAFTA trials (Regions 1, 2, 3, 5, and 10); 6 Australia; 22 EU (10 NZ; 12 SZ); 18 residue decline**	
Pepper trials:	**8 NAFTA (Regions 2, 3, 5, 8, and 10); 6 Australia; 6 EU (6 SZ); 9 residue decline**	

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Tomato	356-430	1	88	<0.010	0.762	0.602	0.051	0.091	0.123
Peppers (bell)	361-412	1	24	<0.010	0.284	0.256	0.092	0.106	0.095
Peppers (non-bell)	385-481	1	15	0.017	0.46	0.44	0.090	0.156	0.145
Peppers (bell and non-bell)	361-481	1	39	<0.010	0.460	0.440	0.090	0.125	0.118

CUCURBIT VEGETABLES, CG 9 (US GAP: 298 g a.i./ha, 1 day PHI)		**PMRA # 1941430, 1941387, 1941386, 1999116, 1941385, 1941399, 1941401, 1999123, 1941400**
Squash trials:	**6 NAFTA (Regions 1, 2, 3, 5, and 10); 1 residue decline**	
Cucumber trials:	**6 NAFTA (Regions 2, 3, 5, and 6); 6 residue decline**	
Melon trials:	**6 NAFTA (Regions 2, 5, 6, and 10); 4 Brazil; 6 EU (6 SZ); 6 residue decline**	

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Squash (summer, including zucchini)	381-412	1	10	<0.010	0.11	0.10	0.01	0.03	0.04
Squash (winter)	404-407	1	6	<0.010	0.10	0.018	0.011	0.013	0.004
Squash (all)	381-412	1	16	<0.010	0.11	0.10	0.01	0.024	0.03
Cucumber	399-420	1	32	<0.010	0.172	0.152	0.042	0.056	0.040
Melons	400-421	1	27	<0.010	0.304	0.266	0.028	0.050	0.068

CITRUS FRUIT, CG 10 (US GAP: 298 g a.i./ha, 1 day PHI; AU GAP 200 g a.i./ha, 1 day PHI)									**PMRA # 1941408, 1941409, 1941407, 1941410, 1999125, 1999118**
Orange trials:	**12 NAFTA (Regions 3, 6, and 10); 10 Australia; 4 Brazil; 4 residue decline**								
Grapefruit trials:	**8 NAFTA (Regions 3, 6, and 10); 3 residue decline**								
Lemon trials:	**6 NAFTA (Regions 3and 10); 3 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Oranges	296-413	1	61	0.037	0.460	0.435	0.114	0.168	0.120
Grapefruit	404	1	16	<0.010	0.186	0.112	0.014	0.041	0.056
Lemon	404	1	12	0.025	0.317	0.293	0.050	0.098	0.100
POME FRUIT, CG 11 (CDN GAP: 192 g a.i./ha, 7 day PHI)									**PMRA # 1941349, 1941351, 1941350, 1999105, 1941418, 1941417, 1999126, 1941416**
Apple trials:	**12 NAFTA (Regions 1, 2, 5, 9, 10 and 11); 2 Australia; 4 New Zealand; 4 EU (2 NZ; 2 SZ); 5 residue decline**								
Pear trials:	**8 NAFTA (Regions 1, 10, and 11); 2 Australian; 6 EU (3 NZ; 3 SZ); 5 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Apples	325-420	6-8	56	<0.010	0.297	0.266	0.070	0.086	0.057
Pears	314-426	7-8	32	0.044	0.267	0.261	0.142	0.146	0.063
STONE FRUIT, CG 12 (CDN GAP: 192 g a.i./ha, 7 day PHI)									**PMRA # 1941412, 1941413, 1941411, 1941414, 1941422, 1941403, 1941376, 1941378, 1999114**
Peach trials:	**6 NAFTA (Regions 1, 2, 5, 6, and 10); 7 Australia; 1 New Zealand; 6 EU (2 NZ; 4 SZ); 5 residue decline**								
Plum trials:	**6 NAFTA (Regions 5, 10, and 12); 1 Australia; 1 residue decline**								
Cherry trials:	**6 NAFTA (Regions1, 5, and 10); 1 Australia, 2 New Zealand; 6 EU (3 NZ; 3 SZ); 4 residue decline**								
Apricot trials:	**1 Australia; 1 New Zealand; 1 residue decline**								
Nectarine trials:	**4 Australia; 1 New Zealand; 1 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Peaches	380-419	6-8	48	<0.01	0.636	0.541	0.121	0.164	0.118
Plums	385-415	7	26	0.014	0.362	0.285	0.060	0.093	0.093
Cherries	379-410	7	32	0.26	1.6	1.49	0.820	0.824	0.379
Apricots	379-388	7	8	0.13	0.45	0.39	0.16	0.21	0.12
Nectarine	388-394	7	18	0.074	0.247	0.232	0.150	0.154	0.045
TREE NUTS, CG 14 (CDN GAP: 192 g a.i./ha, 7 day PHI)									**PMRA # 1941348, 1941419**
Almond trials:	**6 NAFTA (Region10); 1 residue decline**								
Pecan trials:	**6 NAFTA (Regions 2, 4, 6, and 8); 1 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Almonds	398-411	7	12	<0.010	0.013	0.013	0.010	0.010	0.001
Pecans	404-407	7	12	<0.010	<0.010	<0.010	<0.010	<0.010	-

SMALL FRUIT CLIMBING, EXCEPT FUZZY KIWI FRUIT, CSG 13-07F (CAN GAP: 192 g a.i./ha, 7 day PHI)									**PMRA # 1941390, 1941391, 1941389, 1999117, 1941388**
Grape trials:	**9 NAFTA (Regions 1, 10, 11, and 12); 9 Australia; 12 EU (6 NZ; 6 SZ); 7 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Grapes	310-438	7-8	64	<0.010	1.900	1.019	0.126	0.262	0.340
LOW GROWING BERRY, CSG 13-07G (US GAP: 298 g a.i./ha, 1 day PHI)									**PMRA # 1941432, 1941431**
Strawberry trials:	**9 NAFTA (Regions 1, 2, 3, 5, 10, and 12); 4 Australia; 3 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Sulfoxaflor									
Strawberries	381-414	1	26	0.020	0.500	0.490	0.184	0.182	0.109
RAPESEED, CSG 20A (CAN GAP: 100 g a.i./ha, 14 day PHI)									**PMRA # 1941370, 1941365, 1941368, 1999112, 1941367**
Canola seed trials:	**9 NAFTA (Regions 2, 5, 11, and 14); 4 Australia; 8 EU (5 NZ; 3 SZ); 6 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Canola	88-111	13-15	36	<0.010	0.224	0.215	0.042	0.054	0.050
COTTONSEED, CSG 20C (US GAP: 298 g a.i./ha, 14 day PHI)									**PMRA # 1941384, 1941379, 1941381, 1941383, 1999115, 1941380**
Cotton seed trials:	**6 NAFTA (Regions 2, 4, 6, 8, and 10); 4 Australia, 6 Brazil; 8 EU (8 SZ); 7 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Cottonseed	389-422	14-15	51	<0.010	0.182	0.176	0.017	0.034	0.037
BARLEY (CAN GAP: 100 g a.i./ha, 14 day PHI)									**PMRA # 1941355, 1941354, 1941353, 1941357, 1941356, 1999107, 1999108**
Barley trials:	**6 NAFTA (Regions 2, 5, 7, and 11); 4 Australia, 2 New Zealand; 15 EU (7 NZ: 8 SZ); 12 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Barley	94-108	12-17	50	<0.010	0.370	0.320	0.048	0.060	0.060
BEANS (US GAP: 298 g a.i./ha, 7 day PHI)									**PMRA # 1941358, 1941359, 1999109**
Dry bean trials:	**4 Brazil; 2 EU (1 NZ; 1 SZ); 2 residue decline**								
Edible podded bean trials:	**6 EU (3 NZ; 3 SZ); 4 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Dry beans	393-411	7	12	0.020	0.112	0.104	0.078	0.068	0.029
Edible podded succulent beans	395-419	7	12	0.024	2.019	1.938	0.104	0.422	0.716

SOYBEANS (US GAP: 298 g a.i./ha, 7 day PHI)									PMRA # 1941425, 1941426, 1941427
Soybean trials:	**15 NAFTA (Regions 2, 4, and 5); 4 Brazil; 4 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Soybean seed	400-416	6-8	44	<0.010	0.214	0.199	0.011	0.031	0.043

WHEAT (CAN GAP: 100 g a.i./ha, 14 day PHI)									PMRA # 1941355, 1941354, 1941353, 1941440, 1941443, 1941444, 1941441, 1941442
Wheat trials:	**10 NAFTA (Regions 2, 4, 5, 6, 7, 8, and 14); 5 Australia; 2 New Zealand; 4 Brazil; 16 EU (7 NZ; 9 SZ); 16 residue decline**								
Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Wheat	94-109	12-17	65	<0.010	0.067	0.056	0.012	0.018	0.012

FIELD ACCUMULATION IN ROTATIONAL CROPS	PMRA # 1999104

Limited field rotational crop data in/on a root crop (radish roots and tops), leafy vegetable (mustard green leaves), cereal grain (sorghum forage, stover, and grain), and grass (forage and hay) were generated from two field trials for sulfoxaflor. Rotational crops were planted after primary crops of spinach, carrot, or leaf lettuce, treated at 400 g a.i./ha, were harvested at 3 day PHI's. Rotational crops were planted at targeted PBIs of ~30, 90, 180, and 270-365 days.

In rotational crop commodities, residues of sulfoxaflor were generally <0.01 ppm at all PBIs. Metabolite X11719474 was identified as the predominant residue in most rotational crop commodities. In general, residues declined with increasing PBI, except in grass hay where residues increased slightly. Metabolite X11719474 was the only identified residue in radish roots where maximum residues ranged from 0.031-0.011 ppm from 30-180 day PBIs, but were <0.01 0.031 ppm by 295-361 day PBI.

Therefore, a 1 year PBI is necessary for sulfoxaflor use in Canada for crops not on the label.

PROCESSED FOOD AND FEED	PMRA # 1941407, 1941459, 1941446, 1941447, 1941448, 1941449, 1941450, 1941452, 1941453, 1941454, 1941455, 1941456, 1941457, 1941462, 1941463, 1941464, 1941465, 1941460, 1999137

Processed Commodity	Processing Factor-Sulfoxaflor
Apple	-
Washed apple	0.7X
Apple sauce	0.6X
Juice	0.4X
Wet pomace	1.1X
Dry pomace	4.2X
Canned apples	<0.03X
Dried apples	0.3X

Barley grain	-
Pearl barley	0.7X
Pot barley	0.9X
Bran	1.0X
Flour	0.8X
Cleaned barley	0.9X
Brewing malt	0.9X
Malt sprouts	1.3X
Beer	0.2X
Spent grains	0.2X
Brewer's yeast	0.1X
Cabbage	-
Inner leaves	0.1X
Outer (wrapper) leaves	1.8X
Cooked head	<0.1X
Cooking liquid	<0.1X
Sauer kraut	0.1X
Sauerkraut juice	0.1X
Canola seed	-
Cleaned seeds	1.1X
Meal	1.9X
Crude oil	<0.3X
Refined oil	<0.3X
Solvent extracted meal	2.2X
Carrot	-
Washed and peeled root	<1.0X
Cooked carrot	<1.0X
Cooking liquid	1.1X
Carrot juice	2.4X
Canned carrot	<1.0X
Cherries	-
Washed cherries	0.8X
Canned cherries	1.0X
Juice	0.9X
Jam	1.1X
Dried cherries	5.2X
Cotton seed	-
Aspirated grain fractions	23X
Delinted seed	1.0X
Hulls	1.8X
Meal	0.8X
Meal presscake	0.8X
Crude oil	<0.1X
Refined oil	<0.1X
Grape	-
Raisins	3.5X
Juice	0.7X
Wine bottled	0.7X
Pomace	1.0X
Head lettuce	-
Wrapper leaves	1.0X
Unwashed heads w/o wrapper leaves	0.6X
Washed heads	0.2X
Washings	0.1X

Leaf lettuce	-
Washed lettuce	0.7X
Washings	0.2X
Bulb onion	-
Peeled onion	- (residues were <LOQ)
Dried onion	- (residues were <LOQ)
Orange	-
Juice	<0.2X
Wet pulp	2.5X
Dried pulp	8.3X
Peel	9.1X
Oil	<0.2X
Marmalade	<0.2X
Canned slices	<0.2X
Potatoes	-
Washed potatoes	1.2X
Peeled potatoes	1.6X
Peel	1.8X
Potato flakes	2.5X
Microwaved potatoes	1.1X
Boiled potatoes	1.0X
Cooking water	<0.8X
Potato chips	2.1X
Dried potatoes	3.6X
French fries	1.6X
Soybeans	-
Aspirated grain fractions	95X
Meal	1.3X
Hulls	1.5X
Pressed cake	1.1X
Expeller crude oil	0.3X
Solvent extracted crude oil	0.3X
Refined oil	<0.1X
Strawberry	-
Washed strawberry	0.9X
Juice	0.3X
Canned strawberry	0.6X
Jam	0.4X
Sugar beet	-
Pulp	<0.8X
Press water	<0.8X
Raw juice	1.4X
Thin juice	1.1X
Lime sludge	<0.8X
Thick juice	4.7X
Raw sugar	1.8X
White sugar	<0.8X
Molasses	10X
Dried pulp	3.0X
Tomato	-
Washed and peeled	1.2X
Juice	1.0X
Canned	0.8X
Ketchup	2.1X
Puree	2.0X
Paste	4.4X

Wheat grain	-
Aspirated grain fraction	21X
Total bran	0.4X
Germ	0.5X
Bran	0.4X
Middlings	0.2X
Shorts	0.2X
Whole meal flour	0.2X
Refined white flour	<0.2X
Whole grain bread	<0.2X
White bread	<0.2X
Gluten feed meal	<0.2X
Starch	<0.2X

LIVESTOCK FEEDING – Dairy cattle **PMRA # 1941339**

Lactating cows were fed a daily mixture of sulfoxaflor, X11719474, and X11721061 at a ratio of 1.0:0.1:0.4 (wt.:wt.:wt.) at 0.45, 2.37, 6.75, 35.19 ppm of sulfoxaflor in the diet for ~30 days. Milk was collected twice a day through the study, and cows were sacrificed within 1-7 hours of the last dose. Depuration in some additional cows at the highest dosing level was investigated. After sacrifice, muscle, liver, kidney, and fat samples were collected and analyzed. The metabolites X11719474 and X11721061 were at or below LOQ (0.010 ppm) in all commodities at the two lowest feeding levels (0.45 and 2.37 ppm). Therefore, since the dietary burdens (0.36 ppm for beef cattle and 0.73 ppm for dairy cattle) are below or very close to the lowest feeding levels, residues of X11719474 and X11721061 are not expected to transfer to ruminant commodities.

			Sulfoxaflor, ppm				
Matrix	**Feeding Level (ppm)**	**n**	**Min**	**Max**	**Median**	**Mean**	**Standard Deviation**
Milk*	0.45	28	0.013	0.038	0.024	0.024	0.006
	2.37	25	0.056	0.123	0.090	0.088	0.017
	6.75	28	0.181	0.288	0.243	0.242	0.026
	35.19	64	0.895	1.679	1.253	1.274	0.210
Fat	0.45	4	<0.010	0.014	0.013	0.012	0.002
	2.37	3	0.032	0.057	0.039	0.043	0.013
	6.75	4	0.091	0.139	0.099	0.107	0.022
	35.19	4	0.449	0.915	0.592	0.637	0.212
Kidney	0.45	4	0.026	0.040	0.034	0.034	0.006
	2.37	3	0.140	0.210	0.184	0.178	0.035
	6.75	4	0.433	0.566	0.461	0.480	0.059
	35.19	4	1.931	2.442	2.282	2.234	0.218
Liver	0.45	4	0.043	0.061	0.057	0.054	0.009
	2.37	3	0.238	0.375	0.283	0.299	0.070
	6.75	4	0.604	0.758	0.744	0.713	0.073
	35.19	4	3.196	4.030	3.766	3.689	0.364
Muscle	0.45	4	0.017	0.026	0.020	0.021	0.004
	2.37	3	0.086	0.155	0.105	0.115	0.036
	6.75	4	0.242	0.311	0.271	0.274	0.035
	35.19	4	1.262	1.691	1.453	1.465	0.221

*For days 8-28 when residues had plateaued.

