Evaluation Report

Application Number: **2007-3235**
Application: A. 3.2 - New Active Ingredient - PRIORITY-Joint Review
Product: Cyprosulfamide Manufacturing Use Concentrate
Registration Number: **29072**
Active ingredients (a.i.): Cyprosulfamide (CYB)

Application Number: **2007-3236**
Application: A. 3.2 - New Active Ingredient - PRIORITY-Joint Review
Product: Converge Flexx Herbicide
Registration Number: **29071**
Active ingredients (a.i.): Isoxaflutole (IXF) Cyprosulfamide (CYB)
PMRA Document Number : 1951010

Purpose of Application

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Cyprosulfamide Manufacturing Use Concentrate and Converge Flexx Herbicide. Converge Flexx Herbicide contains the chemical safener cyprosulfamide and the active ingredient isoxaflutole and is used for weed control in field corn. The cyprosulfamide in the formulation assists the crop to metabolize the herbicide isoxaflutole, thus reducing undesirable herbicide injury to the crop.

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.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the registrant must submit additional scientific information as a condition of registration.

What Is Cyprosulfamide?

Cyprosulfamide is a chemical safener which, when combined with the herbicide active ingredient isoxaflutole in Converge Flexx Herbicide, assists field corn in metabolizing the isoxaflutole. This further prevents the occurrence of injury to the crop and extends the window of application of isoxaflutole to allow early post emergence application up to the 3 leaf stage of field corn.

Health Considerations

Can Approved Uses of Cyprosulfamide Affect Human Health?

Cyprosulfamide is unlikely to affect your health when Converge Flexx Herbicide is used according to label directions.

Potential exposure to cyprosulfamide may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., 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 products containing cyprosulfamide are used according to label directions.

The safener cyprosulfamide and end-use product Converge Flexx Herbicide were not acutely toxic. Consequently, no hazard statements are required on the labels.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants, the subpopulation which would ingest the most cyprosulfamide relative to body weight, are expected to be exposed to less than 0.3% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from cyprosulfamide is not of concern for all population sub-groups. The lifetime cancer risk from the use of cyprosulfamide on field corn, sweet corn and popcorn is considered acceptable.

Animal studies revealed no acute health effects. Consequently, a single dose of cyprosulfamide is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act (FDA)* 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 FDA purposes through the evaluation of scientific data under the *Pest Control Products Act (PCPA).* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using cyprosulfamide on field corn, sweet corn and popcorn were acceptable. The MRLs for this active ingredient can be found in this document.

Occupational Risks From Handling Converge Flexx Herbicide

Occupational risks are not of concern when Converge Flexx Herbicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Converge Flexx Herbicide as well as field workers re-entering freshly treated fields can come in direct contact with Converge Flexx Herbicide residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Converge Flexx Herbicide must wear coveralls over long-sleeved shirt and long pants and rubber boots. In addition, chemical resistant gloves and protective eyewear must be worn during mixing/loading, clean up and repair. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk 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 Cyprosulfamide Is Introduced Into the Environment?

Cyprosulfamide and it degradates are expected to enter groundwater, but are not expected to impact wildlife or plants. When used in combination with the herbicide isoxaflutole, buffer zones are needed for the protection of plants.

Cyprosulfamide is primarily degraded by micro-organisms in soil and aquatic systems. In soil, cyprosulfamide is not persisent, while its degradates are non-persistent to moderately persistent. Cyprosulfamide and its degradates are mobile in soil and have high potential to reach groundwater. In aquatic systems, cyprosulfamide is moderately persistent; while its degradates are expected to be relatively stable. While cyprosulfamide and its degradates are moderately persistent, they are metabolised and unlikely to bioaccumulate.

Cyprosulfamide does not present a risk to earthworms, bees, other beneficial arthropods, birds, small mammals, fish, aquatic invertebrates, algae, and plants. When used in combination with the herbicide isoxaflutole, the end-use product poses a risk to non-target terrestrial and aquatic plants. Its toxicity to plants is attributed to the herbicidal active ingredient isoxaflutole. Precautionary statements are thus included on the end-use product label and buffer zones of 2 metres (terrestrial habitats) and 1 metre (aquatic habitats) are required to mitigate risk to non-target plants from spray drift.

Value Considerations

What Is the Value of Converge Flexx Herbicide?

Cyprosulfamide assists the crop to metabolize the herbicide isoxaflutole, thus reducing undesirable herbicide injury to the crop. The safening effect allows the herbicide to be applied post emergence, up to the three leaf stage of field corn, allowing greater flexibility for weed control.

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 Converge Flexx Herbicide 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 Converge Flexx Herbicide on the skin or through inhalation of spray mists, anyone mixing, loading and applying Converge Flexx Herbicide must wear coveralls over long-sleeved shirt and long pants and rubber boots. In addition, chemical resistant gloves and protective eyewear must be worn during mixing/loading, clean up and repair. In addition, standard label statements to protect against drift during application were added to the label.

Environment

A hazard statement was added to the label to alert users of the end-use product's toxicity to non-target terrestrial and aquatic plants. Its toxicity to plants is attributed to the herbicidal active ingredient isoxaflutole. Buffer zones of 2 metres (terrestrial habitat) and 1 metres (aquatic habitats) are required for their protection. In addition, a hazard statement was also added to alert users of the product's potential to contaminate groundwater.

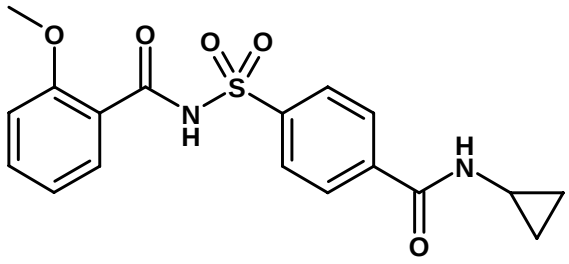
What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the registrant must submit additional scientific information as a condition of registration. More details are presented in this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The registrant must submit the following information.

- Analytical data from at least five batches representing full-scale production for the Cyprosulfamide safener.
- Analytical method for the determination of one impurity in Cyprosulfamide safener.
- Storage stability data for the Converge Flexx formulation representing at least one year of storage at ambient conditions.

CHEMISTRY ASSESSMENT

The Properties and Uses of Cyprosulfamide Manufacturing Use Concentrate

Active substance	Cyprosulfamide
Function	Safener
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	N-[4-(cyclopropylcarbamoyl)phenylsulfonyl]-2-methoxybenzamide
2. Chemical Abstracts Service (CAS)	Benzamide, N-[[4-[(cyclopropylamino)carbonyl]phenyl]sulfonyl]-2-methoxy-
CAS number	221667-31-8
Molecular formula	$C_{18}H_{18}N_2O_5S$
Molecular weight	374.4
Structural formula	
Purity of the active ingredient	97.4% nominal (limits 95.5% - 100.0%)

The Physical and Chermical Properties of Cyprosulfamide Manufacturing Use Concentrate

Property	Result
Colour and physical state	White powder
Odour	No characteristic odour
Melting point	218°C
Boiling point or range	No boiling point at atmospheric pressure
Specific gravity	1.51
Vapour pressure at 20°C	5.72×10^{-9} Pa

Property	Result
Henry's law constant at 20°C	pH 4: << 1.0×10^{-3} Pa·m^3·mol^{-1} pH 7: << 3.44×10^{-6} Pa·m^3·mol^{-1} pH 9: << 1.43×10^{-7} Pa·m^3·mol^{-1} in bidistilled water: << 3.00×10^{-4} Pa·m^3·mol^{-1}
Ultraviolet (UV)-visible spectrum	pH / λ (nm) / ε (l.mol^{-1}.cm^{-1}) 2 / 202 / 43496.37 2 / 243 / 23318.88 2 / 297 / 5118.32 7 / 242 / 24086.44 7 / 297 / 5200.69 10 / 209 / 31762.05
Solubility in water at 20°C	pH 4 0.0034 g/L pH 6.9 1.09 g/L pH 8.1 26.1 g/L In bidistilled water pH 5.1 0.0125 g/L
Solubility in organic solvents at 20°C (g/L)	Solvent / Solubility ethanol 0.47 n-hexane < 0.001 toluene 0.047 dichloromethane 3.5 acetone 3.1 ethyl acetate 0.51 dimethyl sulfoxide > 200
n-Octanol-water partition coefficient (K_{OW})	K_{OW} / log K_{OW} pH 4.0 58.9 1.77 pH 7.0 0.158 -0.80 pH 9.0 0.015 -1.81
Dissociation constant (pK_a)	pKa = 4.2
Stability (temperature, metal)	Stable in the presence of metals and metal ions.

The Physical and Chemical Properties of Converge Flexx Herbicide

Property	Result
Colour	Light beige
Odour	Medium unpleasant, musty odour
Physical state	Viscous liquid
Formulation type	Suspension
Guarantee	Isoxaflutole……240 g/L nominal (limits: 233 g/L – 247 g/L)
Container material and description	HDPE (high density polyethylene containers) 1 L to bulk
Density	1.203 g/mL
pH of 1% dispersion in water	5.3
Oxidizing or reducing action	No oxidizing properties
Storage stability	The product is stable when stored for twelve months at ambient temperature in commercial packaging.
Corrosion characteristics	The product is not corrosive to the packaging material.
Explodability	No components have any explosive properties.

Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the manufacturing use concentrate and the impurities in Cyprosulfamide Manufacturing Use Concentrate have been validated and assessed to be acceptable for the determinations. However, a non specific method of analysis was used to determine one of the impurities in Cyprosulfamide Manufacturing Use Concentrate. The registrant has been requested to provide a specific method.

Method for Formulation Analysis

The methods provided for the analysis of all four formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

Multiresidue Methods for Residue Analysis

Cyprosulfamide was screened through two different multiresidue methods. The first method, DFG Method S 19, published as "Modulare Multimethode zur Bestimmung von Pflanzenschutzmittelrück¬ständen in Lebensmitteln, L 00.00-34", as part of the Collection of Official Methods under Article 64 of the German Food, Commodities and Feed Code and the second through the methods described in the United States Food and Drug Administration (FDA) Pesticide Analytical Manual, Vol. I (PAM I).

The DFG Method S 19 showed that cyprosulfamide was not suitable for analysis by gas chromatography. Therefore, the DFG Method S 19 is not applicable for the determination of cyprosulfamide.

The suitability of the FDA MRM protocols to analyze for residues of cyprosulfamide (AE 0001789), AE 0001789-cyclopropyl-sulfomoylbenzamide (AE 085299, M02), AE 0001789-sulfonamide lactate (AE 230002, M10) and AE 0001789-sulfonamide-alanine (AE 2300003, M11) in non-fatty and fatty foods was evaluated. After following the applicable PAM I protocols, it was concluded that the FDA multi-residue methods are not suitable for residue analysis and enforcement purposes of cyprosulfamide and the metabolites.

Methods for Residue Analysis of Plants and Plant Products

A number of reverse phase high-performance liquid chromatography–electrospray ionization with tandem mass spectrometry (HPLC-MS/MS) methods were developed for the analysis of cyprosulfamide and/or the metabolites M02, M10, M11 in food of plant origin for data gathering (00961, 00962, UB-008-P06-01) and enforcement purposes (00964). All methods fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation (LOQ). A LOQ was reported as 0.01 ppm in plant products for each analyte. Acceptable recoveries (70–120%) of cyprosulfamide and the metabolites were obtained in plant matrices. Extraction efficiency data demonstrated that the enforcement method can account for incurred residues of cyprosulfamide and the metabolites in corn matrices.

Methods for Residue Analysis of Food of Animal Origin

A HPLC-MS/MS method (UB-007-A06-01) was developed for the determination of residues of cyprosulfamide in livestock matrices. A similar method (UB-006-A06-01) was developed for enforcement purposes for the determination of residues of cyprosulfamide and the metabolite M02. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the method LOQ. A LOQ of 0.01 ppm was demonstrated for each analyte in livestock matrices (tissues and eggs) and 0.005 ppm for milk. Acceptable recoveries (70–120%) of cyprosulfamide and M02 were obtained in livestock matrices. Extraction efficiency data demonstrated that the enforcement method can account for incurred residues of cyprosulfamide and M02 in livestock matrices.

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in soil, sediment and water matrices. Methods for residue analysis are summarized in Appendix I, Table 1.

HEALTH ASSESSMENT

TOXICOLOGY

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

Cyprosulfamide was of low acute toxicity via the oral, dermal and inhalation routes to Wistar rats. It was non-irritating when applied to the skin and minimally irritating to the eyes of New Zealand White rabbits. Cyprosulfamide was not a dermal sensitizer in guinea pigs using the Buehler method.

Converge Flexx Herbicide was of low acute toxicity via the oral, dermal and inhalation routes to Wistar rats. It was non-irritating to the skin and minimally irritating to the eyes of New Zealand White rabbits. Although it was not a dermal sensitizer up to a concentration of 10% using the Local Lymph Node Assay in mice, there was some concern that the animals were not challenged with a high enough concentration of the test substance. Review of the formulants in the end-use product revealed select formulants that have been reported to be dermal sensitizers in laboratory animals and/or humans, however, they were not of toxicological concern based on their relatively low concentration in the formulation. In addition, no dose-response relationship in stimulation index was observed with increasing concentrations of test substance and the positive controls validated the study methods. Based on the weight of evidence, Converge Flexx Herbicide was not considered to be a dermal sensitizer.

The pharmacokinetic behaviour of cyprosulfamide was characterized by rapid absorption and elimination from the plasma of rats. Absorption was extensive with between 69-90% of the total recovered radioactivity excreted via the renal route. No significant differences in absorption rates were observed between sexes, or between low dose or high dose tests. Urinary excretion was rapid and was the major route of elimination [70-90% of administered dose (AD) at 96 hours]. Faecal elimination accounted for 9-15% or 26% of AD at the low and high doses, respectively. Excretion was nearly complete within 24 to 48 hours. Expired air did not contain appreciable amounts of cyprosulfamide.

Cyprosulfamide was not extensively metabolized in the rat and the majority of the AD was excreted as unchanged parent compound. The main metabolic reaction was elimination of the cyclopropylamine moiety by hydrolysis of the carboxamide bond in the sulfonylbenzamide moiety, resulting in the most prominent metabolite AE 0001789-descyclopropylamine (2-8% of AD). Hydrolysis of the carboxamide bond in the methoxybenzoyl moiety resulted in the minor

metabolite AE 0001789-cyclopropyl-sulfamoylbenzamide, which can also be formed from the metabolite AE 0001789-desmethyl (desmethylation of parent compound). The minor metabolite AE 0001789-anisic acid resulting from the hydrolysis of the carboxamide bond in the methoxybenzoyl moiety was the only label specific metabolite detected. Each of these minor metabolites represented < 1% of AD. Quantitative whole body autoradiography analysis identified the highest concentrations of cyprosulfamide in the blood and kidneys and generally confirmed the excretion patterns observed during the pharmacokinetic studies.

The main target organ in the mouse, rat and dog via the oral route was the urinary system consisting of the urinary bladder, kidney and urethra. At higher doses, effects in the thymus and liver were observed in the mouse, while testis and haematopoietic effects were observed in rats and dogs, respectively. Males were more sensitive to urinary bladder and urinary tract pathology, while female rats were more sensitive to kidney pathology and urinary tract tumours. In the urinary tract, the key microscopic findings after treatment were urinary sedimentation, formation of calculi/stones, irritation, inflammatory response, dilatation and/or ulceration, and regenerative urothelial hyperplasia. These findings were associated with decreased urinary pH, decreased urine specific gravity, increased blood urea nitrogen and/or increased creatinine levels at higher doses. The testicular effects in rats consisted of increased tubular degeneration, mineralization and oligospermia. Haematopoietic effects in high-dose dogs consisting of decreased red blood cell counts, haematocrit and haemoglobin, were reflective of a mild treatment-related anaemia. In general, there was an increase in mortality (mostly due to renal lesions), clinical signs, decreased body weight/gains and decreased food consumption at high doses.

There was no evidence of genotoxicity in a standard battery of *in vitro* and *in vivo* tests with cyprosulfamide. Increased incidences of transitional cell papillomas in the urinary bladders of female mice and transitional cell carcinomas in the kidney or urinary bladder of rats were observed after chronic exposure at high doses. A mode of action (MOA) framework was used to evaluate the applicability of animal urinary tract tumour data to human risk assessment. A clear description of the key events, with dose and temporal relationships was presented; however, the reversibility of urinary tract lesions after treatment with cyprosulfamide was not investigated. No additional mechanistic studies were submitted. Urinary bladder tumours in mice only occurred in the presence of other urinary tract effects after long-term exposures to doses that produced precipitation of the test substance and generation of urinary crystals/calculi. Calculi were only present at the highest dose tested, but crystals were occasionally present in the urine of mid-dose animals. The low dose was consistently negative for crystals, calculi and other treatment-related effects in the urinary tract. Chemical analysis of urinary tract calculi obtained from cyprosulfamide-treated mice confirmed that the stones were predominantly comprised of the parent compound. Many chemicals such as uracil, melamine, saccharin and others have been identified which fit within this MOA framework. Based on the lack of genotoxicity, the well known biology and toxicology of urinary tract calculi, anatomical differences between rodents and humans, and the lack of carcinogenic effect of related sulfonamide drugs in humans (even at doses that cause formation of sulfonamide crystals in the urinary tract) (Clayson, 1974; Robinson and MacDonald, 2001; Schaeffer and Schaeffer, 2007), cyprosulfamide is not expected to pose a

carcinogenic risk to humans at low exposure levels. A margin of exposure approach was considered to be appropriate for the cancer risk assessment.

Treatment-related histiocytic sarcomas of the haematopoietic system were observed at the highest dose tested in female mice after 18-months of exposure to cyprosulfamide. Based on the increased incidence relative to concurrent controls and laboratory historical control data, the presence of human counterpart conditions (true histiocytic sarcomas, malignant histiocytic lymphomas) and the uncertainty surrounding the mode of action leading to the observed tumours in mice, it was considered appropriate to use a linear low dose extrapolation approach for the cancer risk assessment. Unit risks for cyprosulfamide, denoted by Q_1^* (representing the lower 95% confidence limit on the slope of the dose-response curve in the low-dose region), were calculated based on the data for the histiocytic sarcomas in mice. The Q_1^* of 1.37×10^{-3} (mg/kg bw/day)$^{-1}$ is recommended for use in the cancer risk assessment.

There was no evidence of teratogenicity or increased susceptibility of the young in the developmental studies in the rat or the rabbit. In the rat studies, there was evidence of systemic toxicity in dams with decreased body weight gains, yellow sediment in kidneys, bilateral papillary necrosis and prominent lobulation of the liver at the limit dose but no treatment-related foetal toxicity was observed. In the rabbit developmental studies, more apparent maternal toxicity was noted, including mortality, yellow sediment in urine, fewer faeces, anogenital staining, body weight loss, decreased food consumption and abortions at high doses. There were no treatment-related foetal effects in rabbits.

In the 2-generation reproduction study, reproductive toxicity was observed as a decreased fertility index in the first mating of the F_0 generation and increased pup deaths in the presence of parental toxicity, including female mortalities (due to renal lesions), piloerection, thin appearance/emaciation, decreased body weights, and kidney and spleen toxicity. Similar but less severe parental effects in the absence of treatment-related mortality were also observed in the mid-dose group. In the offspring at the limit dose, decreased body weight/gains were observed in the F_1 and F_2 generations and delayed vaginal opening was observed in the F_1 female offspring. There was no evidence of increased susceptibility of rat pups following exposure to cyprosulfamide.

In the acute neurotoxicity study, the only treatment-related systemic effect was increased urine staining in high dose animals. There was no evidence of treatment-related neurotoxic potential after a single dose of cyprosulfamide. In the subchronic neurotoxicity study, no treatment-related systemic or neurotoxic effects were observed at any doses tested.

A waiver was granted for the short-term dermal rat study, based on the low dermal toxicity and lack of irritation potential after acute exposure and the availability of appropriate NOAELs from the short-term oral studies.

Overall, cyprosulfamide was not genotoxic, and there was no evidence of teratogenic or neurotoxic potential. Toxicological effects on the urinary tract were observed across species in mice, rats and dogs; however, tumours of the renal system were only observed in mice after long-term exposure to high doses of cyprosulfamide. In addition, an increased incidence of histiocytic sarcomas of the haematopoietic system occurred in female mice after 18 months of exposure. In the two-generation reproduction study in rats, treatment-related decreased fertility and pup viability observed in the F_1 generation were noted at doses that caused maternal toxicity, and were considered to be reflective of slight reproductive toxicity. Durational effects of dosing were observed in all species tested. In mice and dogs, increasing the duration of administration resulted in treatment-related renal effects at lower doses, while increased duration of cyprosulfamide treatment in rats resulted in more severe urinary tract lesions.