Commodity	**Feeding level (ppm)**	**Maximum Residues (ppm)**	**MRBD (ppm)**		**Anticipated Residue (ppm)**	
			Beef/Dairy	**Hog**	**Beef/Dairy**	**Hog**
Milk	0.45	0.038	0.73 (dairy)	-	0.062	-
	2.37	0.123				
	6.75	0.288				
	35.19	1.679				

Fat	0.45 2.37 6.75 35.19	0.014 0.057 0.139 0.915	0.36 (beef)	0.05 (hog)	0.011	0.002
Kidney	0.45 2.37 6.75 35.19	0.040 0.210 0.566 2.2442	0.36 (beef)	0.05 (hog)	0.032	0.004
Liver	0.45 2.37 6.75 35.19	0.061 0.375 0.758 4.030	0.36 (beef)	0.05 (hog)	0.049	0.007
Muscle	0.45 2.37 6.75 35.19	0.026 0.155 0.311 1.691	0.36 (beef)	0.05 (hog)	0.021	0.003

LIVESTOCK FEEDING – Laying hens | **PMRA # 1941338**

Laying hens were fed a daily mixture of sulfoxaflor, X11719474, and X11721061 at a ratio of 1.0:0.06:0.13 (wt.:wt.:wt.) that was equivalent to 0.145, 0.757, 2.096, 10.70 ppm of sulfoxaflor in the diet for ~30 days. Eggs were collected each day through the study, and hens were sacrificed within 1-6 hours of the last dose. Depuration in some additional hens was investigated. After sacrifice, muscle, liver, and fat samples were collected and analyzed. Metabolites X11719474 and X11721061 were at or below LOQ (0.010 ppm) in all commodities at the two lowest feeding levels (0.145 and 0.757 ppm). Therefore, since the dietary burden (0.10 ppm) is below the lowest feeding level, residues of X11719474 and X11721061 are not expected to transfer to poultry commodities.

Matrix	**Feeding Level**	**Sulfoxaflor (ppm)**					
		n	**Min**	**Max**	**Median**	**Mean**	**Standard Deviation**
Muscle	0.145	3	<0.010	<0.010	<0.010	<0.010	-
	0.757	3	0.025	0.042	0.035	0.034	0.009
	2.096	3	0.073	0.109	0.086	0.089	0.018
	10.7	3	0.442	0.659	0.448	0.516	0.124
Fat	0.145	3	<0.010	<0.010	<0.010	<0.010	-
	0.757	3	0.011	0.013	0.012	0.012	0.001
	2.096	3	0.028	0.048	0.033	0.036	0.010
	10.7	3	0.153	0.184	0.164	0.167	0.016
Liver	0.145	3	0.012	0.028	0.015	0.018	0.009
	0.757	3	0.052	0.150	0.110	0.104	0.049
	2.096	3	0.153	0.232	0.171	0.185	0.041
	10.7	3	1.111	1.193	1.118	1.141	0.045
Eggs*	0.145	24	<.0.010	<0.010	<0.010	<0.010	-
	0.757	24	0.020	0.059	0.031	0.031	0.007
	2.096	24	0.055	0.099	0.081	0.080	0.011
	10.7	48	0.220	0.594	0.423	0.424	0.075

*Egg samples were from days 10-27 or day 28, when residues had plateaued.

Commodity	**Feeding level (ppm)**	**Maximum residues (ppm)**	**MRBD (ppm)**	**Anticipated residue in poultry (ppm)**
Muscle	0.145 0.757 2.096 10.7	<0.010 0.042 0.109 0.659	0.10 (poultry)	0.007
Fat	0.145 0.757 2.096 10.7	<0.010 0.013 0.048 0.184	0.10 (poultry)	0.007

Liver	0.145 0.757 2.096 10.7	0.028 0.150 0.232 1.193	0.10 (poultry)	0.019
Eggs	0.145 0.757 2.096 10.7	<0.010 0.059 0.099 0.594	0.10 (poultry)	0.007

Table 13 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**		Sulfoxaflor Sulfoxaflor	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**		Sulfoxaflor Sulfoxaflor	
METABOLIC PROFILE IN DIVERSE CROPS		Metabolism is understood in four diverse crops	
ANIMAL STUDIES			
ANIMALS		**Ruminant**	
RESIDUE DEFINITION FOR ENFORCEMENT		Sulfoxaflor	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Sulfoxaflor	
METABOLIC PROFILE IN ANIMALS **(goat, hen, rat)**		Metabolic profile is similar and understood	
FAT SOLUBLE RESIDUE		Yes, but not preferentially	
DIETARY RISK FROM FOOD AND WATER			
Refined chronic non-cancer dietary risk **ADI = 0.010 mg/kg bw for food for all subgroups, except females 13-49 years;** **ADI = 0.0063 mg/kg bw for food for females 13-49 years;** **ADI = 0.010 mg/kg bw for drinking water for all subgroups** **Estimated chronic drinking water concentration = 98.6 Φg/L**	**POPULATION**	**ESTIMATED RISK** **% of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
	All infants < 1 year	17.4	85.5
	Children 1–2 years	38.0	68.9
	Children 3 to 5 years	25.7	54.6
	Children 6–12 years	14.6	34.5
	Males 13–19 years	7.6	22.9
	Males 20+ years	5.6	24.2
	Adults 50+ years	6.0	26.4
	POPULATION	**FOOD Only**	**WATER ONLY**
	Females 13-49 years	9.0	19.3

Refined acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 143 Φg/L** **ARfD = 0.25 mg/kg bw for food for all subgroups except females 13-49 years** **ARfD = 0.0063 mg/kg bw for food for females 13-49 years** **ARfD = 0.25 mg/kg bw for drinking water for all subgroups**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
	All infants < 1 year	9.70	20.97
	Children 1–2 years	15.65	20.34
	Children 3 to 5 years	11.12	15.40
	Children 6–12 years	5.78	8.76
	Males 13–19 years	3.37	5.82
	Males 20+ years	3.35	5.93
	Adults 50+ years	3.63	6.13
	POPULATION	**FOOD ONLY**	**WATER ONLY**
	Females 13-49 years	135.47	2.78
Refined probabilistic dietary exposure analysis, 99.9th percentile. **Residue distribution file for drinking water.** **ARfD = 0.0063 mg/kg bw for food.** **ARfD = 0.25 mg/kg bw for drinking water.**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		FOOD ONLY	**WATER ONLY**
	Females 13–49 years	117.10	6.61

Table 14 Fate and Behaviour in the Environment

Property	Test substance	Value	Comments	PMRA#
Abiotic transformation				
Hydrolysis	Sulfoxaflor	Stable at pH 5, pH 7 and pH 9	Not an important route of dissipation.	1941224
	X11719474	Stable at pH 7	Inferred from results in dark controls from the phototransformation study in sterile buffer. Not an important route of dissipation.	1941225
Phototransformation on soil	Sulfoxaflor	Sulfoxaflor: Could not calculate phototransformation half-life (transformation in dark samples was faster than in irradiated samples)	Sulfoxaflor: Not an important route of dissipation when compared to biotransformation.	1941469

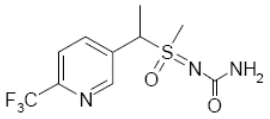
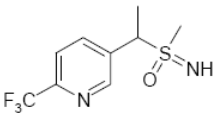
Property	Test substance	Value	Comments	PMRA#
		X11719474: Did not decline sufficiently to calculate half-life	X11719474: Not an important route of dissipation.	
Phototransformation in water	Sulfoxaflor	t½ in sterile buffer: 484 days (continuous irradiation); Predicted environmental half-life at 40°N in summer sunlight: > 1000 days t½ in natural water: 162 days (continuous irradiation); Predicted environmental half-life at 40°N in summer sunlight: 637 days	Not an important route of dissipation.	Sterile buffer: 1941225 Natural water: 1941478
	X11719474	t½ in sterile buffer: 136 days (continuous irradiation); Predicted environmental half-life at 40°N in summer sunlight: 261 days t½ in natural water: 387 days (continuous irradiation); Predicted environmental half-life at 40°N in summer sunlight: > 1000 days	Not an important route of dissipation.	
Phototransformation in air	Sulfoxaflor	Sulfoxaflor is not volatile under field conditions based on vapour pressure and Henry's law constant. Estimated photochemical oxidation half-life: 7.8 hours	Not an important route of dissipation.	1941227
Biotransformation				
Biotransformation in aerobic soil	Sulfoxaflor	Sulfoxaflor: t½: 0.32 to 0.60 day DT_{90}: 1.05 to 1.86 days X11719474: t½: >1000 days DT_{90}: > 1000 days	Sulfoxaflor: Non-persistent. X11719474: Half-life based on simultaneous formation and decline of product. Persistent.	1941466
	Sulfoxaflor	Sulfoxaflor: t½: 0.05 to 0.26 day DT_{90}: 0.16 to 0.87 days X11719474: t½: 85 to 381 days DT_{90}: 283 to > 1000 days	Sulfoxaflor: Non-persistent. X11719474: Half-life based on simultaneous formation and decline of product. Persistent.	1941467

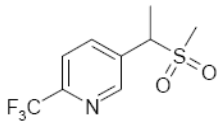
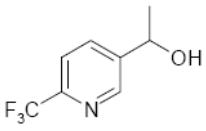
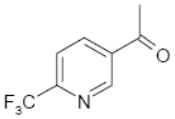
Property	Test substance	Value	Comments	PMRA#
	X11579457	DT_{50}: 96 to 670 days DT_{90}: 270 to > 1000 days	Moderately persistent to persistent.	1941470
	X11419540	DT_{50}: 71 to > 1000 days DT_{90}: 715 to >1000 days	Moderately persistent to persistent.	1941471
Biotransformation in anaerobic soil	Sulfoxaflor	Sulfoxaflor: t½: 0.17 to 2.5 days DT_{90}: 0.6 to 8.3 days X11719474: t½: 320 to 532 days DT_{90}: >1000 days	Sulfoxaflor: Non-persistent. X11719474: Half-life based on simultaneous formation and decline of product. Moderately persistent to persistent.	1941467 1941468
Biotransformation in aerobic water-sediment systems	Sulfoxaflor	In total system: t½: 37 to 88 days DT_{90}: 122 to 294 days	Slightly to moderately persistent.	1941479
Biotransformation in anaerobic water-sediment systems	Sulfoxaflor	In total system: DT_{50}: 103 to 382 days DT_{90}: 200 to > 1000 days	Moderately persistent to persistent.	1941480
	X11719474	In total system: DT_{50}: > 1000 days DT_{90}: >> 1000 days	Persistent.	
Mobility				
Adsorption / desorption in soil	Sulfoxaflor	K_{oc}: 12 to 72 mL/g	High to very high mobility.	1941477
	X11719474	K_{oc}: 7 to 80 mL/g	High to very high mobility.	
	X11579457	K_{oc}: 1 to 29 mL/g	Very high mobility.	
	X11519540	K_{oc}: 3 to 28 mL/g	Very high mobility.	
Field studies				
Field dissipation – sites relevant to Canada (North Dakota and Ontario)	Closer Insecticide	Sulfoxaflor: DT_{50}: < 1 day DT_{90}: 2.05 to 8.98 days Generally found only in the 0-6 inch soil layer; small amounts detected up to 12 inches below ground surface. X11719474: DT_{50}: 40 to 248 days DT_{90}: 359 to 824 days (rates for total soil profile) Reached maximums of over 100% of initial measured concentration. Still detected at the end of the study.	Sulfoxaflor: Non persistent. Low evidence of leaching. X11719474: Slightly persistent to persistent. Half-life based on simultaneous formation and decline of product. Expected to carryover. Evidence of leaching.	1941472

Property	Test substance	Value	Comments	PMRA#
		More than 30% was found at beginning of second growing season. Found up to 36 inches below ground surface. X11579457: Dissipation rate could not be calculated. Reached maximums of 2-7% of initial measured concentration. No longer detected at the end of the study. Generally found only in the 0-6 inch soil layer; small amounts detected up to 24 inches below ground surface. X11519540: Dissipation rate could not be calculated. Reached maximum concentrations of 4-9.9% of the initial measured concentration. Still detected at the end of the study. Found up to 36 inches below ground surface.	 X11579457: Less persistent than X11719474 and X11519540. Not expected to carryover. Low evidence of leaching. X11519540: More persistent than X11579457. Not expected to carryover. Evidence of leaching.	
Field dissipation – other North American sites (California, Florida and Texas)	Closer Insecticide	Sulfoxaflor: DT_{50}: < 1 day to 8.1 days DT_{90}: 4.6 to 27 days Found up to 36 inches below ground surface in California and up to 18 inches in other sites. Low levels / sporadic detection in pore water. X11719474: DT_{50}: 27 to 62 days DT_{90}: 75 to > 1000 days (rates for total soil profile) Reached maximums of 59 - 150% of initial measured concentration. Still detected at the end of the study except in California where higher irrigation increased leaching. More than 30% was found at beginning of second growing season in Texas.	Sulfoxaflor: Some evidence of leaching. Presence in deeper soil layers in California likely due to higher irrigation. X11719474: Slightly persistent to moderately persistent. Half-life based on simultaneous formation and decline of product. Expected to carryover under some conditions. Evidence of leaching.	1941472

Property	Test substance	Value	Comments	PMRA#
		Found up to 36 inches below ground surface. Found in pore water. X11579457: Dissipation rate could not be calculated. Reached maximums of 2-4% of initial measured concentration. Generally no longer detected at the end of the study. Found up to 30 inches below ground surface. Found in pore water. X11519540: Dissipation rate could not be calculated. Reached maximum concentrations of 3-5% of the initial measured concentration. Still detected at the end of the study except for California. Found up to 36 inches below ground surface. Found in pore water.	 X11579457: Less persistent than X11719474. Not expected to carryover. Evidence of leaching. X11519540: More persistent than X11579457. Not expected to carryover. Evidence of leaching.	

Table 15 Transformation Products Formed in the Environment

Code	Chemical name	Molecular weight (g/mole)	Structure	Occurrence (Max %AR) [a]
Major transformation products (> 10%AR or still increasing at the end of the study)				
X11719474	*N*-((methyl) oxido) {1-[6-(trifluoromethyl) pyridine-3-yl] ethyl}-λ4-sulfanylidene) urea	297.00		Soil: Aerobic (99.5) Anaerobic (98) Photolysis (35) Field (>100) Water: Aerobic water/sediment (66) Anaerobic water/sediment (5.6) Crop: Field (uptake from roots, metabolism)
X11579457	[5-[1-(S-methylsulfonimidoyl) ethyl]-2-(trifluoromethyl) pyridine	252.25		Soil: Aerobic (8.5) [b] Field (7) Water: N/A

Code	Chemical name	Molecular weight (g/mole)	Structure	Occurrence (Max %AR) [a]
X11519540	5-(1-methylsulfonyl) ethyl)-2-(trifluoromethyl) pyridine	253.24		Soil: Aerobic (10.9) [b] Field (9.9) Water: N/A
Minor transformation products (< 10%AR)				
X11721061	1-[6-(trifluoromethyl) pyridine-3-yl] ethanol	191.15		Soil: N/A Water: Photolysis (2.3) Crop: Field (metabolism)
X11718922	1-[6-(trifluoromethyl) pyridine-3-yl] ethanone	189.14		Soil: N/A Water: Photolysis (5.6) [c]

[a] AR = applied radioactivity. Mean of two replicates is reported.

[b] Maximum observed % AR from individual replicates (reached at the end of the study): 12.2% for X11519540 and 9.2% for X11579457.

[c] X11718922 was observed in a photolysis study carried out with X11719474 but was not observed in the photolysis study with sulfoxaflor.