A soil metabolite referred to as AE 0852999 (M02), which is also a product of rat metabolism, was determined to be non-genotoxic in a standard battery of tests. In a 28-day rat feeding study, M02 caused decreased body weight gains and food consumption, unusual crystals in the urine, and decreased urinary pH (males only) at low doses. Decreased body weight gains, mild anaemia and urinary tract pathology were observed at higher doses. Although the NOAEL in this study is slightly lower than the NOAEL in the long-term rat study with the parent compound, similar toxicological effects were observed in rats at comparable doses of cyprosulfamide. Overall, the limited toxicology studies provided for M02 suggest that it is not significantly more toxic than the parent compound.

A soil metabolite referred to as AE 0467398 (M03) was not genotoxic. In a 90-day rat feeding study, there was some evidence of kidney effects at high doses. Overall, the limited toxicology studies with M03 suggest that it is not more toxic than the parent compound based on the minimal effects observed at a limit dose in the 90-day rat study and the absence of further treatment-related renal effects such as urothelial hyperplasia.

Results of the acute and chronic tests conducted on laboratory animals with cyprosulfamide and its associated end-use product, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 2, 3, and 4 of Appendix I.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account completeness of the data and potential prenatal and postnatal toxicity with respect to the exposure of and toxicity to infants and children. 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, extensive data were available for cyprosulfamide including prenatal developmental toxicity studies in rats and rabbits, and a 2-generation rat reproduction study.

The developmental toxicity studies did not indicate teratogenic potential or increased susceptibility of fetuses to an in utero exposure relative to the adult. In the 2-generation reproductive toxicity study, a decreased fertility index and increased pup deaths were observed in the presence of parental toxicity in the F_0 generation. Concern for these findings was offset by the fact that they occurred at the limit dose of testing and only occurred after the first mating of the F_0 generation. Decreased body weight/gains in the F_1 and F_2 generation pups and delayed vaginal opening in the F_1 female offspring occurred at a dose slightly higher than the limit dose of testing. There was no evidence of increased susceptibility of young relative to the adult in the reproductive toxicity study.

Overall, there were no residual uncertainties with respect to the completeness of the data and the degree of concern for prenatal and postnatal toxicity was low. On the basis of this information, the 10-fold PCPA factor was reduced to 1-fold.

Determination of Acute Reference Dose

An acute reference dose (ARfD) for cyprosulfamide was not determined because an endpoint of concern attributable to a single exposure was not identified in the oral toxicity studies.

Determination of Acceptable Daily Intake

Non-Cancer Endpoints

The recommended acceptable daily intake (ADI) for cyprosulfamide is 0.39 mg/kg bw/day based on the NOAEL of 39 mg/kg bw/day in the 2-year dietary rat study. The findings at the LOAEL of 159 mg/kg bw/day consisted of increased sulfonamide-like crystals in urine, decreased urinary protein, and kidney and urinary bladder pathology. This is the lowest NOAEL in the database and is protective of effects to the thymus, liver, testis and haematopoietic system (anaemia), as well as the urinary tract tumours observed in mice and rats. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. Further to the discussion in the PCPA Hazard Characterization section above, the degree of concern for prenatal and postnatal toxicity was low. For these reasons, it was considered appropriate to reduce the PCPA factor to 1-fold. The composite assessment factor (CAF) is therefore 100-fold. This ADI also provides margins of 736 and 408 to the NOAELs for urinary tract tumours in mice and rats, respectively and >2000 fold to the NOAEL for pup viability effects in the multi-generation reproduction study.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{39 \text{ mg/kg bw/day}}{100} = 0.39 \text{ mg/kg bw/day of cyprosulfamide}$$

Cancer Endpoints

A Q_1* was determined for cyprosulfamide due to the carcinogenic potential of this compound observed at the highest dose in the mouse 18-month feeding study. The most appropriate Q_1* value was 1.37×10^{-3} $(mg/kg\ bw/day)^{-1}$.

OCCUPATIONAL EXPOSURE

Toxicological Endpoints

Occupational exposure to Converge Flexx Herbicide is characterized as short- to intermediate-term and is predominantly by the dermal route.

Short-term dermal and inhalation:

The NOAEL of 58 mg/kg bw/day from the 90-day rat feeding study, based on increased sulphonamide-like crystals in urine, urothelial hyperplasia and basophilic tubules in the urinary bladder at the LOAEL (240/281 mg/kg bw/day in males/females), was considered the most relevant endpoint for short-term dermal and inhalation risk assessment. The target margin of exposure (MOE) of 100 includes a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variability. The waiver submitted for the rat short-term dermal toxicity study was considered to be acceptable, based on the presence of an appropriate short-term oral endpoint and the low acute toxicity observed via the dermal route. An *in vivo* dermal penetration study was not submitted with the data package. No additional uncertainty factors were required. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed female workers.

The cancer endpoints outlined in the section above were also applied to the occupational risk assessment.

Dermal Absorption:

A default dermal absorption value of 100% was used in the risk assessment.

Occupational Exposure and Risk

Since the active ingredient isoxaflutole is already registered on field corn, the risk assessment was conducted for the safener, cyprosulfamide only.

Mixer/loader/applicator Exposure and Non-Cancer Risk Assessment

Individuals have potential for exposure to Converge Flexx Herbicide during mixing, loading and application. Dermal and inhalation exposure estimates for orkers applying Converge Flexx Herbicide to field corn were generated from PHED.

Exposure to workers mixing, loading and applying Converge Flexx Herbicide is expected to be short- to intermediate term in duration and to occur primarily by the dermal route. Exposure estimates for cyprosulfamide were derived for mixer/loaders/applicators applying Converge Flexx Herbicide to field corn using groundboom application equipment. The exposure estimates are based on mixers/loaders/applicators wearing long sleeves, long pants, shoes plus socks and chemical resistant gloves for the mixer/loaders only.

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

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 for cyprosulfamide were compared to the non-cancer toxicological end points (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 100.

Table 1: Non-Cancer Exposure and Risk Estimates for Cyprosulfamide for Workers Mixing/Loading and Applying Converge Flexx Herbicide to Corn using Groundboom Application Equipment

Scenario	PHED Unit Exposure		Exposure (µg/kg bw/day)[a]		MOE[b]		
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Combined
Farmers	84.12	2.56	19.0	0.579	3047	100 122	2962
Custom Applicator	84.12	2.56	38.1	1.16	1523	50 061	1477

[a] Dermal Exposure Estimates= PHED Exposure (µg ai/kg ai handled) X Rate X Volume handled ((L/day) X Dermal Absorption Factor / bw (70kg)

[b] MOE_{Dermal} = NOAEL Dermal (58 mg/kg bw/d) / Dermal exposure estimates (mg/kg/day)

Since the MOEs are above the target, non-cancer exposure for cyprosulfamide to workers mixing/loading and applying Converge Flexx Herbicide to corn is considered acceptable with the

PPE of long sleeved shirts, long pants and gloves during mixing/loading and long sleeved shirts and long pants during application. Since the PPE on the registered liquid products containing isoxaflutole is more protective, this PPE is required on the Converge Flexx Herbicide label.

Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Converge Flexx Herbicide while scouting in row crops with low crop heights and minimal foliage. Given the nature of activities performed, dermal contact with treated surfaces should be low. Inhalation exposure is not expected to make a significant contribution to exposure. The duration of exposure is considered to be short- to intermediate-term, and the primary route of exposure for workers re-entering treated areas would be through dermal contact with treated foliage.

Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients. Activity transfer coefficients are based on data from scouting in sweet corn. Chemical-specific dislodgeable foliar residue data were not submitted. As such, a default dislodgeable foliar residue value of 20% of the application rate was used in the exposure assessment.

Exposure estimates for cyprosulfamide were compared to the non-cancer toxicological endpoint to obtain the margin of exposure (MOE); the target MOE is 100.

Table 2 Postapplication Margin of Exposure on Corn

Activity	Exposure (mg /kg bw/day)[a]	Margin of Exposure[b]
Scouting in minimal foliage	0.00965	6007

a Estimated as 20% application rate × transfer coefficient (cm^2/hour) × 8 hour/day worked × 100% dermal absorption / 70 kg body weight

b NOAEL/ Exposure; target MOE is 100.

Cancer Risk Assessment

Cancer risks were calculated using a linear low-dose extrapolation approach, in which a Lifetime Average Daily Dose (LADD) is calculated and then multiplied by a Q_1* that has been calculated for cyprosulfamide based on dose response data in the appropriate toxicology study (Q_1* = 1.37 x 10^{-3}). Absorbed average daily dose (ADD; equivalent to the exposure estimate for the calculations of non-cancer MOEs) levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were added to obtain combined ADD values, LADD values were then calculated by amortizing exposure over the working lifetime of the occupational worker based on the use pattern. The LADD was compared to the Q_1* to obtain cancer risk estimates (Table 3).

Table 3: Cancer Exposure and Risk Estimates for Cyprosulfamide for Agricultural Workers Handling Converge Flexx Herbicide and Entering Treated Corn Fields

Scenario	ADD (µg/kg bw/d)	Exposure Frequency (days/year)	Working Duration (years)	LADD[a] (mg/kg bw/d)	Cancer Risk[b]
MLA Farmer	19.58	5	50	1.8×10^{-4}	2.4×10^{-7}
MLA Custom	39.23	14	50	1.0×10^{-3}	1.4×10^{-6}
Farmer Post App	9.65	14	50	2.5×10^{-4}	3.4×10^{-7}
Farmer: MLA + Post App	29.23	19	50	4.3×10^{-4}	5.8×10^{-7}

[a] $LADD = \frac{ADD \times \text{Exposure Frequency (days/year)} \times \text{Working Duration (years)}}{365 \text{ days/year} \times \text{Life Expectancy (75 years)}}$

[b] $Risk = LADD \times Q_1^*$ ($Q_1^* = 1.37 \times 10^{-3}$ (mg/kg/day)$^{-1}$

The Agency has defined that occupational carcinogenic risks that are 1×10^{-6} or lower require no risk management action. Cancer risk estimates for cyprosulfamide are below 2×10^{-6} for all commercial application scenarios.

Since there are no residential uses, no residential exposure is expected.

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 or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature, application equipment and sprayer settings.

FOOD RESIDUES

Residues in Plant and Animal Foodstuffs

The residue definition for enforcement and risk assessment purposes in corn is cyprosulfamide (AE 0001789) and in animal commodities is cyprosulfamide and AE 0001789-cyclopropyl-sulfamoylbenzamide (M02). The data gathering and enforcement analytical methodologies, reverse phase HPLC-MS/MS, are valid for the quantitation of the analytes of interest in plant and livestock commodities. The residues of cyprosulfamide are stable in corn (kernels, forage and stover), soybean seed, head lettuce and potato tuber for up to 360 days and in tomato fruit for up to 180 days when stored in a freezer at -18°C.

Residue data from trials conducted in the NAFTA representative growing regions using the end-use product containing cyprosulfamide in or on field corn (crop group 15) are sufficient to

support the establishment of maximum residue limits. Residue data from US residue trials in or on sweet corn and popcorn in the NAFTA representative growing regions are sufficient to establish the import maximum residue limits.

No residues of cyprosulfamide were detected above the LOQ in rotational crops (edible commodities of soybean, turnips and wheat) at a plantback interval of 30 or 60 days.

The potential for transfer of total cyprosulfamide residues in meat, milk and eggs exists because there are feedstuffs associated with the proposed use on field corn. The data from the cattle feeding and poultry metabolism studies indicate that anticipated residues of cyprosulfamide and M02, expressed as total cyprosulfamide are expected below the LOQ in meat and meat by-products as a result of feeding livestock with crops treated with cyprosulfamide.

Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.03).

Chronic Dietary Exposure Results and Characterization

A basic chronic dietary exposure assessment was performed taking into account proposed MRLs for crops and animal matrices (meat, meat by-products and milk). The basic chronic dietary exposure from all supported cyprosulfamide food uses ranges from 0.0% to 0.1% (0.000076 to 0.000507 mg/kg bw/day) of the acceptable daily intake (ADI) for the total population, including infants and children. Aggregate exposure to cyprosulfamide from food and water is considered acceptable: 0.1% to 0.3% (0.000335 to 0.001127 mg/kg bw/day) of the ADI for the total population. The highest aggregate exposure and risk estimate is for all infants (< 1 year) at 0.3% (0.001127 mg/kg bw/day) of the ADI.

Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

Cancer Dietary Exposure Results and Characterization

A basic cancer dietary exposure assessment for food only was performed taking into account MRLs for crops and animal matrices (meat, meat by-products and milk). The basic cancer dietary exposure from all supported cyprosulfamide food uses ranges from 1.06×10^{-7} to 7.10×10^{-7} (0.000076 to 0.000507 mg/kg bw/day) of the lifetime risk (Q_1^* = 0.00139 mg/kg bw/day) for the total population, including infants and children. A refined cancer dietary exposure assessment for food and water was performed taking into account median residue trial data from treated crops and anticipated residues in animal commodities (meat, meat by-products and milk). The refined cancer dietary aggregate exposure to cyprosulfamide from food and water is below PMRA's level of concern (1.0×10^{-6} mg/kg bw/day): 1.87×10^{-7} to 6.10×10^{-7} (0.000134 mg/kg bw/day to 0.000435 mg/kg bw/day) of the life time risk for the total population, including infants and children.

Maximum Residue Limits

Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Field corn grain	0.01
Sweet corn kernels plus cob with husks removed	0.01 (import)
Popcorn grain	0.01 (import)
Eggs; fat, meat and meat by-products of cattle, goats, hogs, horses, sheep and poultry	0.02
Milk	0.01

For additional information on Maximum Residue Limits (MRL) 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 chronic non-cancer and cancer dietary risk estimates are summarized in Tables 1, 5 and 6 in Appendix I.

ENVIRONMENT ASSESSMENT

Cyprosulfamide enters the terrestrial environment when used as a safener in combination with the herbicide isoxaflutole for control of weeds in corn crops. Cyprosulfamide is not persistent in soil with half-lives of 2-10 days under laboratory conditions and 9-20 days under field conditions. Biotransformation is the major route of transformation under aerobic conditions via mainly three parallel reactions: desmethylation; cleavage of cyclopropylamine; or cleavage of the sulfonamide bond. The combined degradation pathway for cyprosulfamide under different conditions in/on soil is shown in Appendix I, Figure 1-1. The major transformation products

resulting from these reactions are M01, M02, M03, M04, and M06 with corresponding half-lives of 1-8 days (non-persistent), 23-49 days (slightly persistent), 37-44 days (slightly persistent), 8-102 days (non- to moderately persistent), and 2-6 hours (non-persistent) in soil. Cyprosulfamide is stable to hydrolysis and soil photolysis is not an important transformation pathway in the environment as indicated by a relatively long half-life of 63-144 days. Only one major photolysis product was formed, M05, but it transforms as quickly as it is formed with a half-life of 6-21 hours. Under anaerobic soil conditions, cyprosulfamide was moderately persistent with a half life of 56 days. The major transformation products were M01, M02, M03, and M09. M09 was unique to anaerobic soil metabolism. Cyprosulfamide and its transformation products do not strongly bind to soil particles and are potentially mobile in soil. The data indicated a clear correlation with the soil pH and the sorption of cyprosulfamide, M01, M04, and M05: the lower the soil pH the higher the sorption constant. No clear correlation could be observed between OC normalized sorption constant and soil pH for M02 and M03. Considering their mobility and persistence, cyprosulfamide, M01, M02, M03, and M04 are expected to reach groundwater; while the products M05 and M06 will not persist long enough to leach through the soil profile.

Cyprosulfamide could reach surface water systems by spray drift or runoff. Cyprosulfamide is moderately persistent in aquatic systems with a laboratory-derived half-life of 79-156 days. Cyprosulfamide slowly partitions from water to sediment where it biotransforms. Biotransformation proceeds via the same three parallel reactions as under aerobic soil conditions. The combined degradation pathway for cyprosulfamide under different conditions in water is shown in Appendix I, Figure 1-2. As in soil, the major transformation products resulting from these reactions in the aquatic system are M01, M02, M03, M04, and M06. Cyprosulfamide is stable to hydrolysis, but direct phototransformation of cyprosulfamide can be an important fate process in the photolytic zone of aquatic systems. The major products of aqueous photolysis are M07 and M08. While the transformation products are detected in both water and sediment phases, only M01, M02, M07, and M08 would be considered important in the water phase. None of the products appear in the sediment at appreciable concentrations. Under aerobic conditions in aquatic systems, M04 is about as persistent as the parent cyprosulfamide, while the remaining metabolites are expected to be relatively stable. Under anaerobic conditions in aquatic systems, cyprosulfamide was persistent with a half-life of approximately 200 days. Only one major metabolite was observed, M04, which is expected to accumulate in the water phase under anaerobic conditions.

Cyprosulfamide has a very low vapour pressure and is therefore not volatile. Even if the parent substance cyprosulfamide may not reach the atmosphere by volatilization, other routes are conceivable (e.g., spray drift). Should cyprosulfamide reach the air it will react quickly with hydroxyl radicals with a half-life of 4-12 hours. The postulated metabolite M06, which is known to be volatile, is expected to react with hydroxyl radicals with a DT_{50} of 6-12 hours. As the remaining metabolites are even more polar than the parent cyprosulfamide, it was concluded that they would be even less volatile than the parent and are not expected to reach the atmosphere.

Cyprosulfamide and the transformation products M01, M02, M03, M04, M05, and M08 are unlikely to bioaccumulate, as indicated by very low log K_{ow} values at environmentally relevant pH values. The transformation products M06 and M07, which are also rat metabolites are also

unlikely to bioaccumulate. This conclusion is based on the rat metabolism study which indicated no tendency of cyprosulfamide or its metabolites to bioaccumulate.

Identification of the transformation products relevant to the environment are summarized in Appendix I, Table 7. Data on the environmental fate and behaviour of cyprosulfamide and its transformation products are summarized in Appendix I, Table 8.

Effects on Non-Target Species

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 exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. 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 = 2 for non-target arthropods[1]; LOC = 1 for all other species). 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 (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

[1] LOC of 2.0 for non-target arthropods other than bees is based on extensive empirical comparison of risk quotients and known acceptable effects from field and semi-field studies for the two indicator species (*A. rhopalosiphi* and *T. pyri*).

Effects on Terrestrial Organisms

Risk to cyprosulfamide, its associated end-use product Cyprosulfamide and Isoxaflutole SC 240+240 g/L, and its soil metabolites M01, M02, M03, and M05 to terrestrial organisms was based upon the evaluation of toxicity data for the following (Appendix I, Table 9):

- one earthworm species (acute or long-term exposure), one bee species and three other arthropods (oral or contact exposure) representing invertebrates;
- two bird and one mammal species representing vertebrates (acute, short-term, or long-term exposure); and
- eleven crop species representing non-target vascular plants.

The uncertainty factors used in modifying the toxicity values are summarized in Appendix I, Table 10.

For assessment of earthworms, a screening level EEC in soil is 0.047 mg cyprosulfamide/kg dry soil. This is based on the initial EEC on soil immediately following application based on a soil density of 1.5 g/cm^3, soil depth of 15 cm, and the rate of 106 g cyprosulfamide/ha. The metabolites are also screened at this concentration assuming 100% conversion from parent. The unmodified toxicity endpoints used for assessment of acute effects were LC_{50} >1000 mg/kg dry soil for technical cyprosulfamide, M01, M02, M03, and M05; and LC_{50} >205 mg cyprosulfamide/kg dry soil for the associated end-use product. The toxicity endpoint used for assessment of chronic effects of cyprosulfamide was NOEC 4.23 mg/kg dry soil (no effect at highest dose). All screening level RQ values were ≤0.01 (Appendix I, Table 12). Therefore, there are no concerns about the use of cyprosulfamide affecting earthworms.

For assessment of bees and other non-target arthropods, a screening level EEC for acute oral or contact exposure to residues is 106 g cyprosulfamide/ha. For bees, the LD_{50} values in µg/bee were converted to the equivalent rates in kg/ha by multiplying 1.12 according to Atkins et al. (1981) so that the toxicity value can be compared to the exposure value (units must be the same). For technical cyprosulfamide, the converted bee LD_{50} values were >114 and >112 kg/ha for oral and contact exposure, respectively. For the associated end-use product, the converted bee LD_{50} values were >61 and >56 kg cyprosulfamide/ha for oral and contact exposure, respectively. For beneficial arthropods, the LR_{50} values were >101 g cyprosulfamide/ha for contact exposure. All screening level RQ values were <1 (Appendix I, Table 12, indicating there are no concerns about the use of cyprosulfamide affecting bees or other non-target arthropods. In addition, the reproductive data for the other non-target arthropods (<50% deviation from control) demonstrate that significant ecological and between season effects are not expected.

For assessment of birds and small wild mammals, the EEC values for cyprosulfamide in potential food items within the treated field were determined immediately after application of 106 g cyprosulfamide/ha. The screening level estimated daily exposure (EDE) values were dependent on the body weight of an organism (20, 100, 1000 g for birds and 15, 35, 1000 g for mammals), food preferences (100% small insects for insectivores, 100% fruits for frugivores, 100% grain and seeds for granivores, and 100% leaves and leafy crops for herbivores), and amount consumed on a daily basis. The EDE values are summarized in Appendix I, Table 11 for each size/ animal/ feeding guild combination. The unmodified cyprosulfamide toxicity endpoints used were LD_{50} >2000 mg/kg bw for acute assessment of birds and small wild mammals; LD_{50} >1068 mg/kg bw/day for short-term dietary assessment of birds; NOEL 17.7 mg/kg bw/day for long-term assessment of birds based on reduced number of eggs laid; and NOEL 173 mg/kg bw/day for long-term assessment of small wild mammals based on increased mortality and reduced weight gain. For assessment of birds and small wild mammals, all screening level RQ values were <1 (Appendix I, Table 12). Therefore, there are no concerns about the use of cyprosulfamide affecting birds and small wild mammals.

For assessment of non-target plants, a screening level EEC is based on direct exposure to the 106 g cyprosulfamide/ha application. To assess the impact of cyprosulfamide alone (500 SC formulation), the toxicity endpoint used was ER_{25} >160 g cyprosulfamide/ha considering both pre- and post-emergent exposure. For the proposed end-use product Cyprosulfamide and Isoxaflutole SC 240+240 g/L, the toxicity endpoint is the 5th percentile hazard rate (HR_5) based on the species sensitivity distribution of the EC_{50} data for the most sensitive endpoint. In this case, the most sensitive endpoint for the majority of the plant species is biomass. The range of ER_{50} values for biomass of eleven plant species was 1.6 to >101 g cyprosulfamide/ha with an HR_5 of 2.7 g cyprosulfamide/ha. The screening level RQ value for cyprosulfamide alone (500 SC formulation) was <1, while the RQ value for the proposed end-use product was 39 (Appendix I, Table 12). Therefore, cyprosulfamide by itself is not of concern and the toxicity of the proposed end-use product is attributed to the herbicidal active ingredient isoxaflutole. For the proposed end-use product, an RQ for drift deposition at 1 metre downwind (6% of applied) from the point of application indicates that impacts on non-target terrestrial plants adjacent to the treatment area are still of concern (RQ 2.4). Therefore, risk mitigation is necessary for the protection of non-target terrestrial plants adjacent to the treatment area. Based on the risk identified to non-target terrestrial plants as a result of drift, a buffer zone of 2 metres is required for terrestrial habitats.

Effects on Aquatic Organisms

Risk of cyprosulfamide, its associated end-use product Converge Flexx Herbicide, and its metabolites M01, M02, M03, M05, M07 and M08 to aquatic organisms was based upon the evaluation of toxicity data for the following (Appendix I, Table 9):

- one freshwater and one marine invertebrate shrimp species and one bivalve species (acute or chronic exposure);
- three freshwater and one marine fish species (acute or early life stage exposure); and
- one sensitive algal species, and one vascular plant species.

The uncertainty factors used in modifying the toxicity values are summarized in Appendix I, Table 10.

Screening level EEC values for cyprosulfamide in water were calculated assuming a reasonable conservative scenario of direct application to water bodies of two different depths (80 cm and 15 cm). The 80-cm water body is chosen to represent a permanent body of water and 15 cm is chosen to represent a seasonal body of water. The permanent body of water was used to assess the risk to organisms that depend on it (i.e., fish); whereas the seasonal body of water was used to assess the risk to organisms that use seasonal bodies of water (i.e., amphibians). The pesticide is assumed to be instantaneously and completely mixed within the water body.

For assessment of fish, aquatic invertebrates, algae, and aquatic vascular plants, a screening level EEC of cyprosulfamide in permanent water body (80-cm water depth) is 0.013 mg/L based on an application rate of 106 g cyprosulfamide/ha. The metabolites are also screened at this concentration assuming 100% conversion from parent.

The unmodified toxicity endpoints used for assessment of acute effects were LC_{50} >100 mg/L for acute exposure of fish and invertebrate (crustaceans and molluscs) to technical cyprosulfamide; EC_{50} >20 mg cyprosulfamide/L for acute exposure of invertebrates the associated end-use product; and EC_{50} >100 mg/L for acute exposure of invertebrates to the metabolites M01, M02, M03, M05, M07, or M08. The toxicity endpoints used for assessment of long-term effects were NOEC 57.2 mg/L for chronic exposure of invertebrates to technical cyprosulfamide based on lack of brood development and reduced adult female length/ weight; and NOEC 4.67 mg/L for fish early life stage exposure to technical cyprosulfamide based on reduced length/ weight. For algae, the unmodified toxicity endpoints used were EC_{50} >100 mg/L for technical cyprosulfamide and M05; yield EC_{50} 1.01 mg cyprosulfamide/L for the associated end-use product; cumulative biomass EC_{50} 29 and 54 mg/L for M03 and M08, respectively; and yield EC_{50} 27, 73, and 28 mg/L for M01, M02, and M07, respectively. For aquatic vascular plants, the unmodified toxicity endpoints were EC_{50} >100 mg/L for technical cyprosulfamide, M01, M02, M03, M07, and M08; EC_{50} 0.0059 mg/L for the associated end-use product based on cumulative biomass (frond number); and EC_{50} 59 mg/L for M05 based on yield (frond number).

With the exception of aquatic vascular plant exposure to the end-use product, all screening level RQ values were <1 (Appendix I, Table 12). Therefore, there are no concerns about the use of cyprosulfamide affecting fish, aquatic invertebrates, and algae.

Based on toxicity data, it was concluded that the effects of Converge Flexx Herbicide on aquatic vascular plants were due to the herbicide active ingredient isoxaflutole. This can be confirmed by the results of the risk assessment where the screening level RQ values for cyprosulfamide and its metabolites were <1; however, the screening level RQ value for Converge Flexx Herbicide was 4.4 (Appendix I, Table 12). Therefore, there are no concerns about cyprosulfamide by itself or its metabolites affecting aquatic vascular plants.

A refined EEC for cyprosulfamide as a result of drift was also determined for a permanent water

body (80-cm water depth) to further assess the risk of Converge Flexx Herbicide to aquatic vascular plants. The maximum drift from a ground boom sprayer and medium textured spray quality (ASAE) one-metre downwind is 6% (see PRO2005-06 for more information on drift). The resulting EEC of cyprosulfamide for a permanent water body (80-cm water depth) is 0.00078 mg cyprosulfamide/L. The resulting RQ indicates that aquatic vascular plants are at low risk beyond 1 metre from the edge of the spray swath (RQ <1). Therefore, a default buffer zone of 1 metre is required for aquatic habitats.

For assessment of amphibians, a screening level EEC of cyprosulfamide in a seasonal water body (15-cm water depth) is 0.071 mg/L based on an application rate of 106 g cyprosulfamide/ha. Based on fish toxicity data, RQ values were <1 for both acute and chronic exposure (Appendix I, Table 12). Therefore, there are no concerns about the use of cyprosulfamide affecting amphibians.

The addition of the safener cyprosulfamide to the formulation reduces the risk of isoxaflutole toxicity to non-target terrestrial plants by a factor of 4 and aquatic planrs by a factor of 2 (Appendix I, Table 13).

VALUE ASSESSMENT

Converge Flexx Herbicide is a selective herbicide for use as a pre-plant surface (up to 14 days prior to planting), pre-emergence or early post emergence (up to 3 leaf stage of field corn) treatment on field corn. The product is applied once per growing season at rates between 79-105 g isoxaflutole/ ha with the co-formulated safener cyprosulfamide.

Effectiveness against Pests

Efficacy data were submitted from 22 small scale field plots conducted in 2005 and 2006 throughout several locations in Ontario. The herbicide treatments were applied using small plot application equipment, and were within the growth stage range indicated on the label.

The efficacy of Converge Flexx Herbicide was visually assessed as percent weed control and compared to an untreated weedy check. Observations were made up to three times throughout the growing season.

Acceptable Efficacy Claims

The submitted efficacy data support the weed control claims summarized in Table below. Accepted use claims for Converge Flexx Herbicide are identical to Converge Pro Herbicide, with the addition of an early post emergence application timing permitted up to the 3 leaf stage of field corn.

Weed control claims for Converge Flexx Herbicide

Herbicide rate	Weeds controlled
79 g a.i./ha *or* *0.33L of product /ha*	common lamb's quarters*, common ragweed*, large and smooth crabgrass, dandelion (seedling) eastern black nightshade, plantain (seedling), red root pigweed*, tall waterhemp*, velvetleaf, wild mustard, witch grass, wormseed mustard
105 g a.i./ha *or* *0.44L of product/ha*	barnyard grass, green foxtail

* including conventional, triazine and ALS herbicide tolerant populations

Phytotoxicity to Host Plants

Crop tolerance data from 34 field corn small plot trials conducted in multiple locations across Ontario and Quebec in 2005 and 2006 were submitted in support of host crop tolerance claims for several combinations of pre-plant surface, pre-emergence and post emergence timings on conventional and no-till cropping systems. Only some trials contained treatments at the 2x rate of Converge Flexx Herbicide.

Crop injury was visually assessed up to 3 times during the growing season. Crop yield, expressed as either a percentage of the weed free check or as a percentage of the commercial standard was reported in twelve dedicated crop tolerance trials.

Acceptable Claims for Host Plants for Converge Flexx Herbicide

Crop injury to field corn treated with Converge Flexx Herbicide applied alone or in tank mixture with atrazine and or glyphosate was always less than 5%. Crop yield was also comparable to registered commercial treatments.

Impact on Succeeding Crops

Two end use products containing isoxaflutole are presently registered for use in Canada without a crop safener: Converge Pro Suspension Concentrate Herbicide (Registration Number 27446) containing isoxaflutole at 480 g/L and Converge 75 WDG Herbicide (Registration Number 26142) containing isoxaflutole at 75%.

The proposed application rates per hectare of Converge Flexx Herbicide are identical to those of both Converge 75WDG and Converge Pro SC Herbicides in terms of the active ingredient isoxaflutole. One application per year is recommended for all three products therefore the maximum seasonal amount of isoxaflutole applied per hectare with Converge Flexx Herbicide (105g a.i./ha/year) will remain identical to that which results from an application of either Converge 75WDG or Converge Pro SC Herbicide.

The addition of a safener is not expected to have an impact on the carryover of isoxaflutole. No further rotational crop data is required to support the following rotational crops that appear on the Converge Herbicide labels.

Accepted rotational crops and planting intervals

Four months after a spring application of 102000014305 SC Herbicide
• Winter Wheat
The year following an application of 102000014305 SC Herbicide:
• Alfalfa
• Canola
• Field corn
• Spring oats
• Processing peas
• Potato
• Soybean
• Timothy
• Tomato*
• Spring wheat
The second year following an application of 102000014305 SC Herbicide
• Dry common beans (all types)

**Caution should be used when planting tomato the year following an application of Converge Flexx Herbicide + atrazine if conditions were exceptionally dry during the season of application.*

The Converge Flexx Herbicide, Converge 75 WDG Herbicide and Converge Pro Herbicide labels will all carry identical use instructions for pre-plant surface and pre-emergence applications. However, the Converge Flexx Herbicide label will also include an early post-emergence use pattern for application to corn up to the 3-leaf stage. An early post-emergence application could result in an extension of the window of application of isoxaflutole by approximately 10-14 days. This increase in the application window would not be expected to alter carryover of isoxaflutole residues at biologically active levels beyond those already established following applications of Converge 75 WDG Herbicide or Converge Pro Herbicide. Chemical hydrolysis and microbial degradation are the principal mechanisms of isoxaflutole transformation, both of which would be more rapid during periods of higher soil temperature. These conditions would be experienced during summer months, as opposed to spring. Thus, residues of isoxaflutole resulting from application of Converge Flexx Herbicide, Converge 75 WDG or Converge Pro Herbicide would be present in soil during the period of most rapid degradation, and the residue level carryover to subsequent years unlikely to differ between product delivery.

PEST CONTROL PRODUCT POLICY CONSIDERATIONS

Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, cyprosulfamide was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of cyprosulfamide were also considered, including transformation products formed in the environment, and contaminants and formulants in the technical product and the end-use product. Cyprosulfamide and its transformation products were evaluated against the following Track 1 criteria: persistence in soil ≥182 days; persistence in water ≥182 days; persistence in sediment ≥365 days; persistence in air ≥2 days; and bioaccumulation log K_{ow} ≥5. In order for cyprosulfamide or its transformation products to meet Track 1 criteria, the criteria for both bioaccumulation and persistence (in one medium) must be met. The technical product and end-use product, including formulants, were assessed against the contaminants identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern, Part 3 Contaminants of Health or Environmental Concern.* The PMRA has reached the following conclusions:

- Cyprosulfamide does not meet Track 1 criteria. Cyprosulfamide does not meet the Track 1 criterion for persistence, as its half-life values are 4-12 hours in air, 68-94 days in water, 3-10 days in soil, and 83-149 days in sediment. Cyprosulfamide does not meet the Track 1 criterion for bioaccumulation, as its octanol-water partition coefficient is -0.8 at pH 7. Therefore, cyprosulfamide is not considered a Track 1 substance.

- Cyprosulfamide does not form any transformation products that meet the Track 1 criteria. All transformation products considered relevant to soil (M01, M02, M03, and M04) have log K_{ow} values of <0, which not meet the Track 1 criterion for bioaccumulation. The additional tranformation products relevant to water include the aqueous photolysis products M07 and M08. The low K_{ow} value for M08 is -2.9 which also does not meet the Track 1 criterion for bioaccumulation. The rat metabolism study, in which M07 was a metabolite, indicated no tendency of cyprosulfamide or its metabolites to bioaccumulate.

- There are no Track 1 formulants or contaminants in the technical or end use products.

Formulants and Contaminants of Health or Environmental Concern

During the review process, formulants and contaminants in the technical and end-use products are assessed against the formulants and contaminants identified in the *Canada Gazette*, Part II,

Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. This list of formulants and contaminants of health and environmental concern are identified using existing policies and regulations including: the federal Toxic Substances Management Policy; the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol); and the PMRA Formulants Policy as described in the PMRA Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*. The *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* is maintained and used as described in the PMRA Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

The *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* consists of three parts:

- 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.

The contaminants to which Part 3 applies meet the federal Toxic Substances Management Policy criteria as Track 1 substances, and are considered in section 6.1. The following assessment refers to the formulants and contaminants in Part 1 and Part 2 of the list.

Cyprosulfamide Manufacturing Use Concentrate and the end-use product Converge Flexx Herbicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental*

SUMMARY

Human Health and Safety

The toxicology database submitted for cyprosulfamide is adequate to define the majority of potential toxic effects that may result from exposure to cyprosulfamide. In subchronic and chronic studies on laboratory animals, the primary targets were the urinary bladder and kidney, with effects on thymus, liver, testis and the haematopoietic system at higher doses. There was evidence of carcinogenicity in the urinary bladders and kidneys of mice and rats, but only at doses where distinct precursor urinary tract changes were previously noted. In addition, histiocytic sarcomas of the haematopoietic system were observed in female mice at high doses and a linear approach was used for the cancer risk assessment. There was no evidence of increased susceptibility of the young in the reproduction and developmental studies, or neurotoxic potential after acute and subchronic exposure. 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.

Mixer, loader applicators handling Converge Flexx Herbicide and workers re-entering treated corn fields to perform scouting in row crops with low crop heights and minimal foliage are not expected to be exposed to levels of Converge Flexx Herbicide that will result in an unacceptable risk when the Converge Flexx Herbicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residue in corn plants and animals is adequately understood. The residue definition for risk assessment and enforcement is cyprosulfamide for corn and cyprosulfamide plus the metabolite M02 in foods of animal origin. The use of cyprosulfamide on field corn does not constitute an unacceptable chronic or cancer 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.

Environment

There are no concerns about the use of cyprosulfamide affecting earthworms, bees, other beneficial arthropods, birds, mammals, fish, aquatic invertebrates, and algae. Although there are no concerns about cyprosulfamide by itself affecting plants, risk of adverse effects on plants as a result of the use of its associated end-use product could not be ruled out from an initial screening level assessment. The toxicity to plants is attributed to the herbicidal active ingredient isoxaflutole. A refined assessment of drift deposition at 1 metre downwind from the point of application indicates there is still concern about negative impacts on non-target terrestrial plants adjacent to the treatment area; while aquatic vascular plants will not be affected beyond 1 metre from the edge of the spray swath. Therefore, a default buffer zone of 1 metre is required for aquatic habitats. Based on the risk identified to non-target terrestrial plants as a result of drift, a buffer zone of 2 metres is required for terrestrial habitats.

Value

The data submitted to register the crop safener, cyprosulfamide, in formulation with the herbicide active ingredient, isoxaflutole, as Converge Flexx Herbicide are adequate to describe its efficacy for use in field corn. A single pre-plant, pre-emergence or early post emergence application (up to the three leaf stage of field corn) provides control of common lamb's quarters, common ragweed, large and smooth crabgrass, dandelion (seedling) eastern black nightshade, plantain (seedling), red root pigweed, tall waterhemp, velvetleaf, wild mustard, witch grass, wormseed mustard, barnyard grass and green foxtail. The submitted phytotoxicity and yield data demonstrate an adequate margin of safety of labelled host crops to Converge Flexx Herbicide (Group 27) provides an alternative mode of action to commonly used Group 2 and Group 4 herbicides.

Conclusion

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Cyprosulfamide Manufacturing Use Concentrate and Converge Flexx Herbicide. Converge Flexx Herbicide contains the chemical safener cyprosulfamide and the active ingredient isoxaflutole and is used for weed control in field corn. The cyprosulfamide in the formulation assists the crop to metabolize the herbicide isoxaflutole, thus reducing undesirable herbicide injury to the crop.

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.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the registrant. For more details, refer to the Section 12 Notice associated with these conditional registrations.

- Analytical data from at least five batches representing full-scale production for Cyprosulfamide safener.

- Analytical method for the determination of one impurity in Cyprosulfamide safener.

- Storage stability data for the Converge Flexx formulation representing at least one year of storage at ambient conditions.

List of Abbreviations

µg	microgram
a.i.	active ingredient
AD	administered dose
ADD	absorbed average daily dose
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
d	day
DM	dry matter
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
ELS	early life stage

ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
F_0 generation	parental generation; adults that start the study
F_1 generation	1st offspring generation; breeding adults descended from F_0 generation
F_2 generation	2nd offspring generation; descended from F_1 generation
FDA	*Food and Drugs Act*
F	female
FIR	food ingestion rate
g	gram(s)
GAP	good agricultural practice
h	hours
ha	hectare(s)
HPLC	high performance liquid chromatography
HR_5	5th percentile hazard rate of species sensitivity distribution
K_d	soil-water partition coefficient
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LADD	lifetime average daily dose
LC_{50}	lethal concentration for 50% of the population
LD_{50}	lethal dose for 50% of the population
LOAEL	lowest observable adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantitation
LR_{50}	lethal rate for 50% of the population
M	males
m	metres
MAS	maximum average score
mg	milligram(s)
ml	millilitre
MIS	maximum irritation score
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
PBI	plant back interval

PCPA	*Pest Control Product Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
Q_1*	cancer potency factor
RAC	raw agricultural commodity
RQ	risk quotient
SF	safety factor
$t_{1/2}$	half-life
TSMP	Toxic Substances Management Policy
US EPA	United States Environmental Protection Agency
US	United States
WDG	wettable dry granules

Appendix I Tables and Figures

Table 1 Residue Analysis

Method ID	Analyte	Method Type	LOQ	Matrices	Reference
Plants					
00964	Cyprosulfamide	HPLC-ESI-MS/MS Data-gathering and enforcement	0.01 ppm for each analyte	Field corn (grain, forage, stover), sweet corn (kernels plus cob with husks removed), wheat grain, soybean seed, lemon fruit and potato tuber	1409664, 1409668, 1409665
00962	Cyprosulfamide, thiencarbazone-methyl, BYH 18636-MMT and BYH 18636-N-desmethyl	HPLC-ESI-MS/MS Data-gathering			1409663
00961	Cyprosulfamide, M10, M11 and M02				1409662, 1409669
UB-008-P06-01				Field corn (forage, grain, stover)	1409673, 1409669
Animal					
UB-007-A06-01	Cyprosulfamide	HPLC-ESI-MS/MS Data-gathering	0.01 ppm for each analyte in tissues and eggs	Beef (fat, kidney, liver, muscle), cow milk (whole milk, skimmed milk, cream)	1409661, 1409672, 1409667

Method ID	Analyte	Method Type	LOQ	Matrices	Reference
UB-006-A06-01	Cyprosulfamide and M02	HPLC-ESI-MS/MS Data-gathering and enforcement	and 0.005 ppm for each analyte in milk	Beef (fat, kidney, liver, muscle), cow milk (whole milk, skimmed milk, cream), chicken muscle (white and dark meat)	1409674, 1409671, 1409675, 1409670
Soil					
01030	AE 0001789[1]	HPLC-MS/MS m/z 373-176	2 µg/kg		1409697
Soil and Sediment					
UB-001-S06-02	AE 0001789 AE 1448796 AE 0852999 AE 0893016 AE 0467398 AE 1272799	HPLC-MS/MS m/z 373-176 359-239 239-92 334-137 200-80 333-136	LOQ of the method is 2 ng/g for the parent compound and all metabolites in soil and in sediment.		1409680 and 1409677
Water					
01024	AE 0001789	HPLC-MS/MS m/z 373-176	0.05 µg/L		1409681
UB-005-W06-02	AE 0001789 AE 0852999	HPLC-MS/MS m/z 376-176 239-92	LOQ of the method is 2 µg/L for the parent compound and its metabolite.		1409682
[1] Cyprosulfamide (parent compound)					