Table 16 Toxicity to Non-Target Terrestrial Species

Organism	Exposure	Test substance	Endpoint value	Reference
Invertebrates				
Earthworm (*Eisenia fetida*)	14-d Acute	Sulfoxaflor	LC_{50}: 0.885 mg a.i./kg dry artificial soil; NOEC (mortality and weight loss): 0.313 mg a.i./kg dry artificial soil	1941505
	14-d Acute	X11719474	LC_{50}: >1000 mg/kg dry artificial soil; NOEC (weight loss): 200 mg/kg dry artificial soil	1941506
	56-d Chronic	Closer Insecticide	Adult survival: 28-d LC_{50}: >1.28 mg a.i./kg dry natural soil; 56-d NOEC 0.64 mg a.i./kg dry soil Adult Biomass: 28-d NOEC: 1.28 mg a.i./kg dry natural soil (highest concentration tested) Number of Juveniles: 56-d NOEC: 0.64 mg a.i./kg dry natural soil	1959836
Honeybee (*Apis mellifera*)	48-h Oral	Sulfoxaflor	LD_{50}: 0.146 µg a.i./bee	1941502
	48-h and 96-h Oral	X11719474	LD_{50}: >100 µg/bee	1941503
	48-h Oral	X11721061	LD_{50}: >100 µg/bee	2044394
	48-h Oral	Closer Insecticide	LD_{50}: 0.0515 µg a.i./bee	1941151
	72-h Contact	Sulfoxaflor	LD_{50}: 0.379 µg a.i./bee	1941504
	48-h Contact	Transform WG Insecticide	LD_{50}: 0.224 µg a.i./bee	1941101
	48-h	Closer	LD_{50}: 0.130 µg a.i./bee	1941153

Organism	Exposure	Test substance	Endpoint value	Reference
	Contact	Insecticide		
	24-h Contact, weathered foliar residues on crops	Transform WG Insecticide	Corrected mortality reached maximum of 15% when exposed to residues weathered for 3, 6, and 24 hours after a single application at 100 or 200 g a.i./ha. RT_{25} < 3 hours	1941102
	24-h Contact, weathered foliar residues on crops	Closer Insecticide	Corrected mortality reached maximum of 4% when exposed to residues weathered for 3, 6, and 24 hours after a single application at 200 g a.i./ha. RT_{25} < 3 hours	2048774
	Larvae feeding test (single dose)	Sulfoxaflor	Larvae mortality: 7-d LD_{50} > 2 µg a.i./bee larvae	2219817
	Larvae feeding test (multiple dose)	Sulfoxaflor	Larvae mortality: 7-d LD_{50} > 0.2 µg a.i./bee larvae	2173237
	Semi-field (tunnel)	Closer Insecticide	Daytime application (in other words, during bee flight) on blooming crop at 6.25, 12.5, 24, 48 and 96 g a.i./ha: - Transient increase in worker bee mortality: 7X increase on DAA0 in highest treatment group; dose-dependent trend. Returned to control levels byDAA3. - Transient decline in flight intensity: 5X decrease on DAA0 in highest treatment group; no clear dose-dependent trend. Returned to control levels by DAA3. - Slight intoxication symptoms (cramped bees) on DAA0. - Effects on brood inconclusive due to factors such as a long pre-exposure period in tunnels, presence of *Varroa* mites in controls and an observation period too short to detect brood effects (7d). Reference toxicant was used (dimethoate).	2044397
	Semi-field (tunnel)	Closer Insecticide	Evening application on blooming crop at 48 g a.i./ha: - Transient increase in worker bee mortality: 6X increase on DAA0. Returned to control levels by DAA3. - Slight transient decline in flight intensity: Less than 1.5X decrease on DAA0. Returned to control levels by DAA1. - Lack of coordination and intensive cleaning on DAA0. - No clear effect on brood development: similar amount of nectar, pollen, eggs, larvae, capped and empty cells than in control. However, observation	2044396

Organism	Exposure	Test substance	Endpoint value	Reference
			period too short (9d). Colony strength not assessed. Daytime application on blooming crop at 24 g a.i./ha: - Transient increase in worker bee mortality: 9X increase on DAA0. Returned to control levels by DAA3. - Slight transient decline in flight intensity: Less than 1.5X decrease on DAA0. Returned to control levels by DAA1. - Lack of coordination and intensive cleaning on DAA0. - No clear effect on brood development: similar amount of nectar, pollen, eggs, larvae, capped and empty cells than in control. However, observation period too short (9d). Colony strength not assessed. Daytime application on blooming crop at 48 g a.i./ha: - Transient increase in worker bee mortality: 20X increase on DAA0. Returned to control levels by DAA3. - Slight transient decline in flight intensity: 2X decrease on DAA0. Returned to control levels by DAA1. - Cramps, lack of coordination and intensive cleaning on DAA0-1. - No clear effect on brood development: similar amount of nectar, pollen, eggs, larvae, capped and empty cells than in control. However, observation period too short (9d). Colony strength not assessed. Reference toxicant was used (dimethoate).	
	Semi-field (tunnel)	GF-2626[a]	Pre-bloom application at 48 g a.i./ha: - Slight transient increase in worker bee mortality: 2X increase on DAA0. Returned to control levels by DAA2. - Slight transient decline in flight intensity: Less than 1.5X decrease on DAA0. Returned to control levels by DAA2. - No behavioural abnormalities. - Compensation index of 3.5 in treatment at the end of trial compared to 3.4 in control. Brood termination rate of 58.1% compared to 56.4% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Evening application on blooming crop at 24 and 48 g a.i./ha: - Transient increase in worker bee mortality: 3X and 8X increase on DAA0 in the 24 and 48 g a.i./ha treatment groups, respectively. Returned to control levels by DAA2. - Transient decline in flight intensity: Less than 1.5X and 3X decrease in the 24 and 48 g a.i./ha treatment groups, respectively. Returned to control	2173238

Organism	Exposure	Test substance	Endpoint value	Reference
			levels by DAA2. - Lack of coordination and intensive cleaning observed in the 48 g a.i./ha treatment group. No behavioural abnormalities noted in the 24 g a.i./ha group. - Compensation index of 3.4 and 3.6 at end of trial in the 24 and 48 g a.i./ha treatment groups, respectively, compared to 3.4 in control . Brood termination rate of 70.6% and 42.7% in the 24 and 48 g a.i./ha test groups, respectively, compared to 56.4% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Daytime application on blooming crop at 24 g a.i./ha: - Transient increase in worker bee mortality: 5X on DAA0. Returned to control levels by DAA2. - Slight transient decline in flight intensity: Less than 2X decrease on DAA0. Returned to control levels by DAA2. - No behavioural abnormalities. - Compensation index of 4.2 in treatment at the end of trial compared to 3.4 in control. Brood termination rate of 37.5% compared to 56.4% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Reference toxicant (fenoxycarb, applied daytime on blooming crop): - Compensation index of 1.7 at end of trial, brood termination rate of 98.1% [b]	
	Semi-field (tunnel)	GF-2626[a]	Pre-bloom application at 48 g a.i./ha: - No obvious increase in worker bee mortality. - Slight transient decline in flight intensity: Less than 1.5X decrease on DAA0. Returned to control levels by DAA1. - No behavioural abnormalities. - Compensation index of 3.0 in treatment at the end of trial compared to 3.2 in control. Brood termination rate of 65.6% compared to 65.3% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Evening application on blooming crop at 24 g a.i./ha: - Transient increase in worker bee mortality: 3X on DAA0. Returned to control levels by DAA1. - Slight transient decline in flight intensity: Less than 2X decrease on DAA0. Returned to control levels by DAA1. - No behavioural abnormalities. - Compensation index of 3.8 in treatment at the end of trial compared to 3.2 in control. Brood	2173239

Organism	Exposure	Test substance	Endpoint value	Reference
			termination rate of 44.2% compared to 65.3% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Daytime application on blooming crop at 24 g a.i./ha: - Transient increase in worker bee mortality: 3X on DAA0. Returned to control levels by DAA1. - Slight transient decline in flight intensity: Less than 1.5X decrease on DAA0. Returned to control levels by DAA1. - No behavioural abnormalities. - Compensation index of 3.6 in treatment at the end of trial compared to 3.2 in control. Brood termination rate of 47.8% compared to 65.3% in control. Effects on brood considered inconclusive due to high brood termination rate. - Colony strength similar to control. Reference toxicants (fenoxycarb and dimethoate, both applied daytime on blooming crop): - With fenoxycarb: compensation index of 1.9 at end of trial, brood termination rate of 98.6%. With dimethoate: compensation index of 0.3 at end of trial, brood termination rate of 100%.[b]	
Bumblebee (*Bombus terrestris*)	72-h Oral	Closer Insecticide	LD_{50}: 0.027 µg a.i./bee	1941152
	72-h Contact	Closer Insecticide	LD_{50}: 7.554 µg a.i./bee	1941152
Predatory mite (*Typhlodromus pyri*)	14-d Contact, glass plates (screening test)	Closer Insecticide	7-d LR_{50}: >400 g a.i./ha 14-d ER_{50}: >400 g a.i./ha	1959829
Parasitic wasp (*Aphidius rhopalosiphi*)	48-h Contact, glass plates (screening test)	Closer Insecticide	LR_{50}: 0.019 g a.i./ha ER_{50}: >0.015 g a.i./ha (highest rate with enough survival for fecundity assessment)	1959832
	48-h Contact, leaf substrate (extended laboratory)	Closer Insecticide	LR_{50}: 1.28 g a.i./ha ER_{50}: >1.21 g a.i./ha (highest rate with enough survival for fecundity assessment)	1959834
	48-h Contact, leaf substrate, (aged residues of 0 (fresh), 3, 7, or 14 days)	Closer Insecticide	Day 0 corrected mortality was 100% at 6.2, 26 and 45 g a.i./ha Less than 30% effect on mortality and fecundity by 3 days at 6.2 and 26 g a.i./ha and by 14 days at 45 g a.i./ha.	1959835

Organism	Exposure	Test substance	Endpoint value	Reference
Ladybird beetle (*Coccinella septempunctata*)	17-d Contact, leaf substrate (extended laboratory)	Closer Insecticide	LR_{50}: 14 g a.i./ha ER_{50}: >12 g a.i./ha (highest rate with enough survival for fecundity assessment)	1959833
Birds				
Bobwhite quail (*Colinus virginianus*)	Acute	Sulfoxaflor	LD_{50}: 676 mg a.i./kg bw; NOAEL: 360 mg.a.i./kg bw (mortality, body weight loss)	1941481
	Acute	X11719474	LD_{50}: >2250 mg/kg bw; NOEL: 2250 mg/kg bw (no effect at highest dose tested)	1941483
	5-d Dietary	Sulfoxaflor	LC_{50}: >5620 mg a.i./kg diet (LD_{50} >1152 mg a.i./kg bw/d); NOAEC: <562 mg a.i./kg diet (NOAEL <165 mg a.i./kg bw/d) (reduced body weight gain)	1941484
	20-week Reproduction	Sulfoxaflor	NOAEC: 1000 mg a.i./kg diet (NOAEL: 81 mg a.i./kg bw/d) (highest concentration tested)	1941486
Mallard duck (*Anas platyrhynchos*)	5-d Dietary	Sulfoxaflor	LC_{50}: >5620 mg a.i./kg diet (LD_{50}: >1049 mg a.i./kg bw/d) NOAEC: 562 mg a.i./kg diet (NOAEL: 215 mg a.i./kg bw/d) (reduced body weight gain)	1941485
	20-week Reproduction	Sulfoxaflor	NOAEC: 200 mg a.i./kg diet (NOAEL: 26 mg a.i./kg bw/d) (highest concentration tested)	1941487
Zebra finch (*Poephila guttata*)	Acute	Sulfoxaflor	LD_{50}: >80 mg a.i./kg bw (should be interpreted with caution, due to the propensity of the species to regurgitate the dose) NOEL: 29 mg a.i./kg bw (mortality, regurgitation)	1941482
Mammals				
Rat	Acute	Sulfoxaflor	LD_{50}: 1000 mg a.i./kg bw	1941262
	Acute	X11719474	LD_{50}: 2000 mg a.i./kg bw	1941323
	2-generation Reproduction (dietary exposure)	Sulfoxaflor	Parental toxicity: NOAEL: 24.6 mg a.i./kg bw/d (highest dose tested) Offspring and reproductive toxicity: NOAEL: 6.07 mg a.i./kg bw/d; LOAEL: 24.6 mg a.i./kg bw/d (decreased pup survival in F_1 and F_2 generations)	1941292
Mouse	Acute	Sulfoxaflor	LD_{50}: 750 mg a.i./kg bw	1941263
Vascular plants				

Organism	Exposure	Test substance	Endpoint value	Reference
Crop species	21-d Seedling emergence ; Tier 2 test	Closer Insecticide	ER_{25} >400 g a.i./ha (all tested species) ER_{50} >400 g a.i./ha (all tested species)	1941158
	21-d Vegetative vigour; Tier 1 (limit) test	Closer Insecticide	ER_{25} >200 g a.i./ha (all tested species) ER_{50} >200 g a.i./ha (all tested species)	1941155
	21-d Vegetative vigour; Tier 1 (limit) and Tier 2 (onion only) tests	Closer Insecticide	ER_{25} >200 g a.i./ha (all tested species) ER_{50} >200 g a.i./ha (all tested species)	1941156

[a] No information on how GF-2626 compares to Closer Insecticide and Transform WG Insecticide.
[b] Details of brood effects observed with reference toxicant provided to support discussion; other results with reference toxicants not reported in this Table.

Table 17 Risk Assessment on Non-Target Terrestrial Species Other Than Bees, Birds and Mammals

Organism	Type of exposure	Test substance	Endpoint value	EEC [a]	RQ
Invertebrates					
Earthworm, *Eisenia fetida*	Acute	Sulfoxaflor	LC_{50}/2 = 0.44 mg a.i./kg soil	0.05 mg a.i./kg soil	0.11
	Chronic	Sulfoxaflor	NOEC = 0.64 mg a.i./kg soil	0.05 mg a.i./kg soil	0.08
	Acute	X11719474	LC_{50}/2 >500 mg/kg soil	0.091 mg/kg soil	<0.0002
Honey bee, *Apis mellifera*	Contact	Closer Insecticide	48-h LD_{50}= 0.13 µg a.i./bee	0.23µg a.i./bee	1.8
	Oral	See Appendix I, Table 19			
Predatory mite, *Typhlodromus pyri*	Contact, glass plate	Closer Insecticide	LR_{50} >400 g a.i./ha	In field: 155.1 g a.i./ha	0.4
				Off-field (early season airblast appl., 74% drift): 114.8 g a.i./ha	0.3
				Off-field (late season airblast appl., 59% drift): 91.5 g a.i./ha	0.2

Organism	Type of exposure	Test substance	Endpoint value	EEC [a]	RQ
Parasitic wasp, *Aphidius rhopalosiphi*	Contact, glass plate	Closer Insecticide	LR_{50} = 0.019 g a.i./ha	In field: 155.1 g a.i./ha	8163
				Off-field (early season airblast appl., 74% drift): 114.8 g a.i./ha	6041
				Off-field (late season airblast appl., 59% drift): 91.5 g a.i./ha	4816
	Contact, leaf substrate	Closer Insecticide	LR_{50} = 1.28 g a.i./ha	In field: 155.1 g a.i./ha	121
				In field with 80% foliar deposition: 124.1 g a.i./ha	96
				In field with 20% foliar deposition: 31.0 g a.i./ha	24
				Off-field (early season airblast appl., 74% drift): 114.8 g a.i./ha	90
				Off-field (early season airblast appl., 74% drift × 0.1): 11.5 g a.i./ha	9
				Off-field (late season airblast appl., 59% drift): 91.5 g a.i./ha	71
				Off-field (late season airblast appl., 59% drift × 0.1): 9.2 g a.i./ha	7
Ladybird beetle, *Coccinella septempunctata*	Contact, leaf substrate	Closer Insecticide	LR_{50} = 14 g a.i./ha	In field: 155.1 g a.i./ha	11
				In field with 80% foliar deposition: 124.1 g a.i./ha	8.9
				In field with 20% foliar deposition: 31.0 g a.i./ha	2.2
				Off-field (early season airblast appl., 74% drift): 114.8 g a.i./ha	8.2
				Off-field (early	0.8

Organism	Type of exposure	Test substance	Endpoint value	EEC [a]	RQ
				season airblast appl., 74% drift × 0.1): 11.5 g a.i./ha	
				Off-field (late season airblast appl., 59% drift): 91.5 g a.i./ha	6.5
				Off-field (late season airblast appl., 59% drift × 0.1): 9.2 g a.i./ha	0.6
Vascular plants					
Crop species	Seedling emergence		ER_{25} >400 g a.i./ha	111.9 g a.i./ha	<0.3
	Vegetative vigour		ER_{25} >200 g a.i./ha	155.1 g a.i./ha	<0.8

[a] EEC = expected environmental exposure.