Table 2 Acute Toxicity of Cyprosulfamide and Its Associated End-use Product Converge Flexx Herbicide

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Cyprosulfamide (Safener)				
Oral	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1409691
Dermal	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1409692
Inhalation	Rat	LC_{50} > 3.513 mg/L	Low Toxicity	1409693
Skin irritation	Rabbit	MAS = 0/8 MIS = 0/8	Non-irritating	1409694
Eye irritation	Rabbit	MAS = 0.9/110 MIS = 10/110	Minimally irritating Conjunctiva discharge scores not provided; based on diffuse crimson colour conjunctivitis (individual vessels not discernible) observed in all animals at 1 h, a maximum discharge score of 3 was assigned for this time-point	1409695
Skin sensitization	Guinea pig	Negative	Not a dermal sensitizer	1409696
Acute Toxicity of End-Use Product –Converge Flexx Herbicide				
Oral	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1409073
Dermal	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1409074
Inhalation	Rat	LC_{50} > 2.674 mg/L	Low Toxicity	1409075
Skin irritation	Rabbit	MAS = 0/8 MIS = 0/8	Non- irritating	1409076

Eye irritation	Rabbit	MAS = 6.7/110 MIS = 14.7/110	Minimally irritating Conjunctival discharge scores not provided; based on diffuse crimson/beefy red conjunctivitis (individual vessels not easily discernible) observed in 2 animals at 1-24 h and 1 animal at 1-48 h, maximum discharge scores of 3 were assigned for these time-points	1409077
Skin sensitization	Mouse	Negative	Not a dermal sensitizer	1409078

a MAS = maximum average score for 24, 28 and 72 hours
b MIS = maximum irritation score

Table 3 Toxicity Profile of Cyprosulfamide

Study Type	Species	Resultsa (mg/kg/day in M/F)	Reference
21-day dermal irritation	Rat	Study waiver was accepted based on the lack of dermal toxicity, dermal and eye irritation and sensitization potential after acute exposure, as well as the availability of short-term oral toxicology endpoints that can be used in the risk assessment.	1409704
90-day dietary	Mouse	NOAEL: 1110/398 mg/kg bw/day M/F LOAEL: Not established/1297 mg/kg bw/day M/F, based on decreased food consumption, body weights, red foci in ovaries, increased severity and incidence of lymphocytolysis in thymus	1409698
90-day dietary	Rat	NOAEL: 58/70 mg/kg bw/day M/F LOAEL: 240/281 mg/kg bw/day M/F, based on increased sulphonamide-like crystals in urine, urothelial hyperplasia and basophilic tubules in urinary bladder	1409699
28-day dietary (range-finding)	Dog	Effect levels not established since study was considered supplemental. Compound-related effects on the urinary tract were observed, with clinical signs and body weight loss occurring at the high dose.	1409697
90-day dietary	Dog	NOAEL: 221/221 mg/kg bw/day M/F LOAEL: 416/341 mg/kg bw/day M/F, based on one female mortality due to renal lesions, decreased body weights/gains, food consumption; urinary tract pathology including increased blood urea nitrogen and creatinine; mild anaemia	1409701
1-year dietary	Dog	NOAEL: 66/67 mg/kg bw/day M/F LOAEL: 226/242 mg/kg bw/day M/F, based on increased granular material in urine, slight anaemia (non-adverse), decreased urine specific gravity and urinary tract pathology	1409703

Carcinogenicity (18-month dietary)	Mouse	NOAEL: 50/354 mg/kg bw/day M/F LOAEL: 287/616 mg/kg bw/day M/F, based on decreased body weights (females) and urinary tract pathology	1409712
Chronic/ Carcinogenicity (2-year dietary)	Rat	NOAEL: 39/56 mg/kg bw/day M/F LOAEL: 159/220 mg/kg bw/day M/F, based on increased soiled anogenital staining, increased sulphonamide-like crystals in urine, decreased urinary protein and urinary tract pathology	1409710
Two-generation reproduction	Rat	**Parental toxicity**: NOAEL: 39.2/55.3 mg/kg bw/day M/F LOAEL: 202.3/260.3 mg/kg bw/day M/F, based on decreased body weights, food consumption, and kidney and spleen pathology **Offspring toxicity:** NOAEL: 202.3/260.3 mg/kg bw/day M/F LOAEL: 1006.9/1350.2 mg/kg bw/day M/F, based on decreased body weights/gains and delayed vaginal opening in the F_1 generation **Reproductive toxicity:** NOAEL: 202.3/260.3 mg/kg bw/day M/F LOAEL: 1006.9/1350.2 mg/kg bw/day M/F, based on decreased fertility and increased pup viability effects in the F_1 generation	1409714
Developmental toxicity	Rat	**Maternal:** NOAEL: 250 mg/kg bw/day LOAEL: 1000 mg/kg bw/day, based on decreased body weight gains, increased yellow sediment in kidneys, bilateral papillary necrosis; prominent lobulation and mixed cell infiltrate in liver **Developmental:** NOAEL: 1000 mg/kg bw/day LOAEL: Not established	1409715
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 125 mg/kg bw/day LOAEL: 500 mg/kg bw/day , based on increased mortality, yellow sediment in urine and few faeces prior to death; body weight loss and decreased food consumption **Developmental:** NOAEL: 125 LOAEL: Not established; foetal effects were not assessed at 500 mg/kg bw/day due to excessive maternal toxicity	1409716
Developmental toxicity (supplemental)	Rabbit	Effect levels not established since study was considered supplemental. Compound-related increased abortions, yellow sediments in urine, body weight loss and decreased food consumption were observed. No compound-related foetal effects were noted.	1409717

Reverse gene mutation assay	Salmonella typhimurium strains TA98, TA100, TA102, TA1535, TA 1537	Negative	1409706
Gene mutations in mammalian cells in vitro	Chinese hamster ovary cells (HPRT locus)	Negative	1409708
In vitro mammalian chromosomal aberration	Chinese hamster V79	Negative	1409707
In vivo mammalian cytogenetics	Mouse	Negative	1409709
Metabolite Studies			
AE 0852999 – AE 0001789-cyclopropyl-sulfomoylbenzamide			
28-day (dietary)	Rat	NOAEL: 22.8/25.5 mg/kg bw/day M/F LOAEL: 59.5/67.2 mg/kg bw/day M/F, based on decreased body weight gains, food consumption, increased unusual crystals (fine sticks often arranged in sheaves and/or fine needles, fan-shaped or clumped-arranged), decreased urinary pH in males	1409728
Reverse gene mutation assay	Salmonella typhimurium strains TA98, TA100, TA102, TA1535, TA 1537	Negative	1409722
Gene mutations in mammalian cells in vitro	Chinese hamster ovary cells (HPRT locus)	Negative	1409723
In vitro mammalian chromosomal aberration	Chinese hamster V79	Negative	1409721
AE 0467398 – AE0001789-sulfamoyl benzoic acid			
90-day (dietary)	Rat	NOAEL: 116/142 mg/kg bw/day M/F LOAEL: 888/1094 mg/kg bw/day M/F, based on increased urothelial mineralization in kidney	1409725
Reverse gene mutation assay	Salmonella typhimurium strains TA98, TA100, TA102, TA1535, TA 1537	Negative	1409724
Gene mutations in mammalian cells in vitro	Chinese hamster ovary cells (HPRT locus)	Negative	1409726
In vitro mammalian chromosomal aberration	Chinese hamster V79	Negative	1409727
Special studies			

Acute neurotoxicity (gavage)	Rat	**Systemic:** NOAEL: 508 mg/kg bw/day M/F LOAEL: 2060 mg/kg bw/day M/F, based on increased urine staining **Neurotoxicity:** NOAEL: 2060 mg/kg bw/day M/F LOAEL: Not established	1409719
90- day neurotoxicity (dietary)	Rat	**Systemic and neurotoxicity:** NOAEL: 592/748 mg/kg bw/day M/F LOAEL: Not established	1409720

Pharmacokinetics	Rat	**Absorption** Rapidly absorbed [approximately 70-90% at low dose (2 mg/kg bw) and 69-72% at high dose (200 mg/kg bw), both at 96 hours]. Absorption (as percent administered dose [AD]) was decreased at the high dose suggesting saturation of the absorption kinetics. At the high dose, the plasma decline curves were bimodal (i.e., a discontinuous excretion pattern) indicating delayed absorption or delayed gastric emptying of some of the dose between 4 and 48 hours post-dosing. Plasma T_{max} values for both doses ranged from ~10-60 minutes post-dosing. **Distribution** Maximum concentration of radioactivity in organs and tissues was found 1 hour after dosing. At all time-points examined, high radioactivity was mainly observed in the kidney and liver. The residues in all other organs and tissues were fairly evenly distributed and always lower than the residues observed in blood. Residues in all organs and tissues decreased rapidly between 1-72 hours. In all organs/tissues, residues were < LOD or <LOQ at later time-points (72-168 h post-dosing). There was no evidence of bioaccumulation in the tissues. Expired air did not contain significant levels of ^{14}C-labelled volatiles. **Excretion** Excretion of the low dose was rapid (79-98% of AD at 24 hours) and occurred mostly via the urine (70-90% of AD at 96 h). At the high dose, excretion was much slower reflecting the delayed absorption (50% and 94% of AD at 48 hours in males and females, respectively) and the primary route of excretion was via the urine (69-72% of AD at 96 h). The $T_{1/2}$ of elimination for both doses ranged from 13-23 h. All excretion (85-100%) was virtually complete by 96 h. **Metabolism** Metabolism was limited, with approximately 80-95% of AD excreted as unchanged parent compound. The major metabolite AE 0001789-descyclopropylamine (resulting from elimination of the cyclopropylamine moiety by hydrolysis of the carboxamide bond) represented 2-8% of AD. Three minor metabolites were identified: 1) AE 0001789-cyclopropyl- sulfamoylbenzamide [sulfonylbenzamide-ring label], 2) AE 0001789-anisic acid [methoxybenzoyl-ring label] and 3) AE 0001789-desmethyl, and represented <1 % of AD.	1409686 & 1409687

Autoradiography	Rat Single oral dose of 4.95 mg/kg bw One male rat per time-point sacrificed at 1, 4, 8, 24, 48, 72, 120, 168 h post-dosing Radioactivity levels in excreta and whole body sections were determined	Cyprosulfamide was rapidly absorbed and distributed among most organs and tissues within 1 h post-dosing. Absorption was apparently discontinuous, possibly due to delayed gastric emptying between 4-48 h post-dosing. This finding was supported by high amounts of radioactivity remaining in the GI tract associated with an inflated stomach until 48 h post-dosing and from slight increased radioactivity in most organs and tissues at 48 h. Excretion of radioactivity via expired air was negligible (<0.01% of AD). Highest concentrations of radioactivity were detected in the renal medulla of the kidney and in the blood. Moderate concentrations were observed in the liver, renal cortex of kidney, lung, myocardium, brown and perirenal fat, skin, and the major glands (adrenal, thyroid, pineal, salivary, pituitary). Peak values were observed 1 h post-dosing and declined to below the LOD within 48 h. Excretion was primarily via the urine (81-84% of AD at 168 h) and was nearly complete within 48-72 h. Faecal excretion accounted for 10-14% of AD.	1409685 & 1409688

a Effects observed in males as well as females unless otherwise reported

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

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	UF/SF[1] or Target MOE[2]
Acute dietary	**ARfD = Not Required**			
Chronic Dietary	NOAEL = 39	2-year rat combined chronic/ carcinogenicity	Increased soiled anogenital staining, increased sulphonamide-like crystals in urine, decreased urinary protein and urinary tract pathology	100
	ADI = 0.39 mg/kg bw/day			
Short-term Dermal and Inhalation	NOAEL = 58	90-day rat feeding	Increased sulphonamide-like crystals in urine, urothelial hyperplasia and basophilic tubules in urinary bladder	100
Cancer unit risk	Q_1* = 1.37 x 10^{-3} (mg/kg bw/day)$^{-1}$	18-month dietary study in the mouse	Histiocytic sarcomas of the haematopoietic system in mice	N/A

1 Dietary scenarios

2 Exposure scenarios

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN CORN (POST-EMERGENT)			**PMRA # 1409737, 1409733,**
Matrix	Field Corn[1] (Variety: Garst Corn Seed 8451RR)		
Test Site	Greenhouse		
Treatment	Foliar		
Application Timing	Post-emergent (BBCH 19)		
Rate	739 g a.i./ha or 812 g a.i./ha		
End-use product	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 formulated as a suspension concentrate		
Matrix	**PHI (days)**	**[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**	**[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**
Forage	44	2.441	2.878
Sweet corn grain	44	0.023	0.027
Sweet corn cob	44	0.019	0.019
Stover	77	3.035	2.829
Grain	77	0.050	0.051
[1] Field corn was harvested at the milk stage (BBCH 85) to simulate sweet corn.			
Metabolites Identified	**Major Metabolites (> 10% TRR)**		
Radiolabel Position	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789		[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789
Forage	Cyprosulfamide		Cyprosulfamide
Sweet corn grain	Cyprosulfamide		Cyprosulfamide
Stover	Cyprosulfamide, M10		Cyprosulfamide, M16
Grain	M05		M05
	Minor Metabolites (< 10% TRR)		
Forage	M05, M16, M10, M02, M08		M05, M16
Sweet corn grain	M05		
Sweet corn cob	Cyprosulfamide, M16		Cyprosulfamide, M16
Stover	M05, M16, M02, M08		M05
Grain	Cyprosulfamide, M16		Cyprosulfamide, M16
NATURE OF THE RESIDUE IN CORN (PRE-EMERGENT)			**PMRA # 1409734**
Matrix	Corn (Variety: Garst Corn Seed 8451RR)		
Test Site	Greenhouse		
Treatment	Broadcast spray to soil		
Application Timing	Pre-emergence		
Rate	766 g a.i./ha or 754 g a.i./ha		
End-use product	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 or [Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 (formulation used not stated)		

Matrix	**PHI (days)**	**[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**	**[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**
Forage	80	0.134	0.011
Sweet corn grain	80	0.007	0.004
Sweet corn cobs	80	0.010	0.003
Stover	139	0.258	0.019
Grain	139	0.015	0.009
Metabolites Identified	**Major Metabolites (> 10% TRR)**		
Radiolabel Position	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789		[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789
Forage	M11, M15, M10		Due to low TRRs, no residues were identified in any of the RACs.
Stover	M11, M13, M10		
	Minor Metabolites (< 10% TRR)		
Forage	M13, M12, M02		Due to low TRRs, no residues were identified in any of the RACs.
Stover	M02, M19		
NATURE OF THE RESIDUE IN CORN (SEED TREATMENT)			**PMRA # 1409735**
Matrix	Corn (Variety: Gustafson HC33RR x LH Corn Seed)		
Test Site	Greenhouse		
Treatment	Seed treatment		
Application Timing	Seed treatment		
Rate	2.92 g a.i./kg seed or 2.85 g a.i./kg seed		
End-use product	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 or [Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 (formulation used not stated)		
Matrix	**PHI (days)**	**[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**	**[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**
Forage	76	0.098	0.008
Sweet corn grain	76	0.006	0.004
Sweet corn cob	76	0.007	0.004
Stover	112	0.207	0.016
Grain	112	0.010	0.009
Metabolites Identified	**Major Metabolites (> 10% TRR)**		
Radiolabel Position	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789		[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789
Forage	M11, M10		Due to low TRRs, no residues were identified in any of the RACs.
Stover	M11, M15, M10		
	Minor Metabolites (< 10% TRR)		

Forage	M02	Due to low TRRs, no residues were identified in any of the RACs.
Stover	M02	

NATURE OF THE RESIDUE IN SORGHUM (SEED TREATMENT)	**PMRA # 1409732**
Matrix	Sorghum
Test Site	Greenhouse
Treatment	Seed treatment
Application Timing	Seed treatment
Rate	50.31 g a.i./100 kg seed (low) or 75.90 g a.i./100 kg seed (high)
End-use product	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 (formulation used not stated)

Matrix	**PHI (days)**	**[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 TRR (ppm)**	
		Low treatment rate	**High treatment rate**
Forage	90	<0.005	<0.005
Stover	116	<0.005	<0.005
Grain	116	<0.005	<0.005

Plant Metabolism

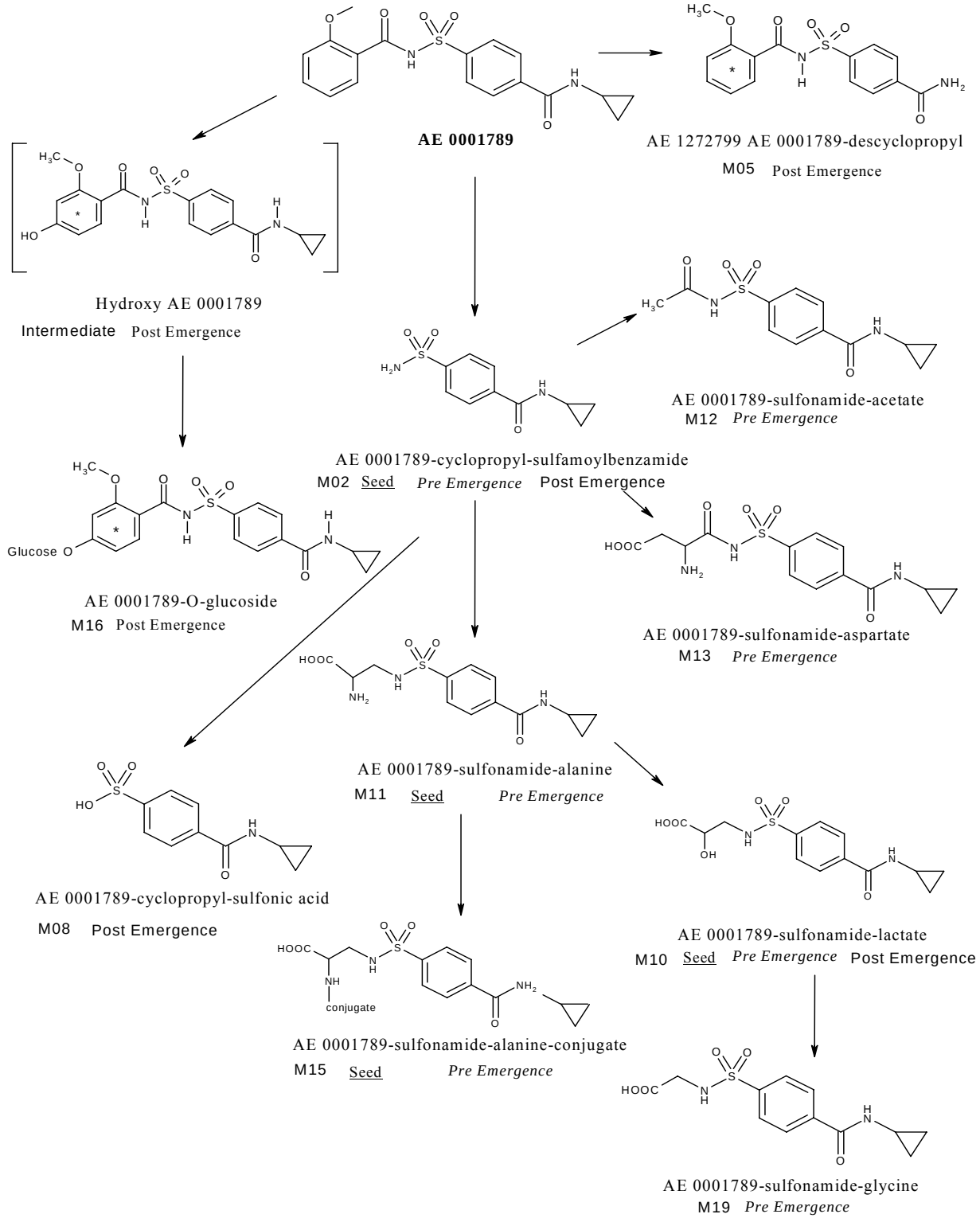
The metabolic pathway observed in the seed treatment and pre-emergence studies is consistent, resulting from the rapid degradation of cyprosulfamide in the soil via cleavage of the carboxamide bond to produce AE 0001789-cyclopropyl-sulfamoylbenzamide (M02) followed by crop uptake. Once M02 is absorbed by the plant it is further conjugated to produce the AE 0001789-sulfonamide acetate (M12), AE 0001789-sulfonamide aspartate (M13) and AE 0001789-sulfonamide alanine (M11). The AE 0001789-sulfonamide alanine can be conjugated further to form the AE 0001789 sulfonamide-alanine-conjugate (M15) or deaminated to produce the AE 0001789-sulfonamide lactate (M10) which in turn can be decarboxylated to produce the AE 0001789-sulfonamide-glycine (M19) metabolite. The uptake of the sulfonylbenzamide specific soil metabolite (AE 0001789-cyclopropyl-sulfamoylbenzamide; M02) by the crop is consistent with the higher residues observed in the S-labelled studies versus the M-labelled studies.

For the post-emergence application, although there is some uptake from the soil as evidenced by the identification of minor amounts of AE 0001789-cyclopropyl-sulfamoylbenzamide (M02) and AE 0001789-sulfonamide lactate (M10), the majority of the AE 0001789 residues were absorbed through the leaves. The metabolism of cyprosulfamide in leaves involves hydroxylation of the methoxybenzoyl ring and the subsequent conjugation to glucose to produce AE 0001789-O-glucoside (M16) or the loss of the cyclopropyl moiety to produce the AE 0001789-descyclopropyl (M05) metabolite.

CONFINED ROTATIONAL CROP STUDY USING SPRING WHEAT, SWISS CHARD AND TURNIPS		**PMRA # 1409757**
Radiolabel Position	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789	[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789

Test site		Greenhouse	
Formulation used for trial		[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 or [Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 (formulation used not stated)	
Application rate and timing		One application at 212-218 g a.i./ha; 30 days, 120 days and 276 days prior to sowing Swiss chard, turnips and wheat.	
Metabolites Identified		**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Matrix	**PBI (days)**	[Sulfonylbenzamide-ring-UL-^{14}C]	
Forage	30	M02	-
Hay	30	M02	-
Straw	30	M02	-
Straw	120	M02	-
Forage	276	M02	-
While all residues were characterized based on their extraction characteristics, no metabolite identification was completed on samples from the methoxybenzoyl-labelled study due to low residue levels. The HPLC profile of extracted Swiss chard and turnip tops samples from the sulfonylbenzamide-labelled study at 30 days consisted of up to 7 minor components, none of which accounted for residues >0.01 ppm. Metabolite identification was not completed on any other Swiss chard or turnip RACs due to low residue levels. The major metabolite identified in the wheat forage, hay and straw of the rotational crops was M02. Since this metabolite was not detected in the rotational crops from the limited rotational crop field trials at a 30-day PBI, M02 was not included in the residue definition for plants.			

Proposed Metabolic Scheme in Plants



NATURE OF THE RESIDUE IN LAYING HEN	PMRA # 1409738, 1409739

Six laying hens were dosed orally with either [Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789 or [Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789 for 14 consecutive days at a dose level of 2.1 or 2.4 mg/kg body weight (corresponding to ~30 ppm in the daily diet). Hens were sacrificed 6 hrs after the last dose and samples of organs and tissues were taken for analysis. Samples of eggs and excreta were collected daily for analysis. The majority of the administered dose was excreted rapidly. Residue levels in eggs and fat were very low, with the highest concentrations of residues measured in liver and muscle.

Matrices	**% of Administered Dose**			
	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789		**[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789**	
Excreta	92		84	
Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	Sulfonylbenzamide	Methoxybenzoyl	Sulfonylbenzamide	Methoxybenzoyl
Eggs	M02	Cyprosulfamide, M07	Cyprosulfamide	-
Fat	Cyprosulfamide, M02	-	-	-
Liver	M02	Cyprosulfamide, M07	Cyprosulfamide	-
Muscle	M02	-	Cyprosulfamide	-

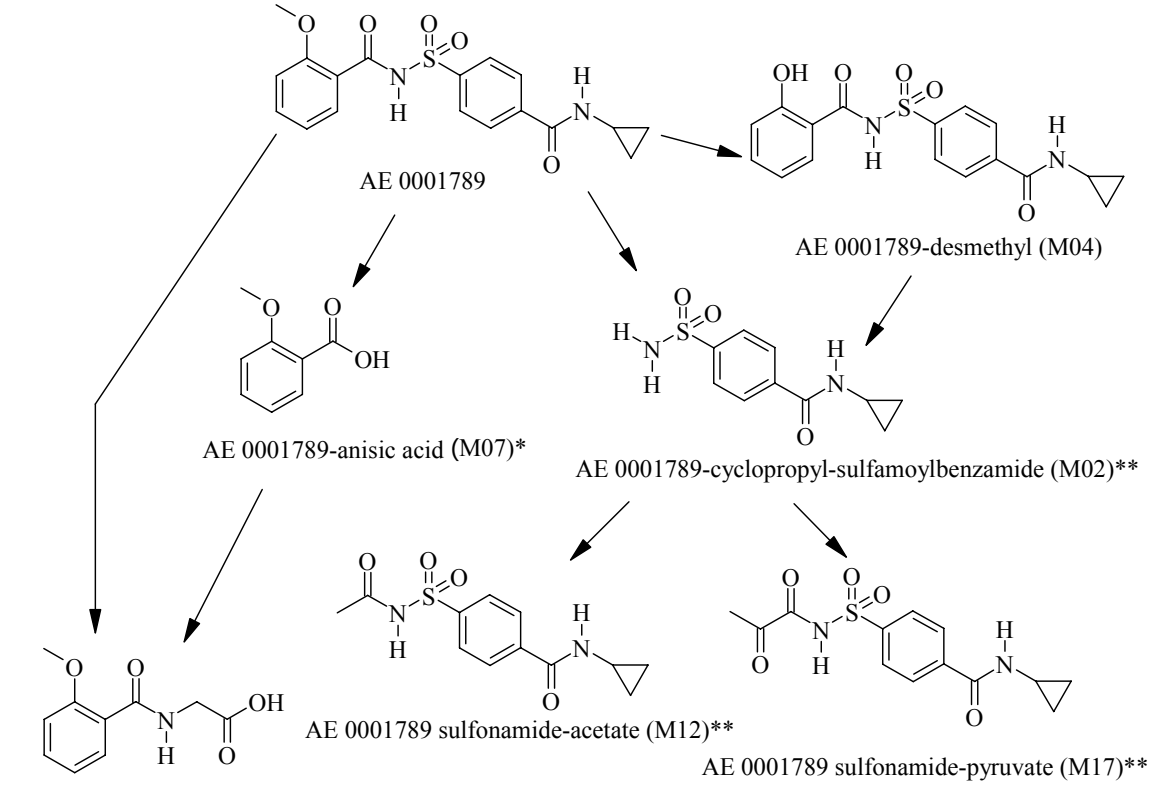
NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA # 1409740, 1409741**

In the [sulfonylbenzamide-UL-^{14}C] AE 0001789 study, two lactating goats were dosed orally, once daily, via capsule at a dose level of 1.34 mg a.i./kg body weight (22.9 ppm in feed) for 5 consecutive days. In the [methoxybenzoyl-UL-^{14}C] AE 0001789 study, one lactating goat was dosed orally, once daily, via capsule at a dose level of 1.4 mg a.i./kg body weight (25.3 ppm in feed) for 5 consecutive days. Milk samples were collected twice daily, urine and feces were collected once daily. The goats were sacrificed ca. 6 hrs after the last dosage, and muscle (round, flank, loin), fat (perirenal, omental subcutaneous), liver, kidneys were collected.

Matrices	**% of Administered Dose**			
	[Sulfonylbenzamide-ring-UL-^{14}C]-AE 0001789		**[Methoxybenzoyl-ring-UL-^{14}C]-AE 0001789**	
Urine and feces	71.5		82.2	
Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	Sulfonylbenzamide	Methoxybenzoyl	Sulfonylbenzamide	Methoxybenzoyl
Milk	Cyprosulfamide, M12, M02	Cyprosulfamide, M18	M17, M04	M04, M07
Fat	Cyprosulfamide	Cyprosulfamide	M04, M02	M04, M07, M18

Kidney	Cyprosulfamide, M02	Cyprosulfamide	M04	M04, M07, M18
Liver	Cyprosulfamide, M02	Cyprosulfamide, M07	M04	M04, M18
Muscle	Cyprosulfamide, M02	Cyprosulfamide	-	M04, M07, M18

Proposed Metabolic Scheme in Livestock



*Methoxybenzoyl label-specific metabolite
**Sulfonylbenzamide label-specific metabolite

Animal Metabolism

Cyprosulfamide was not extensively metabolized. The major metabolic pathways in the goat were consistent with the major metabolic pathways identified in the poultry, however, in the goat, metabolites M02 and M07 underwent further conjugation.

The major metabolic pathway for [sulfonylbenzamide-UL-^{14}C] AE 0001789 in lactating goats involved hydrolysis of the amide bond of the sulfonylbenzamide moiety to produce M02 followed by conjugation to form the N-acetyl and N-pyruvyl derivatives of the sulfonamide. The major metabolic pathway for [methoxybenzoyl-UL-^{14}C] AE 0001789 in a lactating goat involved hydrolysis of the amide bond of the sulfonylbenzamide moiety followed by conjugation of the resulting anisic acid (M07) with glycine to form methoxyhippuric acid (M18). Demethylation (M04) of the parent compound was considered a minor metabolic pathway for both radiolabels. The metabolic pathways identified in poultry and ruminants are consistent with the rat metabolism.

INTERIM STORAGE STABILITY	**PMRA # 1409729, 1409730**

Samples of corn (kernel, forage, stover), soybean seed, head lettuce, potato tuber and tomato fruit were spiked at nominal levels between 163 and 262 µg/kg with cyprosulfamide or between 0.21 and 0.52 mg/kg with M02, M10 and M11 (each calculated and expressed as cyprosulfamide equivalents). Spiked samples were stored at -18°C for approximately 0, 30, 90, 180 and 360 days. Residues of cyprosulfamide in/on plant matrices were determined by HPLC-MS/MS according to method 00964 and residues of the metabolites were determined by HPLC-MS/MS according to method 00961. Adequate concurrent method validation data were provided. The results demonstrate that residues of cyprosulfamide are stable in corn kernels, corn forage, corn stover, soybean seed, potato tuber and head lettuce for a period of 360 days and in tomatoes for a period of 180 days when stored at ≤-18°C and residues of M02, M10 and M11 are stable in all matrices tested up 360 days.

The freezer storage stability study for cyprosulfamide in plant matrices is the interim data to a full 18-month study. The submitted field accumulation and processing studies are considered conditionally acceptable pending the submission of the 18-month freezer storage stability study.

No freezer storage stability data for cyprosulfamide and M02 in animal matrices is required given that all animal matrices were analyzed within 20 days.

CROP FIELD TRIALS ON FIELD CORN	**PMRA# 1409753**
GAP: Maximum seasonal rate of 105 g a.i./ha and a PHI of 110 days.	

A total of 15 supervised residue trials were conducted in 2006 on field corn grown in the NAFTA representative growing regions. The SC 480 formulation, consisting of cyprosulfamide (240 g/L) + isoxaflutole (240 g/L) was applied at rates of 0.206-0.227 kg a.i./ha at the 3 leaf stage (corresponding to BBCH 12-13). Corn silage was harvested at a 60-day PHI and grain and stover were harvested at a 110-day PHI. Residues of cyprosulfamide and the metabolites M02, M10, M11 were analysed according to method UB-008-P06-01. Mean concurrent recoveries for cyprosulfamide and the metabolites for all spiking levels were within the acceptable range of 70-120% (RSD <22%). No quantifiable residues of cyprosulfamide were observed in corn grain, silage and stover.

Commodity	Total Applic. Rate (kg a.i./ha)	PHI (days)	Cyprosulfamide Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Corn silage	0.206-0.227	60	42	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Corn grain		110	42	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Corn stover		110	42	<0.01	<0.01	<0.01	<0.01	<0.01	NA

CROP FIELD TRIALS ON SWEET CORN | **PMRA# 1409742**

GAP: Not proposed for use on sweet corn in Canada.

Five sweet corn and nine field/sweet[1] corn field trials were conducted in 2005 and 2006 in US representative growing regions to evaluate the magnitude of total cyprosulfamide residues in/on sweet corn commodities of forage, ears (kernels plus cob with husk removed, K+CWHR) and stover. In each trial two application patterns were evaluated. In one plot, corn seeds were treated with cyprosulfamide 500 FS (0.025 kg a.i./ha, flowable concentrate for seed treatment) and planted followed by a broadcast post-emergence application of cyprosulfamide 500 SC (0.158 kg a.i./ha, suspension concentrate applied at BBCH 12 to 35) for a total target application rate of 0.183 kg a.i./ha. The second plot received two post-emergence applications of cyprosulfamide 500 SC at a target application rate of 0.225 kg a.i./ha (1st application at BBCH 16 to 36 and 2nd at BBCH 19 to 69). All applications were made using ground-based equipment. Sweet corn forage (BBCH 73 to 79), sweet corn ears (K+CWHR) and stover were collected at normal maturity. Residues of cyprosulfamide and the metabolites M02, M10, M11 were analysed according to method UB-008-P06-01. Mean concurrent recoveries for cyprosulfamide and the metabolites for all spiking levels were within the acceptable range of 70-120% (RSD <15%). Residues of cyprosulfamide were greater than 0.01 ppm in only 2 samples out of 84 in sweet corn ears.

[1]Field corn was harvested at the milk stage to simulate sweet corn.

Commodity	Total Applic. Rate (kg a.i./ha)	PHI (days)	Cyprosulfamide Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Sweet corn ears	0.149-0.193	43-95	62	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	0.222-0.232	13-46	36	<0.01	0.048	0.043[1]	<0.01	0.012	0.009
Sweet corn forage	0.149-0.193	43-95	70	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	0.222-0.232	13-46	36	<0.01	0.408	0.396	<0.01	0.042	0.090
Sweet corn stover	0.149-0.193	88-163	36	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	0.222-0.232	44-113	36	<0.01	1.022	0.910	0.011	0.066	0.210

[1]The majority of residues in sweet corn ears were <0.01 ppm, only 2 samples out of 84 had residues >0.01 ppm. An import MRL of 0.01 ppm is proposed for sweet corn kernels plus cobs with husks removed. The proposed MRL is supported by all of the field corn grain and popcorn grain trials with residues <0.01 ppm (n=88 and n=12), a field corn processing study conducted at exaggerated rates which yielded cyprosulfamide residues <0.01 ppm and metabolism studies conducted at exaggerated rates which yielded residues in the corn grain <0.01 ppm.

CROP FIELD TRIALS ON POPCORN | **PMRA# 1409742**

GAP: Not proposed for use on popcorn in Canada.

Three popcorn field trials were conducted in 2005 and 2006 in US representative growing regions to evaluate the magnitude of total cyprosulfamide residues in popcorn grain and stover. Each trial received the same applications as the aforementioned sweet corn trials. Residues of cyprosulfamide and the metabolites M02, M10, M11 were analysed according to method UB-008-P06-01. Mean concurrent recoveries for cyprosulfamide and the metabolites for all spiking levels were within the acceptable range of 70-120% (RSD <15%). No quantifiable residues of cyprosulfamide were observed in popcorn grain and stover.

Commodity	Total Applic. Rate (kg a.i./ha)	PHI (days)	Cyprosulfamide Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Popcorn grain	0.184-0.188	112-129	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	0.223-0.229	79-88	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
Popcorn stover	0.184-0.188	112-129	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA
	0.223-0.229	79-88	6	<0.01	<0.01	<0.01	<0.01	<0.01	NA

PROCESSED FOOD AND FEED | **PMRA # 1409756**

A field trial was conducted to measure the magnitude of cyprosulfamide residues on corn grain and to evaluate the need for residue analysis of the processed commodities. Three applications of cyprosulfamide 500 SC (500 g a.i./L) were made to corn at a total treatment rate of 1.2 kg a.i./ha (12-fold CDN GAP). The first application was a broadcast foliar application at a target rate of 549 g a.i./ha (BBCH 12-35). The second application was a broadcast foliar application at a target rate of 375 g a.i./ha (BBCH 16-36). The third application was a directed application to the base of the plants and surrounding soil at a target rate of 300 g a.i./ha (BBCH 32). A single control and treated bulk sample of corn grain were collected at maturity (BBCH 89, kernels fully ripe). The residues of cyprosulfamide and the metabolites M02, M11 and M10 were quantitated by the LC-MS/MS method UB-008-P06-02. Residues of cyprosulfamide, M02, M11 and M10 in corn grain were each less than the LOQ of 0.01 ppm following an exaggerated rate application of cyprosulfamide to corn. Therefore, the requirement for a corn processing study was waived.

LIVESTOCK FEEDING – Dairy cattle | **PMRA # 1409755**

Cyprosulfamide was administered via capsule to thirteen lactating Holstein dairy cows for 29 consecutive days. The target dose rates (based on feed dry weight) were 0 ppm feed/day (control), 0.1 ppm feed/day, 1.0 ppm feed/day, 3.0 ppm feed/day or 10 ppm feed/day. Milk was collected twice daily during the dosing period. Milk samples from the 10-ppm dose group were analyzed for cyprosulfamide and M02 residues on study days 0, 1, 3, 7, 10, 14, 17, 21, 24, 26, and 28. Additionally, a portion of the 28-day milk sample from the 10-ppm dose group was separated into milk fat (cream) and skim milk, and each was analyzed. On day 29, the animals were sacrificed and liver, kidney, composite muscle, and composite fat were collected for analysis. Samples were analyzed for total cyprosulfamide residues (cyprosulfamide + M02).

Matrix	Feeding Level (ppm)	n	Min	Max	Median	Mean	Standard Deviation
Milk	10	30	<0.01	<0.01	<0.01	<0.01	-
Milk fat	10	3	<0.01	<0.01	<0.01	<0.01	-
Whey	10	3	<0.01	<0.01	<0.01	<0.01	-
Fat	0.1	3	<0.02	<0.02	<0.02	<0.02	-
Fat	1	3	<0.02	<0.02	<0.02	<0.02	-
Fat	3	3	<0.02	<0.02	<0.02	<0.02	-
Fat	10	3	<0.02	0.028	0.026	0.020	0.011
Kidney	0.1	3	<0.02	<0.02	<0.02	<0.02	-
Kidney	1	3	0.040	0.047	0.041	0.042	0.004
Kidney	3	3	0.074	0.143	0.104	0.107	0.035
Kidney	10	3	0.258	0.473	0.449	0.393	0.118
Muscle	0.1	3	<0.02	<0.02	<0.02	<0.02	-
Muscle	1	3	<0.02	<0.02	<0.02	<0.02	-
Muscle	3	3	<0.02	<0.02	<0.02	<0.02	-
Muscle	10	3	<0.02	<0.02	<0.02	<0.02	-
Liver	0.1	3	<0.02	<0.02	<0.02	<0.02	-
Liver	1	3	0.012	0.015	0.015	0.014	0.002

Liver	3	3	0.028	0.042	0.033	0.034	0.007
Liver	10	3	0.090	0.124	0.104	0.106	0.017

Calculation of Livestock Anticipated Dietary Burden in Beef, Dairy, Poultry and Swine

The potential for transfer of total cyprosulfamide residues in meat and milk exists because there are livestock feedstuffs associated with the proposed uses on field corn. The calculated anticipated dietary burden, based on Canadian MRLs for field, sweet and popcorn grain and medians for forage and stover, is 0.017 ppm for beef cattle, 0.018 ppm for dairy cattle, 0.008 ppm for swine and poultry.

				% Diet				**Anticipated Dietary Burden (ppm)**			
Feedstuff	Type	Residue (ppm)	% DM	Beef	Dairy	Poultry	Swine	Beef	Dairy	Poultry	Swine
Field corn forage	R	0.01	40	40	45	-	-	0.01	0.011	-	-
Field corn stover	R	0.01	83	-	-	-	-	-	-	-	-
Field corn grain	CC	0.01	88	-	-	70	80	-	-	0.007	0.008
Field corn milled byproducts	CC	0.01	85	35	25	-	-	0.004	0.003	-	-
Popcorn grain	CC	0.01	88	-	5	10	-	-	0.001	0.001	-
Popcorn stover	R	0.01	85	-	-	-	-	-	-	-	-
Sweet corn cannery waste	CC	0.01	30	10	10	-	-	0.003	0.003	-	-
Sweet corn forage	R	0.01	48	-	-	-	-	-	-	-	-
Sweet corn stover	R	0.01	83	-	-	-	-	-	-	-	-
Totals				85[1]	85[1]	80[2]	80[2]	0.017	0.018	0.008	0.008

R (roughage); CC (carbohydrates).
[1]Remaining 15% is based on peanut meal.
[2]Remaining 20% is based on canola (15%) and flax meal (5%).

Calculation of the Anticipated Residues for Dietary Exposure Assessment

Matrix	**Maximum Total Residues[1] (ppm)**	**Feeding level (ppm)**	**Transfer Coefficient[2]**	**Anticipated Dietary Burden (ppm)**	**Anticipated Residues[3] (ppm)**
Whole milk	<0.01	0.1	0.1	0.018	0.0018
Beef fat	<0.02	0.1	0.2	0.017	0.0034
Beef kidney	<0.02	0.1	0.2		0.0034
Beef liver	y = 0.0105x + 0.0011	Linear regression	0.0105 x ADB + 0.0011		0.00159
Beef muscle	<0.02	0.1	0.2		0.0034
Chicken muscle	0.117	33.5 (from metabolism study)	0.00349	0.008	0.00003
Chicken fat	0.043		0.00128		0.00001
Chicken liver	0.714		0.0213		0.00017
Eggs	0.037		0.0011		0.000009
Hog fat	<0.02	0.1	0.2	0.008	0.0016
Hog kidney	<0.02	0.1	0.2		0.0016

Hog liver	<0.02	Linear regression	0.0105 x ADB + 0.0011		0.00118
Hog muscle	<0.02	0.1	0.2		0.0016

[1]Maximum Total Residues = cyprosulfamide + M02.
[2]Transfer coefficient is calculated as residue level-to-feed ratios.
[3]Anticipated residues for dietary exposure assessment = Transfer coefficient x anticipated dietary burden.