For all species other than bees, screening level EECs are based on a direct application at maximum cumulative application rate and thus considers the maximum label application rate, the number of applications, the application interval and the dissipation between applications. Calculations were as follows:
For sulfoxaflor: 2 × 96 g a.i./ha at 7 day interval. Dissipation in soil: estimated single first-order DT_{50} of 2.7 days (estimated by multiplying the longest field DT_{90} from a site relevant to Canadian conditions (8.98 days in Ontario) by 0.301). Dissipation on foliage: default half-life of 10 days.

For X11719474, the application rate was determined by assuming 100% conversion of sulfoxaflor to X11719474 immediately after application and correcting for molecular weight. Thus, each application of sulfoxaflor was equivalent to 102.8 g X11719474/ha (96 g a.i./ha × 297 g X11719474 g/mole / 277.27 g sulfoxaflor/mole = 102.8 g X11719474/ha). Dissipation in soil: estimated single first-order DT_{50} of 260 days (estimated by multiplying the longest X11719474 field DT_{90} from a site relevant to Canadian conditions (864 days in Ontario) by 0.301). Dissipation on foliage: default half-life of 10 days.

Off-field EEC: the screening level (on-field) EEC was adjusted according to projected drift at 1m downwind from site of application, which is dependent of the type of equipment used, spray quality and, in the case of airblast applications, the application timing.

For bees, screening level EEC for contact exposure (µg a.i./bee) = 2.4 µg a.i./bee/1kg a.i./ha × application rate (kg a.i./ha); 2.4 µg a.i./bee per 1kg a.i./ha drawn from Koch and Weiβer (1997).

RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern is exceeded (LOC = 0.4 for bees; LOC = 2 for *T. pyri* and *A. rhopalosiphi* in glass plate tests; LOC = 1 for other species).

Table 18 Maximum Residues of Sulfoxaflor (mg a.i./kg) in Pollen, Nectar and Other Plant Tissue

Application Rate	Plant Pollen	Plant Nectar	Plant Tissue[a]	Forager Nectar	Forager Pollen	Reference
Cotton – application during flowering; sampling every day for 10 days						
1 × 50.4 g a.i./ha	1.26			0.13	0.22	2173240
2 × 50.4 g a.i./ha	2.54			0.05	0.83	
2 × 99.7 g a.i./ha	**6.66**			0.07	2.78	
2 × 150 g a.i./ha	2.61			**1.01**	2.23	

Phacelia – application during flowering; sampling on days 0, 5 and 6 after application						
1 × 24 g a.i./ha			0.52	0.05	0.29	2055636
1 × 48 g a.i./ha			1.48	0.09	0.81	
Phacelia – pre-flower application; sampling on days 10, 15 and 16 after application						
1 × 24 g a.i./ha			<0.01	<0.01	<0.01	2055636
1 × 48 g a.i./ha			0.03	<0.01	<0.01	
Phacelia – application during flowering; pollen from inside the hive was sampled 7 days after application., flowers were sampled on days 0, 3, 5 and 7 after application.						
1 × 6.5 g a.i./ha						2044397
1 × 13.6 g a.i./ha						
1 × 24 g a.i./ha			1.76			
1 × 50 g a.i./ha						
1 × 99 g a.i./ha						
Pumpkin – application during flowering; sampling on days 2 and 4 after each application (samples from days 2 and 4 were pooled); sampled flowers were not open at the time of application (residues reflect translocation).						
2 × 25 g a.i./ha	0.08	0.03	0.20			2173235
2 × 100 g a.i./ha	0.38	0.03	1.27			
[a] Whole plant samples in PMRA 2055636, flower samples in PMRA 2044397, leaf tissue for PMRA 2173235. Blank cells indicate that a particular matrix was not sampled. Maximum residue residues observed in pollen (6.66 mg/kg) and nectar (1.01 mg/kg) were used in the risk assessment and are bolded.						

Table 19 Risk Assessment on Honeybees – Acute Oral Exposure

Life stage	Caste [a]	Pollen consum. rate (mg a.i./ bee/d)	Exposure from pollen [b] (ng a.i./ bee/d)	Nectar consum. rate (mg a.i./ bee/d)	Exposure from nectar [b] (ng a.i./ bee/d)	Oral dose [b] (µg a.i./ bee/d)	Toxicity (µg a.i./ bee/d)	RQ
Larvae	Worker	5.4	35.96	114	115.14	0.151	> 0.2 [c]	< 0.76
	Drone	Unknown	Unknown	152	153.52	0.154	> 0.2 [c]	< 0.77
Adult	Forager (nectar)	0.041	0.27	292	294.92	0.295	0.0515	5.73
	Nurse bees	8.85	58.94	140	141.4	0.200	0.05	4.01

[a] Castes associated with the most conservative pollen and nectar consumption rates for larvae and adults were used in the risk assessment.

[b] Oral dose (µg/bee/day) = exposure from pollen + exposure from nectar = [(residue concentration in pollen × pollen consumption rate) + (residue concentration in nectar × nectar consumption rate)] /1000, where most conservative residue concentrations measured in semi-field studies for pollen and nectar were 6.66 and 1.01 mg a.i./kg, respectively. mg/kg = ng/mg.

[c] The LD_{50} is expressed as greater than the highest test level as mortality did not reach 50% over the test period. When the LD_{50} was extrapolated beyond the dose-response curve, LD_{50} = 0.265 µg a.i./bee larvae. Risk quotients calculated with the extrapolated value (RQ ≈ 0.6) also exceed the LOC.

RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern is exceeded (LOC = 0.4).

Table 20 Screening Level Risk Assessment on Birds and Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE (mg a.i./kg bw) [a]	RQ
Small Bird (0.02 kg)				
Acute	8	Insectivore (small insects)	7.82	0.98
Reproduction	26	Insectivore (small insects)	7.82	0.3
Medium Sized Bird (0.1 kg)				
Acute	8	Insectivore (small insects)	6.1	0.8
Reproduction	26	Insectivore (small insects)	6.1	0.2
Large Sized Bird (1 kg)				
Acute	8	Herbivore (short grass)	6.36	0.8
Reproduction	26	Herbivore (short grass)	6.36	0.2
Small Mammal (0.015 kg)				
Acute	75	Insectivore (small insects)	4.5	0.06
Reproduction	6.07	Insectivore (small insects)	4.5	0.7
Medium Sized Mammal (0.035 kg)				
Acute	75	Herbivore (short grass)	14.08	0.2
Reproduction	6.07	Herbivore (short grass)	14.08	2.3
Large Sized Mammal (1 kg)				
Acute	75	Herbivore (short grass)	7.53	0.1
Reproduction	6.07	Herbivore (short grass)	7.53	1.2

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(bw in g) $^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(bw in g) $^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(bw in g) $^{0.822}$
bw: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher *et al.* (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.
RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern (LOC = 1) is exceeded.

Table 21 Further Characterization of the Reproductive Risk to Mammals

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues			
			On-field		Off-field		On-field		Off-field	
			EDE (mg a.i./kg bw)[a]	RQ	EDE (mg a.i./kg bw) [a]	RQ	EDE (mg a.i./kg bw) [a]	RQ	EDE (mg a.i./kg bw) [a]	RQ
Medium Sized Mammal (0.035 kg)										
Reproduction	6.07	Insectivore (small insects)	3.94	0.6	2.92	0.5	2.20	0.4	1.63	0.3
		Insectivore (large insects)	0.99	0.2	0.73	0.1	0.47	0.08	0.35	0.06
		Granivore (grain and seeds)	0.99	0.2	0.73	0.1	0.47	0.08	0.35	0.06
		Frugivore (fruit)	1.97	0.3	1.46	0.2	0.94	0.2	0.7	0.1
		Herbivore (short grass)	14.08	2.3	10.42	1.7	5.00	0.8	3.7	0.6
		Herbivore (long grass)	8.6	1.4	6.36	1.05	2.81	0.5	2.08	0.3
		Herbivore (forage crops)	13.03	2.1	9.64	1.6	4.31	0.7	3.19	0.5
Large Sized Mammal (1 kg)										
Reproduction	6.07	Insectivore (small insects)	2.11	0.3	1.56	0.3	1.17	0.2	0.87	0.1
		Insectivore (large insects)	0.53	0.09	0.39	0.06	0.25	0.04	0.19	0.03
		Granivore (grain and seeds)	0.53	0.09	0.39	0.06	0.25	0.04	0.19	0.03
		Frugivore (fruit)	1.05	0.2	0.78	0.1	0.50	0.08	0.37	0.06
		Herbivore (short grass)	7.53	1.2	5.57	0.9	2.67	0.4	1.98	0.3
		Herbivore (long grass)	4.59	0.8	3.40	0.6	1.50	0.2	1.11	0.2
		Herbivore (forage crops)	6.96	1.1	5.15	0.8	2.30	0.4	1.70	0.3

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987).
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(bw in g) $^{0.822}$
bw: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994).
The off-field assessment was based on the highest projected drift deposition relevant to the sulfoxaflor use pattern (74% drift for early season airblast applications with fine spray)
RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern (LOC = 1) is exceeded.

Table 22 Toxicity to Non-Target Aquatic Species

Organism	Exposure	Test substance	Endpoint value	PMRA#
Water flea (*Daphnia magna*)	48-h Acute	Sulfoxaflor	EC_{50}: >399 mg a.i./L; NOEC: 110 mg a.i./L (immobilization)	1941493
	48-h Acute	X11719474	EC_{50}: >205 mg/L; NOEC: 205 mg/L (highest concentration tested)	1941494
	21-d Chronic	Sulfoxaflor	EC_{50}: >101 mg a.i./L; NOEC: 50.5 mg a.i./L (reproduction rate and days to first brood)	1941495
Midge (*Chironomus dilutus*)	10-d Acute, spiked water	Sulfoxaflor	LC_{50}: 0.161 mg TRR/kg dry sediment; NOEC: 0.0488 mg TRR/kg dry sediment (mean dry weight) [a]	1941500
Midge (*Chironomus riparius*)	28-d Chronic, spiked water	Sulfoxaflor	EC_{50}: >0.0949 mg TRR/L overlying water; NOEC: 0.0455 mg TRR/L overlying water (emergence) [a]	1959983
Rainbow trout (*Oncorhynchus mykiss*)	96-h Acute	Sulfoxaflor	LC_{50}: >387 mg a.i./L; NOEC: 387 mg a.i./L (highest concentration tested)	1941488
	96-h Acute	X11719474	LC_{50}: >478 mg/L; NOEC: 478 mg/L (highest concentration tested)	1941491
Bluegill sunfish (*Lepomis macrochirus*)	96-h Acute	Sulfoxaflor	LC_{50}: >363 mg a.i./L; NOEC not reliable	1941489
Common carp (*Cyprinus carpio*)	96-h Acute	Sulfoxaflor	LC_{50}: >402 mg a.i./L; NOEC: 402 mg a.i./L (highest concentration tested)	1941490
Fathead minnow (*Pimephales promelas*)	30-d (post hatch) Early life stage	Sulfoxaflor	LC_{50}: >10 mg a.i./L; NOEC: 0.63 mg a.i./L (reduced mean fry weight)	1941492
Green alga (*Pseudokirchneriella subcapitata*)	96-h Acute	Sulfoxaflor	72-h and 96-h E_rC_{50}, E_yC_{50}, and E_bC_{50}: >101 mg a.i./L; 72-h and 96-h NOEC: 101 mg a.i./L (highest concentration tested)	1941496
Blue-green alga (*Anabaena flos-aquae*)	96-h Acute	Sulfoxaflor	72-h E_rC_{50}: >95.6 mg a.i./L; 72-h E_yC_{50}: 83.8 mg a.i./L; 72-h E_bC_{50}: 90.3 mg a.i./L; 72-h NOEC: 11.95 mg a.i./L 96-h results not reliable	1941498
Diatom (*Navicula pelliculosa*)	96-h Acute	Sulfoxaflor	72-h and 96-h E_rC_{50} and E_yC_{50}: >95.6 mg a.i./L; 72-h E_bC_{50}: 66.1 mg a.i./L; 96-h E_bC_{50}: 81.2 mg a.i./L; 72-h and 96-h NOEC: 3.54 mg a.i./L	1941499
Duckweed (*Lemna gibba*)	7-d Dissolved	Sulfoxaflor	E_rC_{50} and E_yC_{50}: >98.8 mg a.i./L; NOEC: 98.8 mg a.i./L (highest concentration tested)	1941501
Mysid shrimp (*Americamysis bahia*)	96-h Acute	Sulfoxaflor	EC_{50}: 0.643 mg a.i./L; NOEC: 0.389 mg a.i./L (immobilization)	1941510
	28-d Chronic	Sulfoxaflor	LC_{50}: 0.633 mg a.i./L (nominal concentrations); NOEC: 0.11 mg	1941511

Organism	Exposure	Test substance	Endpoint value	PMRA#
			a.i./L (days to first brood, mean measured concentrations)	
Eastern oyster (*Crassostrea virginica*)	96-h Acute	Sulfoxaflor	EC_{50}: 86.5 mg a.i./L; NOEC: 57.3 mg a.i./L (inhibition of shell growth)	1941508
Sheepshead minnow (*Cyprinodon variegatus*)	96-h Acute	Sulfoxaflor	LC_{50}: 266 mg a.i./L; NOEC: 96.3 mg a.i./L (loss of equilibrium or lying on the bottom)	1941507
	30-d (post hatch) Early life stage	Sulfoxaflor	LC_{50}: >9.89 mg a.i./L; NOEC: 1.21 mg a.i./L (reduced mean fry length)	1941512
Saltwater diatom (*Skeletonema costatum*)	96-h Acute	Sulfoxaflor	72-h E_rC_{50}, E_yC_{50} and E_bC_{50}: >104 mg a.i./L; 72-h NOEC: 104 mg a.i./L (highest concentration tested) 96-h results not reliable	1941497

[a] The NOEC is expressed in terms of total radioactive residues (TRR) in overlying water. The majority of residues were attributed to sulfoxaflor, but approximately one third of residues were attributed to the X11719474 transformation product. Results of an available acute spiked sediment toxicity study were not used in the risk assessment for sediment-dwelling invertebrates, as spiked sediment is not considered a realistic exposure scenario for sulfoxaflor residues given that sulfoxaflor and X11719474 are very soluble in water and they do not partition to sediments to a great extent.

Table 23 Risk Assessment on Non-Target Aquatic Species

Organism	Type of Exposure	Test compound	Endpoint value	EEC [a]	RQ
Freshwater species					
Invertebrates [water flea, *Daphnia magna*]	Acute	Sulfoxaflor	LC_{50}/2 >199.5 mg a.i./L	0.023 mg a.i./L	<0.0001
		X11719474	EC_{50}/2 >102.5 mg/L	0.026 mg/L	<0.0003
	Chronic	Sulfoxaflor	NOEC = 50.5 mg a.i./L	0.023 mg a.i./L	0.0005
Sediment-dwelling invertebrates [midge, *Chironomus riparius*]	Chronic, spiked water	Sulfoxaflor	NOEC = 0.0455 mg TRR/L	0.023 mg a.i./L	0.5
Fish [bluegill sunfish, *Lepomis macrochirus*]	Acute	Sulfoxaflor	LC_{50}/10 >36.3 mg a.i./L	0.023 mg a.i./L	<0.0006
Freshwater fish [rainbow trout, *Oncorhynchus mykiss*]	Acute	X11719474	LC_{50}/10 >47.8 mg/L	0.026 mg/L	<0.0005
Fish [fathead minnow, *Pimephales promelas*]	Early Life Stage	Sulfoxaflor	NOEC = 0.63 mg a.i./L	0.023 mg a.i./L	0.04
Amphibians	Acute	Sulfoxaflor	LC_{50}/10 >36.3 mg a.i./L	0.125 mg a.i./L	<0.003
		X11719474	LC_{50}/10 >47.8 mg/L	0.137 mg/L	<0.003
	Early Life Stage	Sulfoxaflor	NOEC = 0.63 mg a.i./L	0.125 mg a.i./L	0.2
Algae [diatom, *Navicula pelliculosa*]	Acute	Sulfoxaflor	EC_{50}/2 = 33.05 mg a.i./L	0.023 mg a.i./L	0.0007

Vascular plants [duckweed, *Lemna gibba*]	Dissolved	Sulfoxaflor	EC_{50}/2 >50 mg a.i./L	0.023 mg a.i./L	<0.0005
Marine/estuarine species					
Invertebrates [mysid shrimp, *Americamysis bahia*]	Acute	Sulfoxaflor	LC_{50}/2 = 0.322 mg a.i./L	0.023 mg a.i./L	0.07
	Chronic	Sulfoxaflor	NOEC = 0.11 mg a.i./L	0.023 mg a.i./L	0.2
Fish [sheepshead minnow, *Cyprinodon variegatus*]	Acute	Sulfoxaflor	LC_{50}/10 = 26.6 mg a.i./L	0.023 mg a.i./L	0.0009
	Early Life Stage	Sulfoxaflor	NOEC = 1.21 mg a.i./L	0.023 mg a.i./L	0.02
Algae [diatom, *Skeletonema costatum*]	Acute	Sulfoxaflor	EC_{50}/2 >52 mg a.i./L	0.023 mg a.i./L	<0.0004

[a] EEC = Expected environmental exposure. At the screening level, EECs are based on a direct application at maximum cumulative application rate and thus considers the maximum label application rate, the number of applications, the application interval and the dissipation between applications.