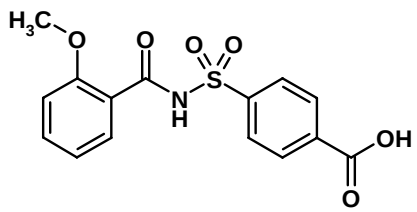
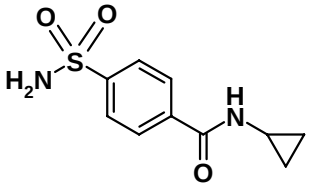
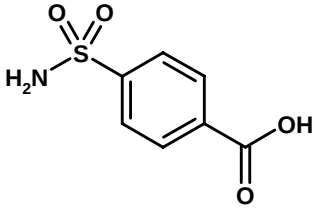
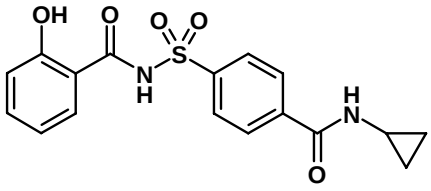
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

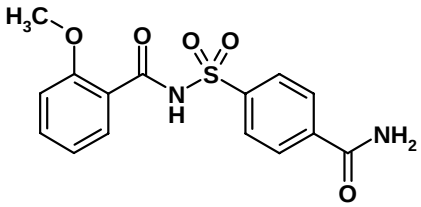
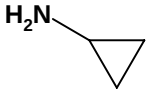
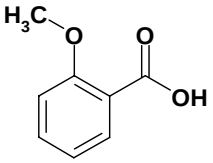
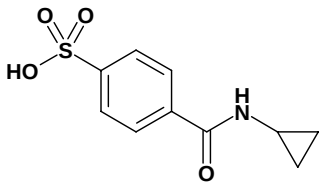
PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (corn)**	Cyprosulfamide
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops**	Cyprosulfamide
METABOLIC PROFILE IN DIVERSE CROPS	The profile in diverse crops cannot be determined, because only corn was investigated.
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	Cyprosulfamide and M02
RESIDUE DEFINITION FOR RISK ASSESSMENT	Cyprosulfamide and M02
METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	The metabolic profile was similar in all animals investigated.
FAT SOLUBLE RESIDUE	No

DIETARY RISK FROM FOOD AND WATER

	Population	**Estimated Chronic Risk (% of ADI)**		**Estimated Cancer Risk**		
		Basic Food	**Basic Food & Water**	**Basic Food**	**Basic Food & Water Level I**	**Refined Food & Water Level II**
Chronic Assessment **ADI** = 0.39 mg/kg bw/day **EEC** = 13.75 µg/L (level I) Cancer Assessment **Q_1*** = 1.37 x 10^{-3} $(mg/kg\ bw/day)^{-1}$ **EEC** = 5 µg/L (level II)	General Population	0.0	0.1	1.84 x 10^{-7}	5.90 x 10^{-7}	1.91 x 10^{-7}
	All infants (<1 year)	0.0	0.3	2.48 x 10^{-7}	**1.58 x 10^{-6}**	5.46 x 10^{-7}
	Children 1-2 yrs	0.1	0.2	7.10 x 10^{-7}	**1.31 x 10^{-6}**	3.67 x 10^{-7}
	Children 3-5 yrs	0.1	0.2	5.18 x 10^{-7}	**1.08 x 10^{-6}**	3.26 x 10^{-7}
	Children 6-12 yrs	0.1	0.1	3.24 x 10^{-7}	7.13 x 10^{-7}	2.23 x 10^{-7}
	Youth 13-19 yrs	0.0	0.1	1.75 x 10^{-7}	4.68 x 10^{-7}	1.55 x 10^{-7}
	Adults 20-49 yrs	0.0	0.1	1.24 x 10^{-7}	5.03 x 10^{-7}	1.68 x 10^{-7}
	Adults 50+ yrs	0.0	0.1	1.06 x 10^{-7}	5.05 x 10^{-7}	1.67 x 10^{-7}
	Females 13-49 yrs	0.0	0.1	1.18 x 10^{-7}	4.96 x 10^{-7}	1.67 x 10^{-7}

Table 7 Transformation products relevant to the environment

Codes	Report name Structure IUPAC name CAS name [CAS number]	Molecular formula Molar mass	Occurrence (max % AR)
M01 AE0893016	AE 0001789-descyclopropylamino  4-[(2-methoxybenzoyl)sulfamoyl]benzoic acid (IUPAC) 4-[[(2-Methoxybenzoyl)amino]sulfonyl]benzoic acid (CAS)	C15 H13 N O6 S 335.3 g/mol	Aerobic soil: 13 Anaerobic soil: 21 Aerobic water/sed: 15 Aerobic water: 11 Aerobic sed: 6
M02 AE0852999	AE 0001789-cyclopropyl-sulfamoylbenzamide  N-cyclopropyl-4-sulfamoylbenzamide (IUPAC) 4-(Aminosulfonyl)-N-cyclopropylbenzamide (CAS)	C10 H12 N2 O3 S 240.3 g/mol	Aerobic soil: 30 Anaerobic soil: 15 Aerobic water/sed: 24 Aerobic water: 18 Aerobic sed: 6 Anaerobic wat/sed: 8 Anaerobic water: 7 Anaerobic sed: 3
M03 AE0467398	AE 0001789-sulfamoylbenzoic acid  4-sulfamoylbenzoic acid (IUPAC) Benzoic acid, 4-(aminosulfonyl)- (CAS, 9CI) [CAS no.: 138-41-0]	C7 H7 N O4 S 201.2 g/mol	Aerobic soil: 28 Anaerobic soil: 53 Aerobic water/sed: 7 Aerobic water: 5 Aerobic sed: 2
M04 AE1448796	AE 0001789-desmethyl  N-cyclopropyl-4-[(2-hydroxybenzoyl) sulfamoyl]benzamide (IUPAC)	C17 H16 N2 O5 S 360.39 g/mol	Aerobic soil: 7 Aerobic water/sed: 17 Aerobic water: 9 Aerobic sed: 8 Anaerobic wat/sed: 21 Anaerobic water: 14 Anaerobic sed: 7

Codes	Report name Structure IUPAC name CAS name [CAS number]	Molecular formula Molar mass	Occurrence (max % AR)
M05 AE1272799	AE 0001789-descyclopropyl  N-{[4-(aminocarbonyl)phenyl]sulfonyl}-2-methoxybenzamide (IUPAC) N-[[4-(Aminocarbonyl)phenyl]sulfonyl]-2-methoxybenzamide (CAS)	C15 H14 N2 O5 S 334.35 g/mol	Soil photolysis: 11
M06 AE2300015	AE 0001789-cyclopropylamine  Cyclopropylamine (9Cl) (IUPAC) Cyclopropaneamine (9Cl, CAS) [CAS no.: 765-30-0]	C3 H7 N 57.1 g/mol	Postulated in soil Postulated in water
M07 AE0854787	AE 0001789-anisic acid  2-methoxybenzoic acid (IUPAC) Benzoic acid, 2-methoxy- (CAS, 9CI) [CAS no.: 579-75-9]	C8 H8 O3 152.2 g/mol	Aquatic photolysis: 31
M08 AE2158927	AE 0001789-cyclopropyl-sulfonic acid  4-[(cyclopropylamino)carbonyl]benzenesulfonic acid (IUPAC) 4-[(cyclopropylamino)carbonyl]benzenesulfonic acid (CAS)	C10 H11 N O4 S 241.3 g/mol	Aquatic photolysis: 56

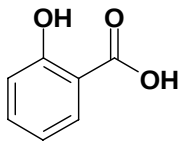
Codes	Report name Structure IUPAC name CAS name [CAS number]	Molecular formula Molar mass	Occurrence (max % AR)
M09 AE0171385	AE 0001789-salicylic acid  2-methoxybenzoic acid (IUPAC) 2-hydroxy benzoic acid (CAS, 9CI) [CAS n.: 69-72-7]	C7 H6 O3 138.12 g/mol	Anaerobic soil: 18

Table 8 Fate and behaviour of cyprosulfamide and its transformation products in the environment

Study	Compound	Range of values	PMRA #	Classification	Risk assessment value
Abiotic transformation					
Hydrolysis	Cyprosulfamide	Stable	1409641	—	Stable
Soil photolysis	Cyprosulfamide	t½ 63-144 days Phoenix, AZ in Jun	1409764	—	max t½ 144 days Phoenix, AZ in June
Aqueous photolysis	Cyprosulfamide	t½ 4.6 days Edmonton, AB in Jun	1409642	—	max t½ 4.6 days Edmonton, AB in June
		t½ 1-2 days 50ºN in late spring/summer	1409643		
	M07	Stable	1409781	—	Stable
	M08	Stable	1409782	—	Stable
Air photolysis	Cyprosulfamide	t½ 4-12 hours	1409599	—	max t½ 12 hours
	M06	t½ 6-12 hours	1409765	—	max t½ 12 hours
Biotransformation					
Aerobic soil	Cyprosulfamide	DT_{50} 2-8 days	1409762	non-persistent	80th centile t½ 9.2 days
		DT_{50} 6-10 days	1409761		
	M01	DT_{50} 1-8 days	1409769	non-persistent	max t½ 8.1 days
	M02	DT_{50} 23-49 days	1409769	slightly persistent	max t½ 49 days
	M03	DT_{50} 37-44 days	1409769	slightly persistent	max t½ 44 days
	M04	DT_{50} 8-13 days	1409768	non-persistent to moderately persistent	80th centile t½ 62 days
		DT_{50} 54-102 days	1409769		
	M05	DT_{50} 6-21 hours	1409767	non-persistent	max t½ 21 hours
	M06	DT_{50} 2-6 hours	1409766	non-persistent	max t½ 10 hours

Study	Compound	Range of values	PMRA #	Classification	Risk assessment value
Anaerobic soil	Cyprosulfamide	DT_{50} 56 days	1409763	moderately persistent	t½ 56 days
Aerobic water/sediment	Cyprosulfamide	DT_{50} 79-158 days	1409785	moderately persistent	max t½ 158 days
	M01	DT_{50} 148 to >1 yr	1409786	moderately persistent to persistent	Stable
	M02	DT_{50} >1 yr	1409786	persistent	Stable
	M03	DT_{50} 61 to >1 yr	1409786	moderately persistent to persistent	Stable
	M04	DT_{50} 16-111 yr	1409786	moderately persistent	max t½ 111 days
Anaerobic water/sediment	Cyprosulfamide	DT_{50} 198 days	1409784	persistent	t½ 198 days
Mobility					
Adsorption/ desorption	Cyprosulfamide	Koc 8.4-89 ml/L	1409775	high to very high mobility	20th centile 9.7 ml/L
	M01	Koc 3.0-32 ml/L	1409776	very high mobility	20th centile 4.6 ml/L
	M02	Koc 25-38 ml/L	1409779	very high mobility	20th centile 23 ml/L
	M03	Koc 1.5-10 ml/L	1409778	very high mobility	20th centile 1.6 ml/L
	M04	Koc 48-93 ml/L	1409777	high to very high mobility	20th centile 54 ml/L
Column leaching	M05	Koc 3.3-47 ml/L	1409780	very high mobility	20th centile 5.3 ml/L
Field studies					
Nebraska	500 SC product	DT_{50} 13.8 days	1409773	non-persistent to slightly persistent	Not applicable
Illinois	500 SC product	DT_{50} 9.5 days	1409772		
Ontario	500 SC product	DT_{50} 20.5 days	1409774		
California	500 SC product	DT_{50} 11.9 days	1409771		

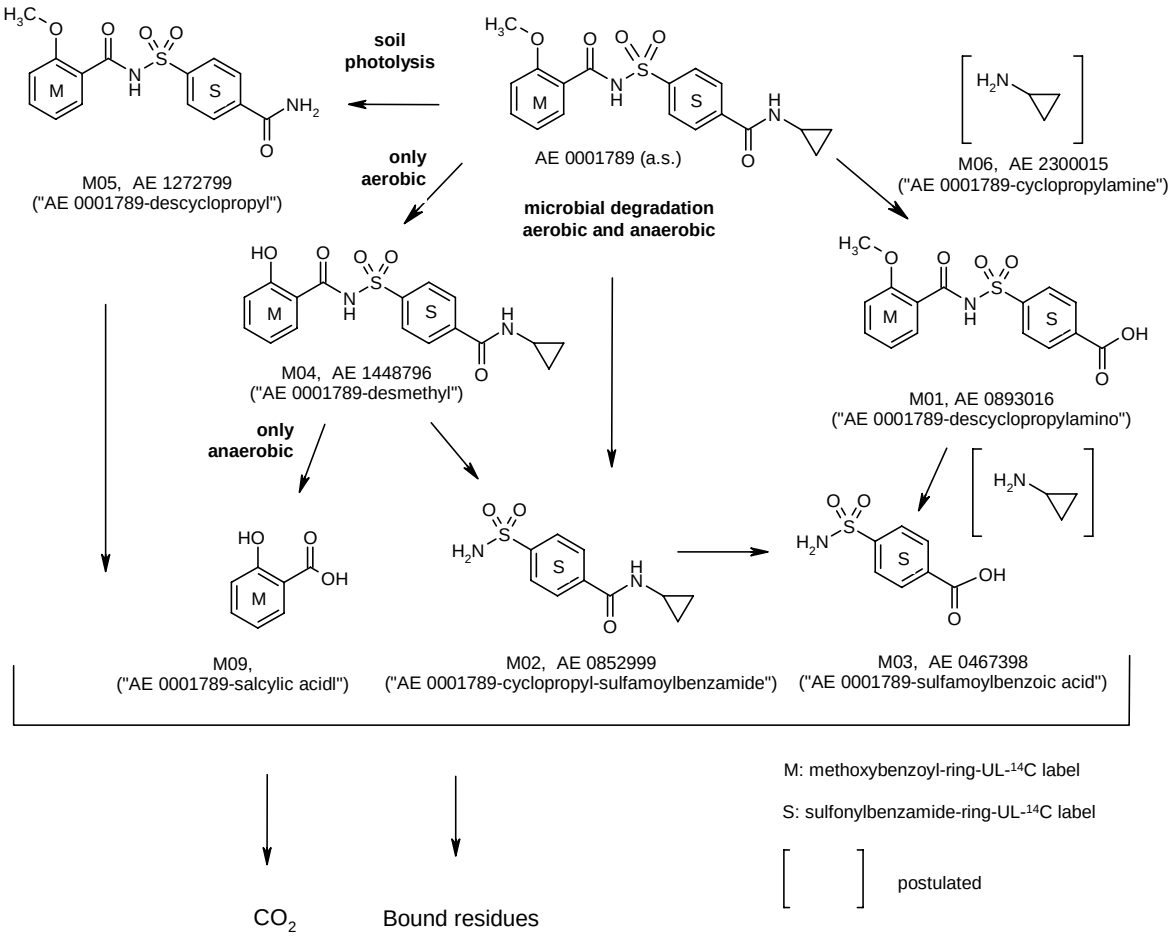


Figure 1-1 Proposed transformation pathway of cyprosulfamide in soil

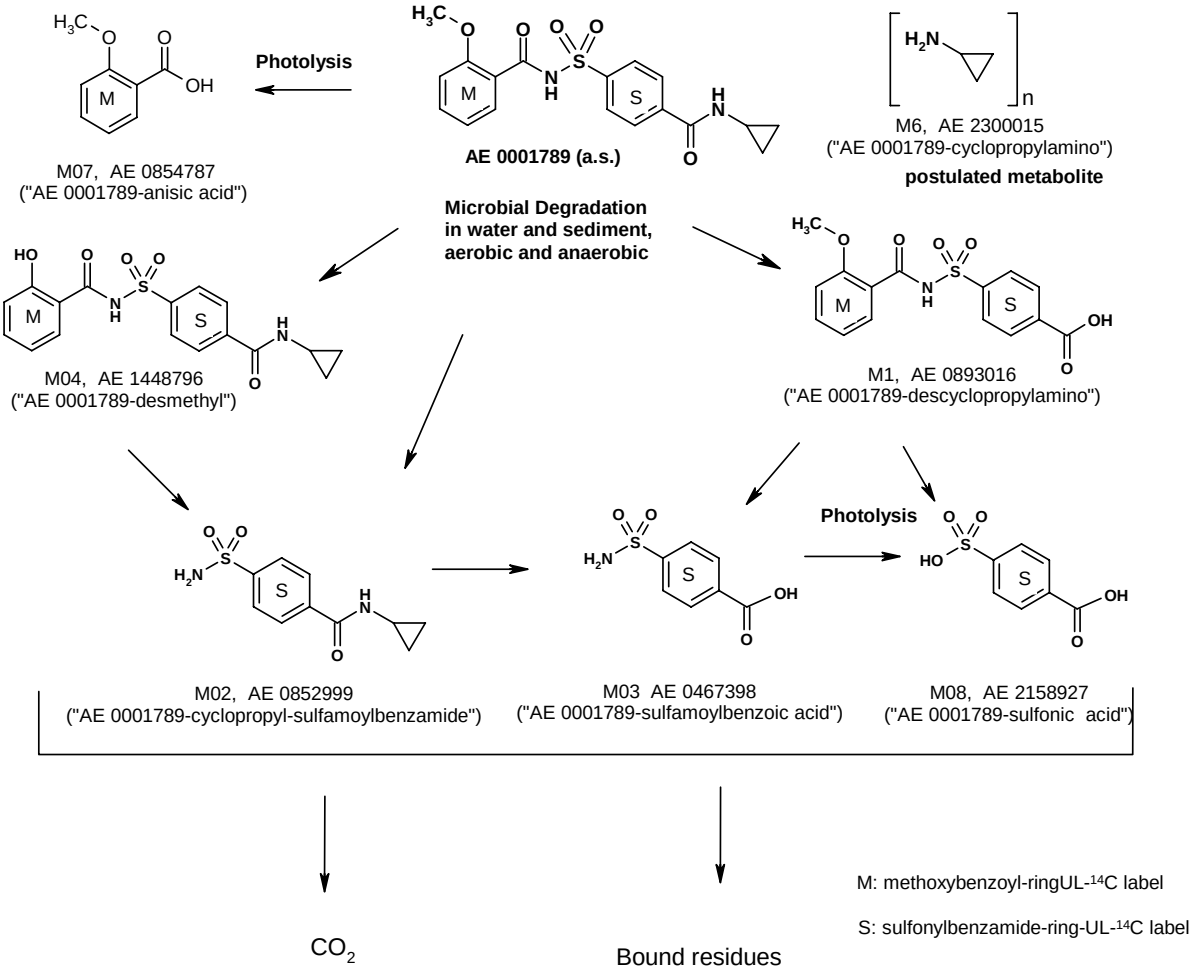


Figure 1-2 Proposed pathway of degradation of cyprosulfamide in water

Table 9 Toxicity to non-target species

Test organism	Study type	Substance	Endpoint value	PMRA#
Terrestrial organisms				
Eisenia fetida (earthworm)	acute	cyprosulfamide	14d LC_{50} >1000 mg/kg dry soil 14d NOEC 316 mg/kg dry soil (↑ weight loss at 562 mg/kg dry soil)	1409837
		product[1]	14d LC_{50} >205 mg /kg dry soil 14d NOEC 205 mg a.s./kg dry soil (no effect at highest dose)	1409052
		M01	14d LC_{50} >1000 mg/kg dry soil 14d NOEC 1000 mg/kg dry soil (no effect at highest dose)	1409838
		M02	14d LC_{50} >1000 mg/kg dry soil 14d NOEC 100 mg/kg dry soil (↑ weight loss at 316 mg/kg dry soil)	1409841
		M03	14d LC_{50} >1000 mg/kg dry soil 14d NOEC 1000 mg/kg dry soil (no effect at highest dose)	1409840
		M05	14d LC_{50} >1000 mg/kg dry soil 14d NOEC 100 mg/kg dry soil (↑ weight loss at 316 mg/kg dry soil)	1409839
	chronic	cyprosulfamide	56d NOEC 4.38 mg/kg dry soil (no effect at highest dose)	1409842
Apis mellifera (honey bee)	oral	cyprosulfamide	48h LD_{50} >101.4 µg/bee 48h NOEL 101.4 µg/bee (no effect at highest dose)	1409832