For sulfoxaflor: 2 × 96 g a.i./ha at 7 day interval. Dissipation in water: half-life of 88 days (longest of two total system half-lives in aerobic water sediment systems).

For X11719474, the application rate was determined by assuming 100% conversion of sulfoxaflor to X11719474 immediately after application and correcting for molecular weight. Thus, each application of sulfoxaflor was equivalent to 102.8 g X11719474/ha (96 g a.i./ha × 297 g X11719474 g/mol / 277.27 g sulfoxaflor/mol = 102.8 g X11719474/ha). It was assumed that no degradation of X11719474 occurred in water.

RQ = risk quotient = exposure/toxicity. Shaded cells indicate that the level of concern is exceeded (LOC = 1) [LOC was not exceeded for aquatic organisms exposed to sulfoxaflor or X11719474]

Table 24 Supported Uses for Transform WG Insecticide

Pest(s)	Product Application Rate(s)	Application Equipment
Barley and Wheat		
Cereal aphids	25-50 g/ha	Ground or aerial
Russian wheat aphid	50-100 g/ha	Ground or aerial
Canola (Rapeseed), Flax Seed and Similar Oilseeds (Crop Subgroup 20A)		
Aphids	25-50 g/ha	Ground or aerial
Lygus bugs	100 g/ha	Ground or aerial

Note: Maximum of two applications with a minimum reapplication interval of 14 days for all uses.

Table 25 Supported Uses for Closer Insecticide

Pest(s)	Product Application Rate(s)	Application Equipment
Brassica (Cole) Leafy Vegetables (Crop Group 5) **Leafy Vegetables (Except Brassica) (Crop Group 4)**		
Aphids	100-150 mL/ha	Ground only
Pome Fruits (Crop Group 11-09)		
Aphids – green apple aphid, rosy apple aphid	100-200 mL/ha	Ground only
San Jose scale	200-400 mL/ha	
Woolly apple aphid (suppression only)	200 mL/ha	
Root and Tuber Vegetables (Crop Group 1)		
Aphids	50-150 mL/ha	Ground only; ground or aerial on potato only
Grapes		
Leafhoppers (suppression only)	200-400 mL/ha	Ground only

Stone Fruits (Crop Group 12-09)		
Aphids – green peach aphid, mealy plum aphid	100-200 mL/ha	Ground only
San Jose scale	200-400 mL/ha	
Tree Nuts (Crop Group 14-11)		
Aphids	100-200 mL/ha	Ground only
San Jose scale	200-400 mL/ha	

Note: Maximum of two applications with a minimum reapplication interval of seven days for all uses.

Table 26 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Sulfoxaflor	Transformation Products	
				X11719474	X11579457
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes	Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	DT_{50}: 0.05 to 0.6 d	DT_{50}: 85 to > 1000 d	DT_{50}: 96 to 670 d
	Water	Half-life ≥ 182 days	DT_{50}: 11 to 65 d	DT_{50}: Aerobic half-life not available. Anaerobic DT_{50} > 1000 d.	DT_{50}: Not available
	Sediment	Half-life ≥ 365 days	DT_{50}: 46 to 102 d	DT_{50}: Aerobic half-life not available. No degradation in anaerobic systems.	DT_{50}: Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Estimated photochemical oxidation half-life: 7.8 h In addition, volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (<2.5 × 10^{-6} Pa) and Henry's law Constant (6.7 × 10^{-12} atm m^3/mol).	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (2.7 × 10^{-7} Pa) and Henry's law Constant (4.5 × 10^{-14} atm m^3/mol).	Not available
Bioaccumulation[4]	Log K_{OW} ≥ 5		0.802	< 0.3	< 0.3
	BCF ≥ 5000		Not available	Not available	Not available
	BAF ≥ 5000		Not available	Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Asse
criterion may be refined if required (in other words, all other TSMP criteria are met).

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Sulfoxaflor	Transformation Products	
			X11719474	X11579457

[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medi
human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) t
persistence is considered to be met.

[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical propert
K_{OW}).

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

Table 1 Differences Between Canadian MRLs, US tolerances, and Codex MR

Commodity	Canada (ppm)	US (ppm)	Codex* (ppm)
Cirtus Fruits (CG 10)	0.7	0.7	0.9
Root and Tuber Vegetables (CG 1)	0.05	0.05	0.03
Leafy Vegetables, brassica (CG 5), except, cauliflower	2.0	2.0	3 (broccoli); 0.4 (cabbages, head)
Cauliflower	0.08	0.08	0.04
Leafy greens (CSG 4A), watercress	6.0	6.0	6 (leafy vegetables)
Leaf petioles (CSG 4B)	2.0	2.0	1.5 (celery)
Cucurbit Vegetables (CG 9)	0.4	0.4	0.5
Pome Fruits (CG11-09)	0.5	0.5	0.4
Dry shelled beans	0.2	0.2	-
Succulent edible podded beans	4.0	4.0	-
Rapeseed (CSG 20A)	0.4	0.4	0.15
Wheat	0.08	0.08	0.2
Barley	0.4	0.4	0.6
Stone Fruits (CG 12-09)	3.0	3.0	2 (except cherry)
Small Fruit Vine Climbing (CSG 13-07F)	2.0	2.0	2 (grape)
Low Growing Berry, except fuzzy kiwi fruit (CSG 13-07G)	0.7	0.7	0.5 (strawberries)
Cotton seed (CSG 20C)	0.2	0.2	0.4
Tree Nuts (CG14-11)	0.015	0.015	0.015
Fruiting Vegetables (CG 8-09)	0.7	0.7	1.5
Green onion (CSG 3-07B)	0.7	0.7	0.7 (spring onion)
Bulb onion (CSG 3-07A)	0.01	0.01	0.01 (onion, bulb; garlic)
Soybeans	0.2	0.2	0.3 (immature soya bean seeds)
Sugar Beet Molasses	0.25	0.25	-
Raisins	6.0	6.0	6
Tomato paste	2.6	2.6	-
Tomato puree	1.2	1.2	-
Leaves of Root and Tuber Vegetables, (CG 2), except turnip forage	3	3.0	-
Meat of cattle, goats, horses, and sheep	0.02	0.15	0.3 (meat from mammals)
Fat of cattle, goats, horses, and sheep	0.01	0.10	-
Fat and meat of hogs and poultry	0.01	0.01	0.1 (poultry meat)
Meat byproducts of cattle, goats, horses, and sheep	0.05	0.40	-
Milk	0.06	0.15	-
Meat byproducts of poultry	0.02	0.01	0.3 (edible offal of poultry)
Eggs	0.01	0.01	0.1
Meat byproducts of hogs	0.01	0.01	-

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

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.

The US tolerances and Canadian MRLs differ from Codex due to differences in data review.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1941211	2009, XR-208 14C-Pyridine Label Impurity Identification, DACO: 2.12.2,2.13.4,IIA 1.10.2 CBI
1941212	2009, Determination of Color, Physical State, Odor, Melting Point and Decomposition Temperature of XDE-208 Pure Active Ingredient, DACO: 2.14.1, 2.14.13, 2.14.2, 2.14.3, 2.14.4, 2.14.5, IIA 2.1.1, IIA 2.1.2,IIA 2.1.3,IIA 2.4.1,IIA 2.4.2 CBI
1941213	2008, XDE-208 TGAI: Determination of Density for Solids, DACO: 2.14.6,IIA 2.2 CBI
1941214	2008, XDE-208 PAI: Determination of Density for Solids, DACO: 2.14.6,IIA 2.2 CBI
1941215	2009, Determination of Vapour Pressure for XDE-208 PAI, DACO: 2.14.9,IIA 2.3.1 CBI
1941217	2009, Determination of Color, Odor, Physical State, Oxidizing and Reducing Action, Explodability, pH and Bulk Density of XDE-208 Technical Grade Active Ingredient, DACO: 2.14.1,2.14.2,2.14.3,2.16,IIA 2.13,IIA 2.4.1,IIA 2.4.2 CBI
1941218	2009, Determination of the Mass, Infrared, Nuclear Magnetic Resonance and Ultraviolet-Visible Spectra of XDE-208, DACO: 2.14.12,IIA 2.5.1.1 CBI
1941219	2009, Determination of the Mass, Infrared, Nuclear Magnetic Resonance and Ultraviolet/Visible Spectra of X11719474, DACO: 2.14.12,IIA 2.5.1.1 CBI
1941220	2009, Determination of Water Solubility for XDE-208 PAI, DACO: 2.14.7,IIA 2.6 CBI
1941221	2009, Determination of Organic Solvent Solubility for XDE-208 TGAI, DACO: 2.14.8,IIA 2.7 CBI
1941222	2009, Determination of Organic Solvent Solubility for XDE-208 PAI, DACO: 2.14.8,IIA 2.7 CBI
1941223	2009, Determination of Octanol-Water Partition Coefficient for XDE-208 PAI by Shake Flask Method, DACO: 2.14.11,IIA 2.8.1 CBI
1941226	2010, Determination of Dissociation Constant of XDE-208 Using UV-Visible Spectrophotometry and Potentiometric Titration Techniques, DACO: 2.14.10,8.2.3.2,IIA 2.9.5 CBI
1941228	2009, Determination of Surface Tension, Flammability, Self-Ignition Temperature and Oxidising Properties for XDE-208 TGAI, DACO: 2.16,IIA 2.11.1,IIA 2.14 CBI
1941229	2009, Determination of Explosive Properties (Thermal and Friction Tests) for XDE-208 TGAI, DACO: 2.16,IIA 2.13 CBI
1941230	2010, Determination of the Stability of XDE-208 Technical to Selected Metals and Metal Ions, DACO: 2.14.13,IIA 2.17.2 CBI
1941239	2010, Analytical Method and Validation for the Determination of Impurities in XDE-208 Technical Grade Material and Alternate Method for Determination of Active Ingredient in XDE-208 Technical Grade Material, DACO: 2.13.1,2.13.4,IIA 4.2.1,IIA 4.2.3 CBI
1941240	2010, Analytical Method and Validation for the Determination of Residual Solvents in XDE-208, DACO: 2.13.1,IIA 4.2.1 CBI

1941250	2010, Method Validation Study for the Determination of Residues of XDE-208 and its Major Metabolites in Soil using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection, DACO: 8.2.2.1,IIA 4.4
1941251	2010, Independent Laboratory Validation of the Analytical Methodology Used for the Determination of XDE-208 (X11422208) and its Metabolites (X11519540, X11579457, and X11719474) in Sandy Loam and Clay Loam Soils, DACO: 8.2.2.1,IIA 4.4
1941252	2010, Method Validation for the Determination of Residues of XDE-208 and its Major Metabolites in Soil by On-Line Solid Phase Extraction and High Performance Liquid Chromatography with Tandem Mass Spectrometry, DACO: 8.2.2.1,IIA 4.4
1941253	2010, Method Validation Study for the Determination of Residues of XDE-208 and its Major Metabolites in Water using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection, DACO: 8.2.2.3,IIA 4.5
1941254	2010, Independent Laboratory Validation of Dow AgroSciences LLC Method - Determination of Residues of XDE-208 and its Major Metabolites in Water using Offline Solid-Phase Extraction and Liquid Chromatography with Tandem Mass Spectrometry Detection, DACO: 8.2.2.3, IIA 4.5
1941255	2010, Method Validation for the Determination of Residues of XDE-208 and its Major Metabolites in Water by On-Line Solid Phase Extraction and High Performance Liquid Chromatography with Tandem Mass Spectrometry, DACO: 8.2.2.3,IIA 4.5
1941088	2010, Group A-Product Identity and Composition, Description of Materials Used to Produce the Product, Production and Formulation Process, Certified Limits, and Enforcement Analytical Method for GF-2372, an end use product containing Sulfoxaflor (XDE-208), DACO: 0.8.11, 0.8.12, 3.2.1, 3.2.2, 3.3.1, 3.4.1, Document J
1941089	2009, Determination of Color, Odor, Physical State, Oxidizing and Reducing Action, Bulk Density, Explodability, and pH of GF-2372, an End Use Product containing XDE-208, DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,IIIA 2.1,IIIA 2.2.2,IIIA 2.4.2,IIIA 2.6.2 C
1941090	2009, Determination of Flammability (solids) and Relative Self-Ignition Temperature for GF-2372, DACO: 3.5.11,IIIA 2.3.2,IIIA 2.3.3 CBI
1941091	2010, Two-Week Accelerated Storage Stability and Flowability of GF-2372, DACO: 3.5.10,8.2.2.1,8.2.3.6,IIIA 2.7.1,IIIA 2.8.1,IIIA 2.8.2,IIIA 2.8.3.1,IIIA 2.8.3.2,IIIA 2.8.5.2,IIIA 2.8.6.2,IIIA 2.8.6.3,IIIA 2.8.6.5,IIIA 2.8.8.1 CBI
1941092	2010, Storage Stability and Package Corrosion Characteristics of GF-2372; Eight-Week Accelerated Study, DACO: 3.5.14,IIIA 2.13 CBI
1941134	2010, Group A-Product Identity and Composition, Description of Materials Used to Produce the Product, Production and Formulation Process, Certified Limits, and Enforcement Analytical Method for GF-2032, an end use product containing Sulfoxaflor (XDE-208), DACO: 0.8.11, 0.8.12, Document J
1941135	2009, Determination of Color, Odor, Physical State, Oxidizing and Reducing Action, Flashpoint, Explodability, pH, Viscosity and Density of GF-2032, an End Use Product containing XDE-208, DACO: 3.5.1,3.5.12,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9,IIIA 2.1,IIIA 2.2.1
1941136	2009, Group B - Physical, Chemical Properties for GF-2032, A Liquid End Use Product containing XDE-208, DACO: 3.5.1,3.5.12,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,IIIA 2.1,IIIA 2.2.1,IIIA 2.2.2,IIIA 2.4.1,IIIA 2.5.2,IIIA 2.6.1 CBI
1941137	2009, Determination of surface Tension and Auto-Ignition Temperature for GF-2032, DACO: 3.5.11,3.7,IIIA 2.3.3,IIIA 2.5.3 CBI
1941138	2010, GF-2032 One Week Low Temperature and Two Week Accelerated Storage Stability in Glass, DACO: 3.5.10,IIIA 2.7.2,IIIA 2.7.4 CBI