Test organism	Study type	Substance	Endpoint value	PMRA#
		product[1]	48h LD_{50} >55 µg/bee 48h NOEL not determined (4% correct mortality at 55 µg/bee)	1409047
	contact	cyprosulfamide	48h LD_{50} >100 µg/bee 48h NOEL 100 µg/bee (no effect at highest dose)	1409832
		product[1]	48h LD_{50} >50 µg/bee 48h NOEL not determined (25% corrected mortality at 50 µg/bee)	1409047
Aphidius rhopalosiphi (parasitoid wasp)	glassplate	product[1]	96h LR_{50} >101 mg/ha 72% dev. from control (reproduction) at 101 mg/ha	1409833
	extended on barley	product[1]	96h LR_{50} >101 mg/ha 18% dev. from control (reproduction) at 101 mg/ha	1409835
Typhlodromus pyri (predatory mite)	glassplate	product[1]	96h LR_{50} >101 mg/ha -28% dev. from control (reproduction) at 101 mg/ha	1409834
Chrysoperla carnea (lace wing)	extended on maize	product[1]	96h LR_{50} >101 mg/ha 2.5% dev. from control (reproduction) at 101 mg/ha	1409836
Coturnix virginianus (bobwhite quail)	acute	cyprosulfamide	LD_{50} >2000 mg/kg bw NOEL 2000 mg/kg bw (no effect at highest dose)	1409787
	short-term	cyprosulfamide	5d LD_{50} >954 mg/kg bw/day 5d NOEL 954 mg/kg bw/day (no effect at highest dose)	1409788
	sub-chronic and reproduction	cyprosulfamide	22wk NOEL 104 mg/kg bw/day (no effect at highest dose)	1409792
Anas platyrhynchos (mallard duck)	short-term	cyprosulfamide	5d LD_{50} >1161 mg/kg bw/day 5d NOEL not reliable (could not be reproduced)	1409790

Test organism	Study type	Substance	Endpoint value	PMRA#
			5d LD_{50} >1068 mg/kg bw/day 5d NOEL 1068 mg/kg bw/day (no effect at highest dose)	1409789
	sub-chronic and reproduction	cyprosulfamide	21wk NOEL 17.7 mg/kg bw/day (↓ eggs laid at 49.3 mg/kg bw/day)	1409791
Rat	acute	cyprosulfamide	LD_{50} >2000 mg/kg bw NOEL 2000 mg/kg bw (no effect at highest dose)	1409691
	reproduction	cyprosulfamide	multi-generation NOEL 173 mg/kg bw/day (↑ mortality, ↓weight gain)	1409714
terrestrial plants; eleven spp.	seedling emergence	product[2]	21d ER_{50} >160 g/ha 21d ER_{25} >160 g/ha	1409799
	vegetative vigour	product[2]	21d ER_{50} >160 g/ha 21d ER_{25} >160 g/ha	1409800
Beta vulgaris (sugar beet)	seedling emergence	product[1]	21d ER_{50} 4.7 g/ha (biomass) 21d ER_{25} 0.62 g/ha (shoot length)	1409801
	vegetative vigour	product[1]	21d ER_{50} >1.6 g/ha (biomass) 21d ER_{25} 0.55 g/ha (biomass)	1409802
Brassica napus (oilseed rape)	seedling emergence	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} 14.1 g/ha (biomass)	1409801
	vegetative vigour	product[1]	21d ER_{50} 10.3 g/ha (biomass) 21d ER_{25} 3.6 g/ha (biomass)	1409802
Cucumis sativus (cucumber)	seedling emergence	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} >25.2 g/ha	1409801
	vegetative vigour	product[1]	21d ER_{50} >50.4 g/ha 21d ER_{25} >50.4 g/ha	1409802
Fagopyrum esculentum (buckwheat)	seedling emergence	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} >25.2 g/ha	1409801
	vegetative vigour	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} >25.2 g/ha	1409802
Glycine max (soybean)	seedling emergence	product[1]	21d ER_{50} >50.4 g/ha 21d ER_{25} >50.4 g/ha	1409801
	vegetative vigour	product[1]	21d ER_{50} >6.3 g/ha 21d ER_{25} >3.1 g/ha	1409802
Helianthus annuus L.	seedling emergence	product[1]	21d ER_{50} >50.4 g/ha 21d ER_{25} 39.4 g/ha (biomass)	1409801

Test organism	Study type	Substance	Endpoint value	PMRA#
(sunflower)	vegetative vigour	product[1]	21d ER_{50} 15.7 g/ha (biomass) 21d ER_{25} 6.3 g/ha (shoot length)	1409802
Lycopersicon (tomato)	seedling emergence	product[1]	21d ER_{50} >50.4 g/ha 21d ER_{25} 32.4 g/ha (survival)	1409801
	vegetative vigour	product[1]	21d ER_{50} >101 g/ha 21d ER_{25} 84.4 g/ha (biomass)	1409802
Avena sativa (oat) *Zea mays* (corn)	seedling emergence	product[1]	21d ER_{50} >101 g/ha 21d ER_{25} >101 g/ha	1409801
	vegetative vigour	product[1]	21d ER_{50} >101 g/ha 21d ER_{25} >101 g/ha	1409802
Hordeum vulgare (barley)	seedling emergence	product[1]	21d ER_{50} >101 g/ha 21d ER_{25} >101 g/ha	1409801
Allium cepa (onion)	vegetative vigour	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} 1.7 g/ha (biomass)	1409802
Lolium perenne (perennial ryegrass)	seedling emergence	product[1]	21d ER_{50} >25.2 g/ha 21d ER_{25} >25.2 g/ha	1409801
	vegetative vigour	product[1]	21d ER_{50} >101 g/ha 21d ER_{25} >101 g/ha	1409802
soil micro-organisms	nitrogen turnover	cyprosulfamide	0 to 4% dev. from control (28 days) up to 1.07 mg/kg dry soil[3]	1409793
		product[1]	-12 to -6% dev. from control (28 days) up to 0.67 mg/kg dry soil[3]	1409053
	carbon turnover	cyprosulfamide	2 to 7% dev. from control (28 days) up to 1.07 mg/kg dry soil[3]	1409794
		product[1]	-4 to 1% dev. from control (28 days) up to 0.67 mg/kg dry soil[3]	1409054
Aquatic organisms				
Oncorhynchus mykiss (rainbow trout)	static acute	cyprosulfamide	96h LC_{50} >101 mg/L 96h NOEC 101 mg/L (no effect at highest dose)	1409804
		product[1]	Not reliable (undissolved test material)	1409044
Lepomis macrochirus (bluegill sunfish)	static acute	cyprosulfamide	96h LC_{50} >109 mg/L 96h NOEC 109 mg/L (no effect at highest dose)	1409806

Test organism	Study type	Substance	Endpoint value	PMRA#
Cyprinodon variegatus (sheepshead minnow)	static acute	cyprosulfamide	96h LC_{50} >106 mg/L 96h NOEC 106 mg/L (no effect at highest dose)	1409795
Pimephales promelas (fathead minnow)	chronic; ELS	cyprosulfamide	35d NOEC 4.67 mg/L (↓ length and weight at 4.67 mg/L)	1409807
Daphnia magna (water flea)	static acute	cyprosulfamide	48h EC_{50} >102 mg/L 48h NOEC 102 mg/L (no effect at highest dose)	1409808
		product[1]	48h EC_{50} >20 mg/L 48h NOEC 20 mg/L (no effect at highest dose)	1409045
		M01	48h EC_{50} >100 mg/L 48h NOEC 25 mg/L (immobilization at 50 mg/L)	1409812
		M02	48h EC_{50} >100 mg/L 48h NOEC 50 mg/L (immobilization at 100 mg/L)	1409814
		M03	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effect at highest dose)	1409813
		M05	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effect at highest dose)	1409811
		M07	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effects at highest dose)	1409809
		M08	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effect at highest dose)	1409810
	chronic	cyprosulfamide	21d NOEC 57.2 mg/L (no brood development and ↓ ♀ length and weight at 112 mg/L)	1409816
Americamysis bahia (mysid shrimp)	static acute	cyprosulfamide	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effect at highest dose)	1409797
	chronic	cyprosulfamide	Not reliable (undissolved test substance)	1409798
Crassostrea virginica (eastern oyster)	flowthrough acute	cyprosulfamide	48h EC_{50} >94 mg/L 48h NOEC 14 mg/L (↓shell deposition)	1409796

Test organism	Study type	Substance	Endpoint value	PMRA#
Pseudokirchneriella subcapitata (green alga)	chronic	cyprosulfamide	48h EC_{50} >99.7 mg/L 48h NOEC 99.7 mg/L (no effect at highest dose)	1409818
		product[1]	48h EC_{50} 1.01 mg/L (yield) 48h NOEC 0.196 mg/L (↓ growth rate and yield at 0.625 mg/L)	1409046
		M01	48h EC_{50} 27 mg/L (yield) 48h NOEC 3.13 mg/L (↓cumulative biomass at 6.25 mg/L)	1409822
		M02	48h EC_{50} 73 mg/L (yield) 48h NOEC 25 mg/L (↓cumulative biomass at 50 mg/L)	1409824
		M03	48h EC_{50} 29 mg/L (cumulative biomass) 48h NOEC 25 mg/L (↓growth rate, yield, umulative biomass at 50 mg/L)	1409823
		M05	48h EC_{50} >100 mg/L 48h NOEC 100 mg/L (no effect at highest dose)	1409821
		M07	48h EC_{50} 28 mg/L (yield) 48h NOEC 12.5 mg/L (↓cumulative biomass at 25 mg/L)	1409819
		M08	48h EC_{50} 54 mg/L (cumulative biomass) 48h NOEC 25 mg/L (↓growth rate, yield, cumulative biomass at 50 mg/L)	1409820
Lemna gibba (duck weed)	chronic	cyprosulfamide	7d EC_{50} >104 mg/L 7d NOEC 51.1 mg/L (↓frond number (growth rate, yield, cumulative biomass) at 104 mg/L)	1409825

Test organism	Study type	Substance	Endpoint value	PMRA#
		product[1]	7d EC_{50} 0.0059 mg/L (cumulative biomass (frond number)) 7d NOEC 0.0020 mg/L (cell abnormalities, ↓growth rate and yield (frond number, frond area) at 30.5 mg/L)	1409057
		M01	7d EC_{50} >94.4 mg/L 7d NOEC 94.4 mg/L (no effects at highest dose)	1409830
		M02	7d EC_{50} >101 mg/L 7d NOEC 101 mg/L (no effects at highest dose)	1409827
		M03	7d EC_{50} >98.4 mg/L 7d NOEC 98.4 mg/L (no effects at highest dose)	1409831
		M05	7d EC_{50} 69 mg/L (yield frond number) 7d NOEC <5.61 mg/L (↓frond number (growth rate, yield, cumulative biomass) at 5.61 mg/L)	1409829
		M07	7d EC_{50} >104 mg/L 7d NOEC 6.51 mg/L (↓frond number (growth rate, yield, cumulative biomass) at 12.7 mg/L)	1409826
		M08	7d EC_{50} >115 mg/L 7d NOEC 14 mg/L (↓yield (dry weight, frond number) at 28.2 mg/L)	1409828

1 Refers to the product Cyprosulfamide and Isoxaflutole SC 240+240 g/L containing 20.5% cyprosulfamide (a.s.)

2 Refers to the product Cyprosulfamide 500 SC containing 42.3% cyprosulfamide (a.s.)

3 At soil density of 1.5 g/cm^3: 0.67 mg cyprosulfamide/kg dw corresponds to 500 g cyprosulfamide/ha (5-cm soil depth) or 1500 g cyprosulfamide/ha (15-cm soil depth); 1.07 mg cyprosulfamide/kg dw corresponds to 800 g cyprosulfamide/ha (5-cm soil depth) or 2400 g cyprosulfamide/ha (15-cm soil depth)

Table 10 Endpoints used for risk assessment and the uncertainty factors applied

Taxonomic group	Exposure	Endpoint	Uncertainty Factor
Earthworm	Acute	LC_{50}	0.5
	Chronic	NOEC	1.0
Bees	Acute	LD_{50}	1.0
Other non-target arthropods	Acute	LR_{50}	1.0
Birds	Acute oral	LD_{50}	0.1
	Dietary	LD_{50}	0.1
	Reproduction	NOEL	1.0
Mammals	Acute oral	LD_{50}	0.1
	Reproduction	NOEL	1.0
Non-target terrestrial plants	Acute	HR_5 of SSD of ER_{50}[2]	1.0
Aquatic invertebrates	Acute	EC_{50}	0.5
	Chronic	NOEC	1.0
Fish	Acute	LC_{50}	0.1
	Chronic	NOEC	1.0
Amphibians	Acute	Fish LC_{50}	0.1
	Chronic	Fish NOEC	1.0
Algae	Chronic	EC_{50}	0.5
Aquatic vascular plants	Chronic	EC_{50}	0.5

Table 11 Screening level estimated daily exposure (EDE) values for birds and mammals

Organism	FIR[1] (g dw/day)	Feeding guild	Matrix	EEC[2] (mg/kg dw)	EDE[3] (mg/kg bw/day)
20 g bird	5.078	Insectivore	Small insects	20.95	5.34
		Granivore	Grain and seeds	3.58	0.91
		Frugivore	Fruit	10.80	2.75
100 g bird	19.95	Insectivore	Small insects	20.95	4.17
		Granivore	Grain and seeds	3.58	0.71
		Frugivore	Fruit	10.80	2.15
1000 g bird	58.12	Insectivore	Small insects	20.95	1.22
		Granivore	Grain and seeds	3.58	0.21
		Frugivore	Fruit	10.80	0.63
		Herbivore	Leaves, leafy	130.59	7.59

[2] 5th percentile hazard rate of the species sensitivity distribution of ER50 values

			crops		
15 g mammal	2.18	Insectivore	Small insects	20.95	3.04
		Granivore	Grain and seeds	3.58	0.52
		Frugivore	Fruit	10.80	1.57
35 g mammal	4.37	Insectivore	Small insects	20.95	2.62
		Granivore	Grain and seeds	3.58	0.45
		Frugivore	Fruit	10.80	1.35
		Herbivore	Leaves, leafy crops	130.59	16.31
1000 g mammal	68.72	Insectivore	Small insects	20.95	1.44
		Granivore	Grain and seeds	3.58	0.25
		Frugivore	Fruit	10.80	0.74
		Herbivore	Leaves, leafy crops	130.59	8.97

1 Food ingestion rate (FIR) based on Nagy (1987)
2 Estimated environmental concentration (EEC) based on Hoerger and Kenaga nomogram, expressed in terms of cyprosulfamide
3 Estimated daily exposure (EDE) = FIR/BW*EEC expressed in terms of cyprosulfamide

Table 12 Risk to non-target organisms

Organism	Exposure	Substance	Endpoint[1]	EEC[2]	Units	RQ[3]
Terrestrial organisms						
Earthworm	acute	cyprosulfamide	LC_{50}/2 >500	0.047	mg/kg dw	<0.01
		product[4]	LC_{50}/2 >102	0.047	mg/kg dw	<0.01
		M01	LC_{50}/2 >500	0.047	mg/kg dw	<0.01
		M02	LC_{50}/2 >500	0.047	mg/kg dw	<0.01
		M03	LC_{50}/2 >500	0.047	mg/kg dw	<0.01
		M05	LC_{50}/2 >500	0.047	mg/kg dw	<0.01
	reproduction	cyprosulfamide	NOEC 4.38	0.047	mg/kg dw	0.01
Bee	oral	cyprosulfamide	LC_{50}×1.12 >114	0.1	kg/ha	<0.01
		product[4]	LC_{50}×1.12 >61	0.1	kg/ha	<0.01
	contact	cyprosulfamide	LC_{50}×1.12 >112	0.1	kg/ha	<0.01

Organism	Exposure	Substance	Endpoint[1]	EEC[2]	Units	RQ[3]
		product[4]	LC_{50}×1.12 >56	0.1	kg/ha	<0.01
Predatory arthropod	contact	product[4]	LR_{50} >101	106	g/ha	<1.04
Parasitic arthropod	contact	product[4]	LR_{50} >101	106	g/ha	<1.04
20 g bird, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	5.34	mg/kg bw	<0.03
	dietary	cyprosulfamide	LD_{50}/10 >496	5.34	mg/kg bw	<0.06
	reproduction	cyprosulfamide	NOEL 17.7	5.34	mg/kg bw	0.30
20 g bird, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.91	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	0.91	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 17.7	0.91	mg/kg bw	0.05
20 g bird, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	2.75	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	2.75	mg/kg bw	<0.03
	reproduction	cyprosulfamide	NOEL 17.7	2.75	mg/kg bw	0.16
100 g bird, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	4.17	mg/kg bw	<0.02
	dietary	cyprosulfamide	LD_{50}/10 >496	4.17	mg/kg bw	<0.04
	reproduction	cyprosulfamide	NOEL 17.7	4.17	mg/kg bw	0.24
100 g bird, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.17	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	0.17	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 17.7	0.17	mg/kg bw	0.04
100 g bird, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	2.15	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	2.15	mg/kg bw	<0.02
	reproduction	cyprosulfamide	NOEL 17.7	2.15	mg/kg bw	0.12
1000 g bird, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	1.22	mg/kg bw	<0.01

Organism	Exposure	Substance	Endpoint[1]	EEC[2]	Units	RQ[3]
	dietary	cyprosulfamide	LD_{50}/10 >496	1.22	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 17.7	1.22	mg/kg bw	0.07
1000 g bird, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.21	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	0.21	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 17.7	0.21	mg/kg bw	0.01
1000 g bird, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	0.63	mg/kg bw	<0.01
	dietary	cyprosulfamide	LD_{50}/10 >496	0.63	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 17.7	0.63	mg/kg bw	0.04
1000 g bird, herbivore	acute	cyprosulfamide	LD_{50}/10 >200	7.59	mg/kg bw	<0.04
	dietary	cyprosulfamide	LD_{50}/10 >496	7.59	mg/kg bw	<0.08
	reproduction	cyprosulfamide	NOEL 17.7	7.59	mg/kg bw	0.43
15 g mammal, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	3.04	mg/kg bw	<0.02
	reproduction	cyprosulfamide	NOEL 173	3.04	mg/kg bw	0.02
15 g mammal, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.52	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	0.52	mg/kg bw	<0.01
15 g mammal, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	1.57	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	1.57	mg/kg bw	0.01
35 g mammal, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	2.62	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	2.62	mg/kg bw	0.02
35 g mammal, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.45	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	0.45	mg/kg bw	<0.01
35 g mammal, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	1.35	mg/kg bw	<0.01

Organism	Exposure	Substance	Endpoint[1]	EEC[2]	Units	RQ[3]
	reproduction	cyprosulfamide	NOEL 173	1.35	mg/kg bw	0.01
35 g mammal, herbivore	acute	cyprosulfamide	LD_{50}/10 >200	16.31	mg/kg bw	<0.08
	reproduction	cyprosulfamide	NOEL 173	16.31	mg/kg bw	0.09
1000 g mammal, insectivore	acute	cyprosulfamide	LD_{50}/10 >200	1.44	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	1.44	mg/kg bw	0.01
1000 g mammal, granivore	acute	cyprosulfamide	LD_{50}/10 >200	0.25	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	0.25	mg/kg bw	<0.01
1000 g mammal, frugivore	acute	cyprosulfamide	LD_{50}/10 >200	0.74	mg/kg bw	<0.01
	reproduction	cyprosulfamide	NOEL 173	0.74	mg/kg bw	<0.01
1000 g mammal, herbivore	acute	cyprosulfamide	LD_{50}/10 >200	8.97	mg/kg bw	<0.04
	reproduction	cyprosulfamide	NOEL 173	8.97	mg/kg bw	0.05
Terrestrial plants, eleven spp.	acute	product[4]	HR_5 of ER_{50} 2.7	106 (screen)	g/ha	39
				6.4 (6% drift)	g/ha	2.4
		product[5]	ER25 >160	106	g/ha	<0.67
Aquatic organisms						
Aquatic invert, crustacean	acute	cyprosulfamide	EC_{50}/2 >51	0.013	mg/l	<0.01
		product[4]	EC_{50}/2 >10	0.013	mg/l	<0.01
		M01	EC_{50}/2 >50	0.013	mg/l	<0.01
		M02	EC_{50}/2 >50	0.013	mg/l	<0.01
		M03	EC_{50}/2 >50	0.013	mg/l	<0.01
		M05	EC_{50}/2 >50	0.013	mg/l	<0.01
		M07	EC_{50}/2 >50	0.013	mg/l	<0.01
		M08	EC_{50}/2 >50	0.013	mg/l	<0.01