1941139	2010, Eight-Week Accelerated Storage Stability and Package Corrosion Characteristics of GF-2032 in 1L HDPE and 1L PET Bottles, DACO: 3.5.10,3.5.14,8.2.3.6,IIIA 2.13,IIIA 2.7.2,IIIA 2.8.2,IIIA 2.8.3.1,IIIA 2.8.3.2,IIIA 2.8.5.2,IIIA 2.8.8.2 CBI
1941140	2010, Analytical Method and Validation for the Determination of XDE-208 in GF-2372 and GF-2032 End Use Products and in XDE-208 Technical Grade Active Ingredient, DACO: 3.5.1,3.5.2,3.5.3,IIIA 2.1 CBI
1959806	2010, Document J - Tier II, DACO: 2.11.2,2.11.4 CBI
1959807	2010, Document J - Tier II, DACO: 2.11.2,2.11.4 CBI
2043888	2011, Replicate Values Excel Spreadsheet (Raw data), DACO: 8.2.2.1, 8.2.2.2, 8.2.2.3, 8.2.2.4, 8.2.3.3.3
2366077	2013, Sulfoxaflor Technical Manufacturing Process, DACO: 2.11.3 CBI
2366078	2013, Sulfoxaflor Tech Specification - Updated 2013, DACO: 2.12.1 CBI
2366079	2012, Analysis of Product Samples for Active Ingredient and Impurities in Sulfoxaflor Technical Grade Active Ingredient, DACO: 2.13.3 CBI
2441291	2012, Analytical Method and Validation for the Determination of X12243073 in Sulfoxaflor Technical, an Extension of DAS-AM-G-10-16, DACO: 2.13.1 CBI
2444401	2014, Compilation of Spectral Data for Two Significant Impurities in Sulfoxaflor Technical, DACO: 2.13.1 CBI
2366088	2013, Storage Stability and Package Corrosion Characteristics of GF-2032 in HDPE and PET; Three Year Ambient Study, DACO: 3.5.10,3.5.14 CBI
2366100	2013, Storage Stability and Package Corrosion Characteristics of GF-2372; Three-Year Ambient Study, DACO: 3.5.10,3.5.14 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
1941147	2010, XDE-208: The In Vivo Percutaneous Absorption of Radiolabelled XDE-208 in Formulation (GF-2032) and Two In-Use Spray Dilutions in the Rat (OECD 427), DACO: 5.8,IIIA 7.6.1
1941148	2010, XDE 208: The In Vitro Percutaneous Absorption of Radiolabelled XDE 208 in Formulation (GF 2032) and Two In Use Spray Dilutions Through Rat and Human Skin (OECD 428), DACO: 5.8,IIIA 7.6.2
1941149	2010, Dissipation of Dislodgeable Foliar Sulfoxaflor Residues from Treated Wheat, DACO: 5.9,IIIA 7.7.1
1941150	2010, Dissipation of Dislodgeable Foliar Sulfoxaflor Residues from Treated Broccoli, DACO: 5.9,IIIA 7.7.1
1941259	2007, X11422208: Probe Study to Determine Absorption, Distribution, Metabolism, and Elimination in F344/DuCrl Rats ABD CRL:CD1(ICR) Mice, DACO: 4.5.9,IIA 5.1.1
1941260	2010, XDE-208: Tissue Distribution in F344/DuCrl Rats, DACO: 4.5.9,IIA 5.1.2
1941261	2009, XDE-208: Pharmacokinetics and Metabolism in F344-DuCrl Rats, DACO: 4.5.9,IIA 5.1.3
1941262	2008, XDE-208: Acute Oral Toxicity Study in F344/DuCrl Rats (Up and Down Procedure), DACO: 4.2.1,IIA 5.2.1
1941263	2008, XDE-208: Acute Oral Toxicity Study in CRL:CD1(ICR) Mice (Up and Down Procedure), DACO: 4.2.1,IIA 5.2.1

1941264	2008, XDE-208: Acute Dermal Toxicity Study in Rats - Limit Test, DACO: 4.2.2,IIA 5.2.2
1941265	2009, XDE-208: Acute Dust Aerosol Inhalation Toxicity Study in Fisher 344, DuCrl Rats, DACO: 4.2.3,IIA 5.2.3
1941266	2008, XDE-208: Primary Skin Irritation Study in Rabbits, DACO: 4.2.5,IIA 5.2.4
1941267	2008, XDE-208: Primary Eye Irritation Study in Rabbits, DACO: 4.2.4,IIA 5.2.5
1941268	2008, XDE-208 Technical Grade Active Ingredient: Local Lymph Node Assay in CBA/J Mice, DACO: 4.2.6,IIA 5.2.6
1941269	2009, X11422208: Palatability Probe Study in Female F344/DuCrl Rats (Revision), DACO: 4.3.3,IIA 5.3.1
1941270	2009, X11422208: 28-Day Dietary Toxicity Study in F344 DuCrl Rats, DACO: 4.3.3,IIA 5.3.1
1941271	2007, X11422208: Palatability and Toxicokinetic Probe Study in CRL:CD1(ICR) Mice (Revision), DACO: 4.3.3,IIA 5.3.1
1941272	2008, X11422208: 28-Day Dietary Toxicity Study in CRL:CD1(ICR) Mice, DACO: 4.3.3,IIA 5.3.1
1941273	2010, XDE-208: Palatability and Tolerability Probe in Beagle Dogs, DACO: 4.3.3,IIA 5.3.1
1941274	2009, Revised XDE-208: 28-Day Palatability/Tolerability Probe Study in Beagle Dogs, DACO: 4.3.3,IIA 5.3.1
1941276	2010, XR-208: 90-Day Dietary Toxicity Study in F344/DuCrl Rats with a 28-Day Recovery in F344/DuCrl Rats, DACO: 4.3.1,4.5.13,IIA 5.3.2,IIA 5.7.4
1941277	2010, Revised Report: XR-208: 90-Day Dietary Toxicity Study in Crl:CD1(ICR) Mice, DACO: 4.3.1,IIA 5.3.2
1941278	2010, XDE-208: A 90-Day Oral Gavage Toxicity Study in Beagle Dogs, DACO: 4.3.2,IIA 5.3.3
1941279	2009, XDE-208: 28-Day Dermal Toxicity Study in F344 DuCrl Rats, DACO: 4.3.5,IIA 5.3.7
1941280	2007, Salmonella-Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with XR-208, DACO: 4.5.4,IIA 5.4.1
1941281	2007, Evaluation of XR-208 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.5.6,IIA 5.4.2
1941282	2007, Evaluation of XR-208 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, DACO: 4.5.5,IIA 5.4.3
1941283	2009, Evaluation of XR-208 in the Mouse Bone Marrow Micronucleus Test, DACO: 4.5.7,IIA 5.4.4
1941284	2010, XDE 208: Two-Year Chronic Toxicity/Oncogenicity Study in F344/DuCrl Rats, DACO: 4.4.1,4.4.4,IIA 5.5.1
1941285	2010, XDE-208: Oncogenicity Study in Crl:CD1(ICR) Mice, DACO: 4.4.3,IIA 5.5.3
1941286	2008, Gene Eexpression and Cell Proliferation Analyses in X11422208 Exposed Rats and Mice, DACO: 4.8,IIA 5.5.4
1941287	2010, XR-208: Targeted Gene Expression, Cell Proliferation, and Cytochrome P450 Enzymatic Activity in Rats (Revision), DACO: 4.8,IIA 5.5.4
1941288	2010, XDE-208: Mode of Action Study Investigating Liver Weight Effects in Crl:CD1(ICR) Mice (Revision), DACO: 4.8,IIA 5.5.4
1941289	2010, XDE-208: A Study to Characterize the Induction Profile of XDE-208 in the Livers of C57BL/6J Mice, DACO: 4.8,IIA 5.5.4
1941290	2010, XDE-208: A Study to Investigate the Mode of Action for Liver Effects Observed in Regulatory Toxicology Studies by Use of Dual CAR-PXR Knockout and Humanised Mice, DACO: 4.8,IIA 5.5.4
1941291	2010, XDE-208: Dietary Reproduction & Developmental Toxicity Screening Test in CRL:CD(SD) Rats, DACO: 4.5.1,IIA 5.6.1
1941292	2010, XDE 208: Two Generation Dietary Reproductive Toxicity Study in CRL:CD(SD) Rats, DACO: 4.5.1,IIA 5.6.1
1941293	2008, XDE-208: Dietary Developmental Toxicity Probe Study in CRL:CD(SD) Rats, DACO: 4.5.2,IIA 5.6.10

1941294	2010, XDE-208: Dietary Developmental Toxicity Study in Crl:CD(SD) Rats, DACO: 4.5.2,IIA 5.6.10
1941295	2008, XDE-208: Oral Gavage Developmental Toxicity Probe Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11
1941296	2009, XDE-208: Dietary Developmental Toxicity, Palatability Probe Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11
1941297	2009, XDE-208: Dietary Developmental Toxicity Study in New Zealand White Rabbits, DACO: 4.5.3,IIA 5.6.11
1941298	2010, XDE 208: A Dietary Reproductive Toxicity Cross-Fostering Study in CRL:CD(SD) Rats, DACO: 4.5.2,IIA 5.6.10
1941299	2009, A Study of The Effects of XDE-208 on Neonatal Survival in New Zealand White Rabbits (Revision), DACO: 4.2.9,4.3.8,4.4.5,4.5.3,4.5.8,4.8,IIA 5.10,IIA 5.6.11
1941300	2010, XDE-208: Characterization of the Agonist Effects of XDE-208 on Mammalian Muscle Nicotinic Acetylcholine Receptors, DACO: 4.5.2,IIA 5.6.10
1941301	2010, XDE-208: Investigation of the Critical Window of Exposure for Fetal Abnormalities and Neonatal Survival Effects in Crl:CD(SD) Rats, DACO: 4.5.2,IIA 5.6.10
1941302	2010, XDE-208: Investigation of the Critical Window of Exposure for Fetal Abnormalities and Neonatal Survival Effects in Crl:CD(SD) Rats (PHASE 2), DACO: 4.5.2,IIA 5.6.10
1941303	2010, XDE-208: Observations on the Effects of XDE-208 on the Phrenic Nerve Hemidiaphragm Preparation From New-Born Rat (Revision), DACO: 4.5.2,IIA 5.6.10
1941304	2010, XDE 208: Histopathological Evaluation of Fetal Lung Samples from the Developmental Toxicity Study in Crl:CD(SD) Rats, DACO: 4.5.2,IIA 5.6.10
1941305	2010, XDE-208: Acute Neurotoxicity Study in F344-DuCrl Rats, DACO: 4.5.12,IIA 5.7.1
1941306	2010, XDE-208: A Dietary Developmental Neurotoxicty Study of XDE-208 in Rats, DACO: 4.5.14,IIA 5.7.5
1941307	2007, X11719474: Acute Oral Toxicity Screening Study in F344/DuCrl Rats, DACO: 4.8,IIA 5.8
1941309	2010, X11719474: Acute Oral Toxicity Study in Rats: Acute Toxic Class Method, DACO: 4.8,IIA 5.8
1941310	2012, X11719474: Acute Dermal Toxicity, Skin Irritation and Eye Irritation Screening Studies, DACO: 4.8,IIA 5.8
1941311	2010, X11719474: Cut-Down, Reduced Local Lymph Node Assay in CBA/J Mice (Revision), DACO: 4.8,IIA 5.8
1941312	2010, X11719474: Palatability Probe Study in F344-DuCrl Rats, DACO: 4.8,IIA 5.8
1941313	2010, X11719474: 28-Day Dietary Toxicity Study in F344-DuCrl Rats, DACO: 4.8,IIA 5.8
1941314	2010, X11719474: 90-Day Dietary Toxicity Study in F344-DuCrl Rats, DACO: 4.8,IIA 5.8
1941315	2010, X11719474: A Dose-Ramge Finding and Tolerability Study in Male Beagle Dogs, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,IIA 5.10,IIA 5.8
1941316	2010, X11719474: A 90-Day Oral Gavage Toxicity Study in Male Beagle Dogs, DACO: 4.8,IIA 5.8
1941317	2008, *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with X11719474, DACO: 4.8,IIA 5.8
1941318	2008, Evaluation of X11719474 an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.8,IIA 5.8
1941319	2008, Evaluation of X11719474 in The Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Foward Mutation Assay, DACO: 4.8,IIA 5.8
1941320	2010, X11719474: Targeted Gene Expression, Cell Proliferation, and Cytochrome P450 Enzymatic Activity in Male F344/DuCrl Rats to Determine The Mode of Action for Effects on The Liver, DACO: 4.8,IIA 5.8
1941321	2010, X11719474: Dietary Reproduction - Developmental Toxicity Screening Test in CRL:CD(SD) Rats, DACO: 4.8,IIA 5.8
1941322	2010, X11719474: Dietary Developmental Toxicity Study in CRL:CD(SD) Rats, DACO: 4.8,IIA 5.8

1941323	2010, X11721061: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.8,IIA 5.8
1941324	2010, X11721061: A 1-Week Palatability Study in Male Fisher Rats, DACO: 4.8,IIA 5.8
1941325	2010, X11721061: A 28-Day Oral Dietary Toxicity Study in F344/DuCrl Rats, DACO: 4.8,IIA 5.8
1941326	2009, *Salmonella* & *Escherichia coli*-Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with X11721061, DACO: 4.8,IIA 5.8
1941327	2010, Evaluation of X11721061 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.8,IIA 5.8
1941328	2010, Evaluation of X11721061 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, DACO: 4.8,IIA 5.8
1941329	2010, X11596066: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.8,IIA 5.8
1941330	2010, *Salmonella* & *Escherichia coli*-Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with X11596066, DACO: 4.8,IIA 5.8
1941331	2010, X11579457: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.8,IIA 5.8
1941332	2010, *Salmonella* & *Escherichia coli*-Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with X11579457, DACO: 4.8,IIA 5.8
1941333	2010, X11519540: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.8,IIA 5.8
1941334	2010, *Salmonella* & *Escherichia coli*-Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with X11519540, DACO: 4.8,IIA 5.8
1967120	2010, Oral 90-day toxicity (dog) - Rationale for not Submitting a 1-Year Dog Toxicological Study, DACO: 4.3.2,IIA 5.3.3
1967121	2010, A Retrospective Analysis of Toxicity Studies in Dogs and Impact on the Chronic Reference Dose for Conventional Pesticide Chemicals, DACO: 4.3.2,IIA 5.3.3
1967122	2010, A 1-Year Toxicity Study in Dogs is no Longer a Scientifically Justifiable Core Data Requirement for the Safety Assessment of Pesticides, DACO: 4.3.2,IIA 5.3.3
1998841	2010, XDE-208 Revised Document L- Section 3 - Toxicology, DACO: 4.1
1999110	2010, XDE-208: A One-Year Oral Gavage Toxicity Study in Beagle Dogs, DACO: 4.3.2,IIA 5.3.4
1999138	2010, Evaluation of X11579457 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.5.6,IIA 5.4.2
1999139	2010, Evaluation of X11579457 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guaninephosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, DACO: 4.5.5,IIA 5.4.3
1999140	2010, Evaluation of X11519540 in The Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, DACO: 4.5.5,IIA 5.4.3
1999141	2010, Evaluation of X11519540 in an In Vitro Chromosomal Aberration Assay Utilizing Rat Lymphocytes, DACO: 4.5.6,IIA 5.4.2
1999142	2010, X11519540: Palatability Probe Study in Male F344/DuCrl Rats, DACO: 4.8,IIA 5.8
1999145	2010, XDE-208: Mode of Action and Human Relevance Framework Analysis for XDE-208-Induced Rodent Liver Tumors, DACO: 4.8,IIA 5.5.4
1999146	2010, XDE-208: Mode of Action Evaluation and Human Relevance Framework Analysis for XDE-208-Induced Fetal Abnormalities and Neonatal Death in Rats, DACO: 4.8,IIA 5.5.4
1999147	2010, X11519540: 28-Day Dietary Toxicity Study in F344/DuCrl Rats, DACO: 4.3.3,IIA 5.3.1
1999148	2010, XDE-208: Leydig Cell Mode-of-Action Study in CRL:CD(SD) and F344/DuCrl Rats, DACO: 4.8,IIA 5.5.4
2000044	2010, XDE-208 Revised Document L- Section 3 - Toxicology, DACO: 4.1
2060408	2011, XDE-208 (Sulfoxaflor): Mode of Action and Human Relevance Framework Analysis for XDE-208 Induced Promotion of Fischer 344 Rat Leydig Cell Tumours, DACO: 4.8
2060409	2011, XDE-208 Technical: Screening for Estrogen Receptor and Androgen Receptor Binding and Transactivation and Aromatase Inhibition, DACO: 4.8
2099400	2010, X11719474: Probe study to determine absorption, metabolism and elimination in F344/DuCrl Rats, DACO: 4.5.9

2109852	2010, DAS-Tox Response - CRL_EFD_FULL_GD20_v3.10 (Developmental Parameters for Crl:CD(SD)Rats(Full) v.3.10), DACO: 4.8
2109853	2010, DAS-Tox Response - CRL_Repor_v2.11 (Historical Control Summary), DACO: 4.8
2109854	2010, DAS-Tox Response - HCR Kit Survival (Rabbit Natural Delivery Historical Control Data), DACO: 4.8
2109855	1992, DAS-Tox Response - Marr_1992_Ethylene_Glycol_Skeletal: Developmental Stages of the CD (Sprague-Dawley) Rat Skeleton After Maternal Exposure to Ethylene Glycol, DACO: 4.8
2109856	2011, DAS-Tox Response - Rabbit_HC_information, DACO: 4.8
2109857	2011, Effects of X11422208 Infusion on Hypothalamic Dopamine, Dopac and HVA Efflux - A Microdialysis Experiment in Freely-Moving Rats, DACO: 4.8
2109858	1986, Potential Reversibility of Skeletal Effects in Rats Exposed in Utero to Caffeine, DACO: 4.8
2109859	2011, XDE-208 (Sulfoxaflor): Mode of Action and Human Relevance Framework Analysis of Preputial Gland Carcinomas in the Two-Year F344/DuCrl Rat Carcinogenicity Assay, DACO: 4.8
1941093	2009, GF-2372: Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1,IIIA 7.1.1
1941094	2009, GF-2372: Acute Dermal Toxicity Study in Rats, DACO: 4.6.2,IIIA 7.1.2
1941095	2010, GF-2372: Acute Dust Aerosol Inhalation Toxicity Study in F344/DuCrl Rats, DACO: 4.6.3,IIIA 7.1.3
1941096	2010, GF-2372: Primary Skin Irritation Study in Rabbits, DACO: 4.6.5,IIIA 7.1.4
1941097	2010, GF-2372: Primary Eye Irritation Study in Rabbits, DACO: 4.6.4,IIIA 7.1.5
1941098	2010, GF-2372: Local Lymph Node Assay in CBA/J Mice, DACO: 4.6.6,IIIA 7.1.6
1941141	2009, GF-2032: Acute Oral Toxicity Study in Rats: Acute Toxic Class Method, DACO: 4.6.1,IIIA 7.1.1
1941142	2009, GF-2032: Acute Dermal Toxicity Study in Rats, DACO: 4.6.2,IIIA 7.1.2
1941143	2009, GF-2032: Acute Liquid Aerosol Inhalation Toxicity Study in F344-DuCrl Rats, DACO: 4.6.3,IIIA 7.1.3
1941144	2009, GF-2032: Primary Skin Irritation Study in Rabbits, DACO: 4.6.5,IIIA 7.1.4
1941145	2009, GF-2032: Primary Eye Irritation Stusy in Rabbits, DACO: 4.6.4,IIIA 7.1.5
1941146	2008, GF-2032: Local Lymph Node Assay in CBA/J Mice, DACO: 4.6.6,IIIA 7.1.6
2024787	2010, GF-2032 - Rationale for Study Waiver for MRID 47832409 (acute inhalation), DACO: 4.6.3
1941340	2010, A Nature of the Residue Study with [14C]-XDE-208 Applied to Tomatoes, DACO: 6.3,IIA 6.2.1
1941341	2010, A Nature of the Residue Study with [14C]-XR-208 Applied to Peas, DACO: 6.3,7.4.5,IIA 6.2.1,IIA 6.5.1
1941342	2010, A Nature of the Residue Study with [14C]-XR-208 Applied to Lettuce, DACO: 6.3,IIA 6.2.1
1941343	2010, A Nature of the Residue Study with [14C]-XR-208 Applied to Rice (Amended Report), DACO: 6.3,7.4.5,IIA 6.2.1,IIA 6.5.1
1941344	2009, A Nature of the Residue Study in the Laying Hen with 14C-XDE-208, DACO: 6.2,IIA 6.2.2
1941345	2010, A Nature of the Residue Study in the Laying Hen with [14C]-X11719474, A Metabolite of XDE-208, DACO: 6.2,7.4.5,IIA 6.2.2,IIA 6.5.1
1941346	2010, A Nature of the Residue Study in the Ruminant with 14C-XDE-208, DACO: 6.2,7.4.5,IIA 6.2.3,IIA 6.5.1
1941347	2010, A Nature of the Residue Study in the Ruminant with [14C]-X11719474, Metabolite of XDE-208, DACO: 6.2,7.4.5,IIA 6.2.3,IIA 6.5.1
1999104	2010, Residues in/on a Root, Leafy Vegetable, Cereal, and Forage Grass as Rotated Crops Following Treatment with XDE-208, DACO: 7.4.4,IIA 6.6.3
1999105	2010, Residues of XDE-208 in/on Apple from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2

1999107	2010, Residues of XDE-208 in Barley at Intervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999108	2010, Residues of XDE-208 in/on Barley from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999109	2010, Residues of XDE-208 in Beans at Intervals and Harest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999111	2010, Residues of XDE-208 in Broccoli at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999112	2010, Residues of XDE-208 in Oil Seed Rape at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999113	2010, Residues of XDE-208 in Cauliflower at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999114	2010, Residues of XDE-208 in and on Cherry from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999115	2010, Residues of XDE-208 in Cotton at Imtervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999116	2010, Residues of XDE-208 in Cucumbers at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999117	2010, Residues of XDE-208 in Grapes at Intervals and Harvest Following Multiple Applications of GF-2032 -Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999118	2010, Residues of XDE-208 in/on Grapefruit from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999119	2010, Residues of XDE-208 in/on Lemon from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999120	2010, Residues of XDE-208 in Head Lettuce at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999121	2010, Residues of XDE-208 in Leaf Lettuce at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999123	2010, Residues of XDE-208 in Ooutdoor Melons at Intervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999124	2010, Residues of XDE-208 in/on Mustard Greens from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999125	2010, Residues of XDE-208 in/on Orange from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999126	2010, Residues of XDE-208 in Pears at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999127	2010, Residues of XDE-208 in/on Pepper from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999128	2010, Residues of XDE-208 in Bell Peppers at Intervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999129	2010, Residues of XDE-208 in Chilis Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999130	2010, Residues of XDE-208 in/on Potato from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999131	2010, Residues of XDE-208 in/on Radish from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999132	2010, Residues of XDE-208 in Tomatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999133	2010, Residues of XDE-208 in Cherry Tomatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999134	2010, Residues of XDE-208 in Indoor Tomatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Europe - 2010, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999135	2010, Residues of XDE-208 in/on Tomato from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
1999137	2010, Residues of XDE-208 in Wheat Processed Fractions, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2

1999143	2010, Frozen Storage Stability Study for Sulfoxaflor (XDE-208) and its Major Metabolites in Soil-Interim Report-Six Months Stability Data, DACO: 7.3,IIA 6.1.1
1999144	2010, Frozen Storage Stability Study for Sulfoxaflor (XDE-208) and its Major Metabolites in Water-Interim Report- Six Months Stability Data, DACO: 7.3,IIA 6.1.1
1999149	2010, Frozen Storage Stability of Sulfoxaflor (XDE-208) and its Main Metabolites in Crops Interim Report, DACO: 7.3,IIA 6.1.1
1941354	2010, Residues of XDE-208 in Cereals Following Foliar Application of GF-2032 in New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941355	2010, Residues of XDE-208 in Cereals Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941356	2010, Residues of XDE-208 in Barley at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941357	2010, Residues of XDE-208 in Barley at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941365	2010, Residues of XDE-208 in Canola Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941367	2010, Residue of XDE-208 in and on Canola from the USA and Canada, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941368	2010, Residues of XDE-208 in Oil Seed Rape at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941370	2010, Residues of XDE-208 in Canola Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941425	2010, Residues of XDE-208 Iinsecticide in Soybeans Commodities After Multiple Applications of GF-2032 Formulation, Brazil, 2008-2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941427	2010, Magnitude of Residues of XDE-208 in and on Soybean from the USA - Formulation Bridging Study, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941442	2010, Magnitude of Residues of XDE-208 in-on Wheat from the USA and Canada - Formulation Bridging Study (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941443	2010, Residues of XDE-208 in Wheat at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southeren Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941444	2010, Residues of XDE-208 in Wheat at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941445	2010, Processing Study to Determine the Nature of Residues of 14C-XDE-208, 14C-X11719474 and 14C-X11721061 Following Industrial or Household Preparation, DACO: 7.4.5,IIA 6.5.1
1941447	2010, Residues of XDE-208 in Barley Grain and Process Fractions at Harvest Following Multiple Applications of GF-2032 - 2008, DACO: 7.4.5,IIA 6.5.3
1941449	2010, Residues of XDE-208 in Oil Seed Rape and Process Fractions Following Multiple Applications of GF-2032 - 2008, DACO: 7.4.5,IIA 6.5.3
1941460	2010, Residue of XDE-208 in Soybean Processed Fractions (Amended Report), DACO: 7.4.5,IIA 6.5.3
1941465	2010, Residue of XDE-208 in Wheat Processed Fractions, DACO: 7.4.5,IIA 6.5.3
1941335	2010, Frozen Storage Stability of Sulfoxaflor (XDE-208) and its Main Metabolites in Crops - Interim Report, DACO: 7.3,IIA 6.1.1
1941336	2010, Frozen Storage Stability Study for Sulfoxaflor (XDE-208) and its Major Metabolites in Soil-Interim Report-Six Weeks Stability Data, DACO: 7.3,IIA 6.1.1
1941337	2010, Frozen Storage Stability Study for Sulfoxaflor (XDE-208) and its Major Metabolites in Water-Interim Report-Six Weeks Stability Data, DACO: 7.3,IIA 6.1.1
1941338	2010, XDE-208 Livestock Feedig Study: Magniture of Residue in Eggs, Muscle, Liver and Fat of Laying Hens, DACO: 7.3,7.5,7.6,IIA 6.1.1,IIA 6.4.1
1941339	2010, XDE-208 Livestock Feeding Study: Magnitude of Residue in Milk, Muscle, Fat, Liver and Kidney of Lactating Dairy Cattle, DACO: 7.3,7.5,7.6,IIA 6.1.1,IIA 6.4.2
1941348	2010, Residue of XDE-208 in and on Almonds from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1

1941349	2010, Residues of XDE-208 in Apples Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941350	2010, Residue of XDE-208 in-on Apple from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941351	2010, Residues of XDE-208 in Apples at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941352	2010, Residues of XDE-208 in Apricots Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941353	2010, Residues of XDE-208 in Cereals Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941354	2010, Residues of XDE-208 in Cereals Following Foliar Application of GF-2032 in New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941355	2010, Residues of XDE-208 in Cereals Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941356	2010, Residues of XDE-208 in Barley at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941357	2010, Residues of XDE-208 in Barley at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941358	2010, Residues of XDE-208 Insecticide in Dry Beans After Applications of GF-2032 Formulation, Brazil, 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941359	2010, Residues of XDE-208 in Beans at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941360	2010, Residues of XDE-208 in Broccoli at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941361	2010, Residue of XDE-208 in and on Broccoli from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941362	2010, Residues of XDE-208 in and on Cabbage from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941363	2010, Residues of XDE-208 in Head Cabbage at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941364	2010, Residues of XDE-208 in Broccoli, Cabbage, Chinese Cabbage and Brussels Sprouts Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941365	2010, Residues of XDE-208 in Canola Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941367	2010, Residue of XDE-208 in and on Canola from the USA and Canada, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941368	2010, Residues of XDE-208 in Oil Seed Rape at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941370	2010, Residues of XDE-208 in Canola Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941371	2010, Residue of XDE-208 in, on Carrot from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941372	2010, Residues of XDE-208 in Carrots at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941373	2010, Residues of XDE-208 in Cauliflower at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941374	2010, Residues of XDE-208 in cauliflowers following foliar application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941375	2010, Residues of XDE-208 in and on Celery from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1

1941376	2010, Residues of XDE-208 in Cherries Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941378	2010, Residues of XDE-208 in Cherries at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.5,7.4.6,IIA 6.3.1,IIA 6.5.1
1941379	2008, Residues of XDE-208 Iinsecticide in Cotton After Multiple Applications of GF-2032 Formulation, Brazil, 2008-2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941380	2010, Residue of XDE-208 in, on Cotton from the USA, DACO: 7.4.1,7.4.2,7.4.5,7.4.6,IIA 6.3.1,IIA 6.5.1
1941381	2010, Residues of XDE-208 in Cotton at Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941383	2010, RESIDUES OF XDE-208 IN COTTON AT INTERVALS AND HARVEST FOLLOWING MULTIPLE APPLICATIONS OF GF-2032 - SOUTHERN EUROPE - 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941384	2010, Residues of XDE-208 in cotton following foliar application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941385	2010, Residue of XDE-208 in and on Cucumber from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941386	2010, Residues of XDE-208 in Cucumbers at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941387	2010, Residues of XDE-208 in Zucchinis Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941388	2010, Residue of XDE-208 in and on Grape from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941389	2010, Residues of XDE-208 in Grapes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941390	2010, Residues of XDE-208 in Grapes Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941391	2010, Residues of XDE-208 in Grapes Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941392	2010, Residues of XDE-208 in Lettuce Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941393	2010, Residues of XDE-208 in and on Head Lettuce from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941394	2010, Residues of XDE-208 in Head Lettuce at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941396	2010, Residues of XDE-208 in Lettuce Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941397	2010, Residue of XDE-208 in and on Leaf Lettuce from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941398	2010, Residues of XDE-208 in Leaf Lettuce at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941399	2010, Residues of XDE-208 Insecticide in Melon After Applications of GF-2032 Formulation, Brazil, 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941400	2010, Residues of XDE-208 in and on Muskmelon from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941401	2010, Residues of XDE-208 in Outdoor Melons at Intervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941403	2010, Residues of XDE-208 in Nectarines and Plums Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941404	2010, Residues of XDE-208 in Nectarines Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941405	2010, Residue of XDE-208 in, on Bulb Onion in the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1

1941406	2010, Residues of XDE-208 in and on Green Onion from the USA, DACO: 7.4.1, 7.4.2, 7.4.6, IIA 6.3.1
1941407	2010, Residues of XDE-208 Insecticide in Citrus after Multiple Applications of GF-2032 Formulation, Brazil, 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941408	2010, Residues of XDE-208 in Citrus Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941409	2010, Residues of XDE-208 in Citrus Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941410	2010, Residue of XDE-208 in and on Orange from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941411	2010, Residues of XDE-208 in Peaches at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008 and 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941412	2010, Residues of XDE-208 in Peaches Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941413	2010, Residues of XDE-208 in Peaches Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941414	2010, Residue of XDE-208 in-on Peach from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941416	2010, Residues of XDE-208 in and on Pear from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941417	2010, Residues of XDE-208 in Pears at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941418	2010, Residues of XDE-208 in Pears Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941419	2010, Residues of XDE-208 in and on Pecan from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941420	2010, Residues of XDE-208 in Bell Peppers at Intervals and Harvest Following Multiple Applications of GF-2032 - Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941421	2010, Residues of XDE-208 in Capsicums Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941422	2010, Residues of XDE-208 in and on Plum from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941423	2010, Residue of XDE-208 in, on Potato from the USA and Canada, DACO: 7.4.1, 7.4.2, 7.4.5, 7.4.6, IIA 6.3.1, IIA 6.5.1
1941424	2010, Residues of XDE-208 in Potatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941426	2010, Residue of XDE-208 in-on Soybeans from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941428	2010, Residue of XDE-208 in and on Spinach from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941429	2010, Residues of XDE-208 in Spinach Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941430	2010, Residue of XDE-208 in and on Squash from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941431	2010, Residues of XDE-208 in-on Strawberry from the USA (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941432	2010, Residues of XDE-208 in Strawberries Following Foliar Application of GF-2032 in Australia and New Zealand, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941433	2010, Residue of XDE-208 in and on Sugar Beet from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941434	2010, Residues of XDE-208 in Sugarbeet at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941435	2010, Residues of XDE-208 in Cherry Tomatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1

1941436	2009, Residues of XDE-208 Insecticide in Tomato After Applications of GF-2032 Formulation, Brazil, 2009, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941437	2010, Residue of XDE-208 in and on Tomato from the USA, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941438	2010, Residues of XDE-208 in Tomatoes at Intervals and Harvest Following Multiple Applications of GF-2032 - Northern and Southern Europe - 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941439	2010, Residues of XDE-208 in Tomatoes Following Foliar Application of GF-2032 in Australia, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941440	2010, Residues of XDE-208 Insecticide in Wheat After Applications of GF-2032 Formulation, Brazil, 2008, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941441	2010, Residue of XDE-208 in and on Wheat from the USA and Canada (Amended Report), DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.1
1941450	2010, Residue of XDE-208 in Carrot Processed Fractions (Amended Report), DACO: 7.4.5,IIA 6.5.3
1941452	2010, Residues of XDE-208 in Cherries and Process Fractions Following Multiple Applications of GF-2032 - Northern Europe - 2009, DACO: 7.4.5,IIA 6.5.3
1941453	2010, Residues of XDE-208 in Cotton Processed Fractions, DACO: 7.4.5,IIA 6.5.3
1941454	2010, Residues of XDE-208 in Grapes and Process Fractions Following Multiple Applications of GF-2032 - Northern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941455	2010, Residues of XDE-208 in Head Lettuce and Process Fractions Following Multiple Applications of GF-2032 - Northern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941456	2010, Residues of XDE-208 in Leaf Lettuce and Pprocess Fractions Following Multiple Applications of GF-2032 - Northern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941457	2010, Residue of XDE-208 in Onion Processed Fractions, DACO: 7.4.5,IIA 6.5.3
1941458	2010, Residue of XDE-208 in Orange Processed Fractions (Amended Report), DACO: 7.4.5,IIA 6.5.3
1941459	2010, Residues of XDE-208 in Potatoes and Process Fractions Following Multiple Applications of GF-2032 - Northern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941460	2010, Residue of XDE-208 in Soybean Processed Fractions (Amended Report), DACO: 7.4.5,IIA 6.5.3
1941462	2010, Residues of XDE-208 in Strawberry Processed Fractions, DACO: 7.4.5,IIA 6.5.3
1941463	2010, Residues of XDE-208 in Sugarbeet and Process Fractions Following Multiple Applications of GF-2032 - Southern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941464	2010, Residues of XDE-208 in Tomatoes and Process Fractions Following Multiple Applications of GF-2032 - Southern Europe - 2008, DACO: 7.4.5,IIA 6.5.3
1941465	2010, Residue of XDE-208 in Wheat Processed Fractions, DACO: 7.4.5,IIA 6.5.3
2035644	2010, A Confined Rotational Crop Study with 14C-XDE-208, DACO: 7.4.3
2035645	2011, CL submitting the Confined Rotational Crop Study with 14C-XDE-208, DACO: 0.8

3.0 Environment

PMRA Document Number	Reference
1941101	2010, Laboratory bioassay to determine the acute contact toxicity of GF-2372 to the honeybee, *Apis mellifera*. DACO: 9.2.8
1941102	2009, GF-2372: Toxicity of Residues on Foliage to the Honeybee, *Apis mellifera*. DACO: 9.2.8
1941151	2009, Laboratory bioassay to determine the acute oral toxicity of GF-2032 to the honeybee, *Apis mellifera*. DACO: 9.2.8
1941152	2009, GF-2032: Laboratory bioassays to determine the acute oral and contact toxicity of GF-2032 to the bumblebee, *Bombus terrestris*. DACO: 9.2.8
1941153	2009, Laboratory bioassay to determine the acute contact toxicity of GF-2032 TO THE HONEYBEE, *Apis mellifera*. DACO: 9.2.8

1941155	2008, Effects of XDE-208 (GF-2032, 240 g as/L, SC) on the vegetative vigour of non-target terrestrial plants (Tier 1) - 2008. DACO: 9.8.6
1941156	2010, GF-2032: Effects on the vegetative vigor of non-target terrestrial plants (Tier I). DACO: 9.8.6
1941158	2009, GF-2032: Effects on the seedling emergence and growth of non-target terrestrial plants (Tier II). DACO: 9.8.6
1941224	2009, Hydrolysis of XDE-208 at pH 5, 7, and 9. DACO: 8.2.3.2
1941225	2010, Aqueous Photolysis of XDE-208 and X11719474 in pH 7 Buffer Under Xenon Light. DACO: 8.2.3.3, 8.2.3.3.2
1941227	2010, Estimation of the Photochemical Oxidation Rate of XDE-208. DACO: 8.2.3.3.3
1941466	2010, Aerobic Degradation of XDE-208 in Four US Soils. DACO: 8.2.3.4.2
1941467	2009, Aerobic and Anaerobic Degradation of XDE-208 in Four European Soils. DACO: 8.2.3.4.2, 8.2.3.4.4
1941468	2010, XDE-208: Degradation in One Soil under Anaerobic Conditions Following Incubation under Aerobic Conditions. DACO: 8.2.3.4.4
1941469	2010, Photodegradation of XDE-208 on Soil. DACO: 8.2.3.3.1
1941470	2010, Aerobic Soil Degradation Rate of X11579457 in 4 European Soils. DACO: 8.2.3.4.2, 8.2.3.4.4
1941471	2010, Aerobic Soil Degradation Rate of X11519540 in 4 European Soils. DACO: 8.2.3.4.2
1941472	2010, Dissipation of XDE-208 in Soil under Cropped and Bare-Soil conditions at Multiple Sites across North America. DACO: 8.3.1, 8.3.2, 8.3.2.1
1941477	2010, Adsorption/Desorption of XDE-208 and Adsorption of Three XDE-208 Soil Metabolites. DACO: 8.2.4.2
1941478	2010, Natural Water Photolysis of XDE-208 and the X11719474 Metabolite under Xenon Light. DACO: 8.2.3.3.2
1941479	2010, Aerobic Transformation of XDE-208 in Two European Aquatic Sediment Systems. DACO: 8.2.3.5.2, 8.2.3.5.4
1941480	2010, Anaerobic Aquatic Degradation of XDE-208 in a US Sediment and Pond Water System. DACO: 8.2.3.5.2, 8.2.3.5.4
1941481	2008, XDE-208: An acute oral toxicity study with the northern bobwhite. DACO: 9.6.2.1, 9.6.2.2, 9.6.2.3
1941482	2009, XDE-208 technical: An acute oral toxicity study with the zebra finch (*Poephila guttata*). DACO: 9.6.2.1, 9.6.2.2, 9.6.2.3
1941483	2009, X11719474: An acute oral toxicity study with the northern bobwhite. DACO: 9.6.2.1, 9.6.2.2, 9.6.2.3
1941484	2008, XDE-208: A dietary LC_{50} study with the northern bobwhite. DACO: 9.6.2.4, 9.6.2.5
1941485	2008, XDE-208: A dietary LC_{50} study with the mallard. DACO: 9.6.2.6
1941486	2009, XDE-208 TGAI: A reproduction study with the northern bobwhite. DACO: 9.6.3.1, 9.6.3.2, 9.6.3.3
1941487	2010, XDE-208 TGAI: A reproduction study with the mallard. DACO: 9.6.3.1, 9.6.3.2, 9.6.3.3
1941488	2008, XDE-208: Acute toxicity test to the rainbow trout, *Oncorhynchus mykiss*, determined under static test conditions. DACO: 9.5.2.1, 9.5.2.3
1941489	2008, XDE-208: Acute Toxicity Test To The Bluegill Sunfish, *Lepomis macrochirus*, Determined Under Static Test Conditions. DACO: 9.5.2.2, 9.5.2.3
1941490	2008, XDE-208: Acute toxicity test to the common carp, *Cyprinus carpio*, determined under static test conditions. DACO: 9.5.2.2, 9.5.2.3
1941491	2008, X11719474: Acute toxicity to the rainbow trout, *Oncorhynchus mykiss*, determined under static test conditions. DACO: 9.5.2.3, 9.5.2.4
1941492	2009, Toxicity of XDE-208 technical to fathead minnow (*Pimephales promelas*) in an early-life stage test. DACO: 9.5.3.1
1941493	2008, XDE-208: Static Acute Toxicity Test With The Water Flea, *Daphnia magna*. DACO: 9.3.2
1941494	2008, X11719474: Acute Toxicity to the Water Flea, *Daphnia magna*, Determined Under Static-Renewal Test Conditions. DACO: 9.3.2
1941495	2009, Influence of XDE-208 technical to *Daphnia magna* in a reproduction test. DACO: 9.3.3

1941496	2009, Testing of effects of XDE-208 on the single cell green alga *Pseudokirchneriella subcapitata* in a static 96 h test. DACO: 9.8.2, 9.8.3
1941497	2009, Testing of effects of XDE-208 on the marine diatom *Skeletonema costatum* in a static 96 h test. DACO: 9.8.2, 9.8.3
1941498	2009, Testing of effects of XDE-208 on the blue-green *Alga Anabaena flos-aquae* in a 96 h Static Test. DACO: 9.8.2, 9.8.3
1941499	2009, Testing of effects of XDE-208 on the diatom *Navicula pelliculosa* in a 96 h static test. DACO: 9.8.2, 9.8.3
1941500	2008, XDE-208: Whole Sediment 10 Day Acute Toxicity Test With Midge Larvae (*Chironomus dilutus*). DACO: 9.9
1941501	2009, Toxicity of XDE-208 technical to the aquatic plant *Lemna gibba* in a semi-static growth inhibition test. DACO: 9.8.5
1941502	2007, XR-208: Acute oral toxicity test with the honeybee, *Apis mellifera*. DACO: 9.2.4.2
1941503	2009, Laboratory bioassay to determine the acute oral toxicity of X11719474 to the honeybee, *Apis melllifera*. DACO: 9.2.4.2
1941504	2007, XR-208: Acute contact toxicity test with the honeybee, *Apis mellifera*. DACO: 9.2.4.1
1941505	2008, XDE-208: Determination of Acute Toxicity Of XDE-208 To The Earthworm *Eisenia fetid*a In An Artificial Soil Substrate. DACO: 9.2.3.1
1941506	2008, Determination Of Acute Toxicity Of The Metabolite X11719474 To The Earthworm *Eisenia fetida* In An Artificial Soil Substrate. DACO: 9.2.3.1
1941507	2008, XDE-208: Acute Toxicity Test To The Sheepshead Minnow, *Cyprinodon variegatus*, Determined Under Static Test Conditions. DACO: 9.4.2, 9.4.3, 9.4.4
1941508	2008, XDE-208: Effect on new shell growth of the eastern oyster (*Crassostrea virginica*). DACO: 9.4.2, 9.4.3, 9.4.4
1941510	2009, XDE-208: Static Acute Toxicity Test With The Mysid Shrimp, *Americamysis bahia*. DACO: 9.4.2, 9.4.3, 9.4.4
1941511	2010, XDE-208: Life-cycle toxicity test of the saltwater mysid, *Americamysis bahia*, conducted under flow-through conditions. DACO: 9.4.2, 9.4.3, 9.4.4
1941512	2010, XDE-208: Early Life-Stage Toxicity Test with the Sheepshead Minnow, *Cyprinodon variegatus*, Under Flow-Through Conditions. DACO: 9.4.2, 9.4.3, 9.4.4
1951099	2009, Effects of XDE-208 (GF-2032, 240 g as per l, SC) on seedling emergence of non-target terrestrial plants (Tier 1) - 2008. DACO: 9.8.6
1959829	2009, A rate response laboratory test to determine the effects of GF-2032 on the predatory mite, *Typhlodromus pyri* (Acari: Phytoseiidae), DACO: 9.2.5, 9.2.6
1959832	2009, A rate-response laboratory test to determine the effects of GF-2032 on the parasitic wasp, *Aphidius rhopalosiphi* (Hymenoptera, Braconidae), DACO: 9.2.6
1959833	2009, An extended laboratory test to determine the effects of fresh residues of GF-2032 on the ladybird beetle, *Coccinella septempunctata* (Coleoptera: Coccinellidae), DACO: 9.2.5
1959834	2009, A rate-response laboratory test to determine the effects of GF-2032 on the parasitic wasp, *Aphidius rhopalosiphi* (Hymenoptera, Braconidae), DACO: 9.2.6
1959835	2009, an aged-residue extended laboratory study to determine the effects of GF-2032 on the parasitic wasp, *Aphidius rhopalosiphi* (Hymenoptera, Braconidae), DACO: 9.2.6
1959836	2009, GF-2032: determination of chronic (sub-lethal) toxicity of GF-2032 to the earthworm *Eisenia fetida* in natural soil substrates, DACO: 9.9
1959837	2009, Assessment of the Side Effects of GF-2032 on the Activity of the Soil Microflora, DACO: 9.9
1959983	2009, XDE-208: Chronic Toxicity in Whole Sediment to Freshwater Midge, *Chironomus riparius*, DACO: 9.3.4
2044392	2011, Response to EPA Memorandum "Sulfoxaflor: Preliminary: Preliminary Assessment of Potential Risk Concerns to Pollinators", DACO: 9.2.1
2044394	2010, X11721061 Lab bioassay to determine acute oral toxicity of X11721061 to the honeybee, *Apis mellifera*, DACO: 9.2.4.2,9.2.8
2044396	2010, Toxicity Testing of GF-2032 on Honey Bees (*Apis mellifera* L.) under Semi-Field Conditions-Tunnel Test, DACO: 9.2.9

2044397	2009, GF-2032 A Semi-Field Study to Evaluate Effects on the Honeybee *Apis mellifera* carnica L.; (Hymenoptera, Apidae) in *Phacelia tanacetifolia* in France in 2008, DACO: 9.2.9
2044398	2011, Novel Nicotinic Action of the Sulfoximine Insecticide Sulfoxaflor, DACO: 9.9
2044399	2010, Biological Characterization of Sulfoxaflor, a Novel Insecticide, DACO: 9.9
2044400	2010, Discovery and Characterization of Sulfoxaflor, a Novel Insecticide Targetting Sap-Feeding Pests, DACO: 9.9
2044401	2007, Mutations in Da1 or DB2 Nicotinic Acetylcholine Receptor Subunits Can Confer Resistance to Neonicotinoids in Drosophila melanogaster, DACO: 9.9
2048774	2008, GF-2032: Toxicity of Residues on Foliage to the Honeybee, *Apis mellifera*, DACO: 9.2.4.1
2055636	2011, GF-2626: A Semi-field study to Investigate Residues in Honeybee Products (*Apis mellifera* carnica L,; Hymenoptera, Apidae) in *Phacelia tanacetifolia* in Germany in 2010, DACO: 9.2.4
2173235	2012, Determination of Sulfoxaflor Residues in Various Plant Tissue Following Foliar Application of Low and High Rates of the Insecticide, DACO: 7.4.1
2219817	2012, XDE-208: Acute toxicity effects to honeybee larvae (*Apis mellifera* L.) under laboratory conditions (in vitro), DACO: 9.2.4.3
2173237	2012, XDE-208: Chronic toxicity effects to honeybee larvae (*Apis mellifera* L.) under laboratory conditions (in vitro), DACO: 9.2.4.3
2173238	2012, Study on the Effect of GF -2626 on Honey Bees and their Brood (*Apis mellifera* L.) under SemiField Conditions - Tunnel Test, DACO: 9.2.9
2173239	2012, Study on the Effect of GF-2626 on Honey Bee Brood (*Apis mellifera* L.) under Semi-Field Conditions - Tunnel Test, DACO: 9.2.9
2173240	2012, Sulfoxaflor: a semi-field study in cotton with GF-2372 (sulfoxaflor 50% WP) to determine residues in matrices relevant to exposure of Honey bees and honey bee brood, to enable estimation of exposure of a typical honey bee colony. Field phase conducted in San Joaquin Valley (California, USA), DACO: 9.2.9

4.0 Value

PMRA Document Number	**Reference**
1941103	2010, Part 10 Canadian Efficacy Package to support XDE-208 (Sulfoxaflor) Tri-lateral Registration, DACO: 10.1, 10.2.1, 10.2.2, 10.2.3.1, 10.2.3.4, 10.3.1, 10.3.2
1999094	2010, Efficacy Trial Summary Update, DACO: 10.2.3.1
1999095	2010, Individual Efficacy Trials, DACO: 10.2.3.3
2044400	2010, Zhu, Y., Loso, M.R., Watson, G.B., Sparks, T.C., Roger, R.B., Huang, J.X., Gerwick, B.C., Babcock, J.M., Kelley, D, Hedge, V.B., Nugent, B.M., Renga, J.M., Denholm, I., Gorman, K., DeBoer, G.J., Hasler, J., Meade, T., Thomas, J.D., Discovery and Characterization of Sulfoxaflor, a Novel Insecticide Targeting Sap-Feeding Pests. Journal of Agricultural and Food Chemistry (DOI: 10.1021/jf102765x), DACO: 9.9
2049200	2009, XDE-208 (GF-2032) & DE-175 (GF-1640) *Thrips imaginis* and *Myzus persicae* in nectarines, DACO: 10.6
2049201	2008, Efficacy of GF-2032 (XDE-208) on *Myzus persicae* in peaches in Cova da Biera, Portugal, DACO: 10.6
2049202	2008, Efficacy of GF-2032 (XDE-208) on *Myzus persicae* in peaches (variety spring bell) in Altedo, Italy, DACO: 10.6
2366091	2013, Sulfoxaflor / Leafhopper / Potato, DACO: 10.2.3.3
2366092	2013, Dow NA13C1C052 Aphid and Leafhopper, DACO: 10.2.3.3

B. Additional Information Considered

i) Unpublished Information

1.0 Human and Animal Health

PMRA Document Number	Reference
2115788	2008, Agricultural Reentry Task Force (ARTF), Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients, Submission #2006-0257.