Organism	Exposure	Substance	Endpoint[1]	EEC[2]	Units	RQ[3]
	chronic	cyprosulfamide	NOEC 57.2	0.013	mg/l	<0.01
Aquatic invert, mollusc	acute	cyprosulfamide	EC_{50}/2 >47	0.013	mg/l	<0.01
Fish	acute	cyprosulfamide	LC_{50}/10 >10.1	0.013	mg/l	<0.01
	ELS	cyprosulfamide	NOEC 4.67	0.013	mg/l	<0.01
Amphibians[6]	acute	cyprosulfamide	LC_{50}/10 >10.1	0.071	mg/l	<0.01
	ELS	cyprosulfamide	NOEC 4.67	0.071	mg/l	0.02
Algae	96-hour	cyprosulfamide	EC_{50}/2 >49.9	0.013	mg/l	<0.01
		product[4]	EC_{50}/2 0.50	0.013	mg/l	0.03
		M01	EC_{50}/2 13.5	0.013	mg/l	<0.01
		M02	EC_{50}/2 36.5	0.013	mg/l	<0.01
		M03	EC_{50}/2 14.5	0.013	mg/l	<0.01
		M05	EC_{50}/2 >50	0.013	mg/l	<0.01
		M07	EC_{50}/2 14.0	0.013	mg/l	<0.01
		M08	EC_{50}/2 27.0	0.013	mg/l	<0.01
Aquatic vascular plants	7-day	cyprosulfamide	EC_{50}/2 >52.0	0.013	mg/l	<0.01
		product[4]	EC_{50}/2 3.0	13 (screen)	µg/l	4.4
				0.78 (6% drift)	µg/l	0.26
		M01	EC_{50}/2 >47.2	0.013	mg/l	<0.01
		M02	EC_{50}/2 >50.5	0.013	mg/l	<0.01
		M03	EC_{50}/2 >49.2	0.013	mg/l	<0.01
		M05	EC_{50}/2 34.5	0.013	mg/l	<0.01
		M07	EC_{50}/2 >52.0	0.013	mg/l	<0.01
		M08	EC_{50}/2 >57.5	0.013	mg/l	<0.01

1 Endpoint values are modified according to uncertainty factors listed in Table 4.2-2. In the case of bees, the LD50 in µg/bee is converted to the equivalent rate in kg/ha by multiplying 1.12 according to Atkins et al. (1981)
2 Estimated environmental exposure concentrations based on application rate of 106 g cyprosulfamide/ha (soil EEC for earthworms based on soil density of 1.5 g/cm3, soil depth of 15-cm; dietary EEC for birds and small wild mammals based on EDE values derived in Table 4.2-3; water EEC is based on water depth of 15-cm to represent a seasonal water body for amphibians and 80-cm to represent a permanent water body for remaining aquatic organisms)
3 Risk Quotient (RQ) = exposure / toxicity ; shaded cells indicate that the screening level RQ exceeds the LOC (2.0 for non-target arthropods other than bees; 1.0 for remaining organisms)
4 Product refers to Cyprosulfamide and Isoxaflutole SC 240+240 g/L containing 20.5% cyprosulfamide and 20.5% isoxaflutole; endpoint value is expressed in terms of cyprosulfamide
5 Product refers to Cyprosulfamide 500 SC containing 42.3% cyprosulfamide; endpoint value is expressed in terms of cyprosulfamide
6 Amphibian assessment is based on fish toxicity data

Table 13 Comparative toxicity of Cyprosulfamide + Isoxaflutole versus Isoxaflutole alone to non-target plants

Plant type	**Terrestrial plant**		**Aquatic plant**	
Test species	Most sensitive of 10-11 spp.		*Lemna gibba*	
Test chemical	Cyprosulfamide + Isoxaflutole	Isoxaflutole alone	Cyprosulfamide + Isoxaflutole	Isoxaflutole alone
Toxicity endpoint[1]	EC_{25} 0.55 g a.i./ha	EC_{25} 0.13 g a.i./ha	EC_{50}/2 3.0 µg a.i./L	EC_{50}/2 1.6 µg a.i./L
PMRA#	1409802	1175731	1409057	1175732
EEC[2]	106 g a.i./ha	106 g a.i./ha	13 µg a.i./L	13 µg a.i./L
RQ[3]	193	815	4.4	8.1
Risk reduction	4×	—	2×	—

1 Toxicity endpoints are expressed in terms of isoxaflutole (a.i.), and are modified according to uncertainty factors listed in Table 4.2-2.

2 Estimated environmental exposure concentrations based on application rate of 106 g a.i./ha (water EEC is based on water depth of 80-cm to represent a permanent water body) and expressed in terms of isoxaflutole (a.i.)

3 Risk Quotient (RQ) = exposure / toxicity

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

All of the specified Canadian MRLs are the same as those in the U.S. with the exception of poultry commodities and milk. MRLs will be specified in Canada, however, in the U.S. the proposed uses of cyprosulfamide will fall under category 3 of 40 CFR 180.6 (a). As well, the U.S. establishes MRLs on feed commodities whereas Canada does not.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Eggs	0.02	None	Not reviewed by Codex
Fat, meat and meat byproducts of poultry	0.02	None	
Milk	0.01	None	

* 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.

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1409045 2007, Acute toxicity of AE 0001789 & Isoxaflutole SC 240+240 to the waterflea Daphnia magna in a static laboratory test system - Limit test, EBUBP106, DACO: IIIA 10.2.2.2

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1409048 2006, Toxicity to the predatory mite Typhlodromus pyri SCHEUTEN (Acari, Phytoseiidae) in the laboratory; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/049, DACO: 9.2.8, IIIA 10.5.1

1409049 2006, Toxicity to the parasitoid wasp Aphidius rhopalosiphi (DeStephani-Perez) (Hymenoptera: Braconidae) in the laboratory - isoxaflutole & cyprosulfamide SC 240 + 240 g/l, CW06/048, DACO: 9.2.8, IIIA 10.5.1

1409050 2007, Toxicity to the green lacewing Chrysoperla carnea STEPH. (Neuroptera, Chrysopidae) using an extended laboratory test; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/065, DACO: 9.2.8, IIIA 10.5.2

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earthworms (Eisenia fetida) tested in artificial soil with 5 percent peat, LRT/RG-A-74/06, DACO: 9.2.8, IIIA 10.6.2

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1409057 2007, Lemna gibba G3 - Growth inhibition test with AE 0001789 & isoxaflutole SC 240 + 240 under static conditions (spec No.: 102000014305), EBUBP101, DACO: 9.8.6, 9.8.7, IIIA 10.8.2.1

1409599 2007, AE 0001789: Calculation of the chemical lifetime in the troposphere, MEF-05/092 M1451472-4, DACO: 8.2.3.3.3, IIA 2.10, IIA 7.10

1409641 2005, [Methoxybenzoyl-UL-14C] and [sulfonylbenzamide-UL-14C]AE 0001789: Hydrolytic degradation, MEUBX006, DACO: 8.2.3.2, IIA 2.9.1, IIA 7.5

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1409643 2007, AE0001789: Determination of the quantum yield and assessment of the environmental half-life of the direct photodegradation in water, MEF-05/146, DACO: 8.2.3.3.2, IIA 2.9.3, IIA 7.6

1409691 2006, AE 0001789 - Acute toxicity in the rat after oral administration, AT01958 T 3075317, DACO: 4.2.1, IIA 5.2.1

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1409764 2005, [Methoxybenzoyl-ring-UL-14C and Sulfonylbenzamide-ring-UL-14C]AE 0001789: Phototransformation on soil, 04MEUBX012, DACO: 8.2.3.3.1, IIA 7.1.3

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1409766 2007, AE 0001789-cyclopropylamine (AE 2300015): Rate of degradation in three european soils under aerobic laboratory conditions, MEF-06/081 M1251519-4, DACO: 8.2.3.4.2, IIA 7.2.3

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European soils under aerobic laboratory conditions, MEF-06/027, DACO: 8.2.3.4.2, IIA 7.2.3

1409768 2007, AE 0001789-desmethyl (AE 1448796): Rate of degradation in three European soils under aerobic laboratory conditions, MEF-06/103 M1251528-4, DACO: 8.2.3.4.2, IIA 7.2.3

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1409770 2007, Stability of AE 0001789 and its metabolites AE 1272799, AE 0852999, AE 0893016, AE 0467398 and AE 1448796 in soil during frozen storage (reported through a maximum of 363 days storage), RAUBP005, DACO: 8.3.2, IIA 7.3.1

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1409795 2005, Acute toxicity of AE 0001789 technical to the sheepshead minnow (Cyprinodon variegatus) under static conditions, EBUBP007, DACO: 9.4.2, 9.4.3, 9.4.4, IIA 8.11.1

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1409798 2007, AE 0001789 technical - Life-cycle toxicity test with mysids (Americamysis bahia) under flow-through conditions, EBUBP004, DACO: 9.4.2, 9.4.3, 9.4.4, IIA 8.11.1

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1409800 2007, AE 0001789 SC 500 g/L: Effects on eleven species of non-target terrestrial plants: vegetative vigour test (tier 1), VV 06/028, DACO: 9.8.4,IIA 8.12

1409801 2007, Isoxaflutole + cyprosulfamide SC 240 + 240 g/L - effects on eleven species of non-target terrestrial plants: seedling emergence and seedling growth test (tier 2), SE 06/033 EBUBP062, DACO: 9.8.4, IIA 8.12

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1409803 2006, AE 0001789 - Toxicity to bacteria, 2006/0106/01, DACO: IIA 8.15

1409804 2004, Acute toxicity of AE 0001789 Technical to the rainbow trout (Oncorhynchus mykiss) under static conditions, 201011, DACO: 9.5.2.1, 9.5.2.3, IIA 8.2.1.1

1409806 2004, Acute Toxicity of AE 0001789 to the Bluegill Sunfish (Lepomis macrochirus) Under Static Conditions, EBUBX007 201020, DACO: 9.5.2.2, 9.5.2.3, IIA 8.2.1.2

1409807 2005, Early life stage toxicity of AE 0001789 technical to the Fathead Minnow (Pimephales promelas) under flow-through conditions, EBUBP009, DACO: 9.5.3.1, IIA 8.2.4

1409808 2004, Acute toxicity of AE 0001789 technical to the Daphnia magna under static conditions, 200982, DACO: 9.3.2, IIA 8.3.1.1

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1409811 2006, Acute toxicity of AE 0001789-descyclopropyl (AE 1272799) to the Daphnia magna under static conditions, EBUBP094, DACO: 9.3.2, IIA 8.3.1.1

1409812 2006, Acute toxicity of AE 001789- descyclopropylamino (AE 0893016) to the Daphnia magna under static conditions, EBUBP091, DACO: 9.3.2, IIA 8.3.1.1

1409813 2006, Acute toxicity of AE 0001789-sulfamoylbenzoic acid (AE 0467398) to the Daphnia magna under static conditions, EBUBP076, DACO: 9.3.2, IIA 8.3.1.1

1409814 2006, Acute toxicity of AE0001789 -cyclopropyl-sulfamoylbenzamide (AE 0852999) to the Daphnia magna under static conditions, EBUBP084, DACO: 9.3.2, IIA 8.3.1.1

1409816 2005, Chronic toxicity of AE 0001789 technical to the Daphnia magna - under static-renewal conditions, EBUBP011, DACO: 9.3.3, IIA 8.3.2.1

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1409820 2006, Toxicity of AE 0001789-cyclopropyl-sulfonic acid (AE 2158927) to the green alga Pseudokirchneriella subcapitata, EBUBP100, DACO: 9.8.2, 9.8.3, IIA 8.4

1409821 2006, Toxicity of AE 0001789-descyclopropyl (AE 1272799) to the green alga Pseudokirchneriella subcapitata, EBUBP096, DACO: 9.8.2, 9.8.3, IIA 8.4

1409822 2006, Toxicity of AE 0001789-descyclopropylamino (AE 0893016) to the green alga Pseudokirchneriella subcapitata, EBUBP092, DACO: 9.8.2, 9.8.3, IIA 8.4

1409823 2006, Toxicity of AE 0001789-sulfamoylbenzoic acid (AE 0467398) to the green alga Pseudokirchneriella subcapitata, EBUBP081, DACO: 9.8.2, 9.8.3, IIA 8.4

1409824 2006, Toxicity of AE0001789 -cyclopropyl-sulfamoylbenzamide (AE 0852999) to the green alga Pseudokirchneriella subcapitata, EBUBP085, DACO: 9.8.2, 9.8.3, IIA 8.4

1409825 2005, Toxicity of AE 0001789 technical to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP005, DACO: 9.8.5, IIA 8.6

1409826 2007, Toxicity of AE 0001789-anisic acid (AE 0854787) to duckweed (Lemna

gibba G3) under static-renewal conditions, EBUBP087, DACO: 9.8.5, IIA 8.6

1409827 2007, Toxicity of AE 0001789-cyclopropyl-sulfamoylbenzamide (AE 0852999) to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP086, DACO: 9.8.5, IIA 8.6

1409828 2007, Toxicity of AE 0001789-cyclopropyl-sulfonic acid (AE 2158927) to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP099, DACO: 9.8.5, IIA 8.6

1409829 2006, Toxicity of AE 0001789-descyclopropyl (AE 1272799) to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP095, DACO: 9.8.5, IIA 8.6

1409830 2007, Toxicity of AE 0001789-descyclopropylamino (AE 0893016)) to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP093, DACO: 9.8.5, IIA 8.6

1409831 2007, Toxicity of AE 0001789-sulfamoylbenzoic acid (AE 0467398) to duckweed (Lemna gibba G3) under static-renewal conditions, EBUBP082-1, DACO: 9.8.5, IIA 8.6

1409832 2007, Effects of AE 0001789 00 1C97 0005 (acute contact and oral) on honey bees (Apis mellifera L.) in the laboratory, 25111035, DACO: 9.2.4.1,9.2.4.2,IIA 8.7.1, IIA 8.7.2

1409833 2006, Toxicity to the parasitoid wasp Aphidius rhopalosiphi (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) in the laboratory; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/048, DACO: 9.2.6, IIA 8.8.1.1

1409834 2007, Toxicity to the predatory mite Typhlodromus pyri SCHEUTEN (Acari, Phytoseiidae) in the laboratory; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/049, DACO: 9.2.5, IIA 8.8.1.2

1409835 2007, Toxicity to the parasitoid wasp Aphidius rhopalosiphi (DESTEPHANI-PEREZ) (Hymenoptera: Braconidae) using an extended laboratory test; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/064, DACO: 9.2.6, IIA 8.8.2.1

1409836 2007, Toxicity to the green lacewing Chrysoperla carnea STEPH. (Neuroptera, Chrysopidae) using an extended laboratory test; Isoxaflutole & Cyprosulfamide SC 240 + 240 g/l, CW06/065, DACO: 9.2.5, IIA 8.8.2.4

1409837 2007, AE 0001789 00 1C97 0005: AE 0001789 substance technical: Acute toxicity to earthworms (Eisenia fetida) tested in artifical soil, LKC/RG-A-61/06, DACO: 9.2.3.1, IIA 8.9.1

1409838 2007, AE 0001789-cyclopropyl-sulfamoylbenzamide (AE 0852999): Acute toxicity to earthworms (Eisenia fetida) tested in artificial soil, LKC/RG-A-63/06, DACO: 9.2.3.1, IIA 8.9.1

1409839 2007, AE 0001789-descyclopropyl (AE 1272799): Acute toxicity to earthworms (Eisenia fetida) tested in artificial soil, LRT/RG-A-71/06, DACO: 9.2.3.1, IIA 8.9.1

1409840 2007, AE 0001789-descyclopropylamino (AE 0893016): acute toxicity to earthworms (Eisenia fetida) tested in artificial soil, LRT/RG-A-70/06, DACO: 9.2.3.1, IIA 8.9.1

1409841 2007, AE 0001789-sulfamoylbenzoic acid (AE 0467398): Acute toxicity to earthworms (Eisenia fetida) tested in artificial soil, LKC/RG-A-62/06, DACO:

9.2.3.1, IIA 8.9.1

1409842 2006, AE 0001789: Effects on reproduction and growth of earthworms Eisenia fetida in artificial soil, 30341022, DACO: IIA 8.9.2

3.0 Impact on Human and Animal Health

1409685	2006, [Sulfonylbenzamide-ring-UL-14C]AE 0001789: Distribution of the total radioactivity in male rats determined by quantitative whole body autoradiography, MEF-05/325 M1819142-6, DACO: 4.5.9,IIA 5.1.1
1409686	2006, [Sulfonylbenzamide-UL-14C]AE 0001789: Absorption, distribution, excretion and metabolism in the rat, MEF-05/326 M81819153, DACO: 4.5.9,IIA 5.1.1
1409687	2006, [Methoxy-benzoyl-ring-UL-14C]AE 0001789: Absorption, distribution, excretion and metabolism in the rat, MEF-05/327 M91819154, DACO: 4.5.9,IIA 5.1.2
1409688	2006, [Methoxybenzoyl-ring-UL-14C]AE 0001789: Distribution of the total radioactivity in male rats determined by quantitative whole body autoradiography, determination of the exhaled 14CO2, MEF-05/318 M1819143-7, DACO: 4.5.9,IIA 5.1.2
1409690	2007, The non relevance of the environmental metabolites of cyprosulfamide (AE 0001789), —285709-01-1, DACO: 4.2.9,4.3.8,4.4.5,4.5.8,4.8,8.5.1,8.6,IIA 5.10,IIA 7.13
1409691	2006, AE 0001789 - Acute toxicity in the rat after oral administration, AT01958 T 3075317, DACO: 4.2.1,IIA 5.2.1
1409692	2006, AE 0001789 - Acute toxicity in the rat after dermal application, AT01909, DACO: 4.2.2,IIA 5.2.2
1409693	2006, AE 0001789 - (1st revision of report AT 01279, dated June 23, 2004) - Acute inhalation toxicity in rats, AT01392, DACO: 4.2.3,IIA 5.2.3
1409694	2006, AE 0001789 - Acute skin irritation/corrosion on rabbits, AT01649, DACO: 4.2.5,IIA 5.2.4
1409695	2007, AE 0001789 - Acute eye irritation on rabbits, AT02436, DACO: 4.2.4,IIA 5.2.5
1409696	2006, AE0001789 - Study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman), AT01944, DACO: 4.2.6,IIA 5.2.6
1409697	2005, A 28-day toxicity feeding study in the beagle dog with technical grade AE0001789, 201146, DACO: 4.3.3,IIA 5.3.1
1409698	2006, AE 0001789 - 90-day toxicity study in the mouse by dietary administration, SA 03005, DACO: 4.3.1,IIA 5.3.2
1409698	2006, AE 0001789 - 90-day toxicity study in the mouse by dietary administration, SA 03005, DACO: 4.3.1,IIA 5.3.2
1409699	2006, AE 0001789 - 90-day toxicity study in the rat by dietary administration, SA 02352, DACO: 4.3.1,IIA 5.3.2

1409701	2005, A 90-day toxicity feeding study in the beagle dog with technical grade AE 0001789, 201279, DACO: 4.3.2,IIA 5.3.3
1409703	2007, A chronic toxicity feeding study in the beagle dog with technical grade AE 0001789, 201496-1, DACO: 4.3.2,IIA 5.3.4
1409704	2005, Waiver request for 21-day dermal study on AE 0001789, BCS 07-HC-2, DACO: 4.3.4,4.3.5,IIA 5.3.7,IIA 5.3.8
1409705	2006, AE 0001789 (Project: AE 0001789) - Salmonella/microsome test - Plate incorporation and preincubation method - 1st amendment to Bayer Report AT01348, AT01348, DACO: 4.5.4,IIA 5.4.1
1409706	2007, AE 0001789 - Salmonella/microsome test - Plate incorporation and preincubation method, AT03534, DACO: 4.5.4,IIA 5.4.1
1409707	2006, AE 0001789 (Project: AE 0001789) - In vitro chromosome aberration test with Chinese hamster V79 cells - 1st amendment to Bayer Report AT01674, AT01674, DACO: 4.5.6,IIA 5.4.2
1409708	2006, AE 0001789 - V79/HPRT-Test in vitro for the detection of induced forward mutations, AT02816, DACO: 4.5.5,IIA 5.4.3
1409709	2006, AE 0001789 (Project: AE 0001789) - Micronucleus-test on the male mouse - 1st amendment to Bayer Report AT01302, AT01302, DACO: 4.5.7,IIA 5.4.4
1409710	2007, Chronic toxicity and carcinogenicity study of AE 0001789 in the wistar rat by dietary administration, SA03277, DACO: 4.4.1,4.4.2,4.4.4,IIA 5.5.1,IIA 5.5.2
1409712	2007, Carcinogenicity study of AE 0001789 in the C57BL/6J mouse by dietary administration, SA04065, DACO: 4.4.3,IIA 5.5.3
1409714	2007, AE 0001789 - Two-generation reproduction study in wistar rats by administration in the diet, AT03567, DACO: 4.5.1,IIA 5.6.1
1409715	2006, AE 0001789 - Developmental toxicity study in the rat by gavage, SA 03348, DACO: 4.5.2,IIA 5.6.10
1409716	2006, AE 0001789 - Developmental toxicity study in the rabbit by gavage, SA 03349, DACO: 4.5.3,IIA 5.6.11
1409717	2007, AE 0001789 - Developmental toxicity study in the rabbit by gavage (complementary study), SA04196, DACO: 4.5.3,IIA 5.6.11
1409719	2006, An acute oral neurotoxicity screening study with technical grade AE 0001789 in Wistar rats, 201558, DACO: 4.5.12,IIA 5.7.1
1409720	2006, A subchronic neurotoxicity screening study with technical grade AE 0001789 in Wistar rats, 201573, DACO: 4.5.13,IIA 5.7.4
1409721	2007, AE 0001789-cyclopropyl-sulfamoybenzamide (Project AE 0001789) - In vitro chromosome aberration test with chinese hamster V79 cells TXUBP021, AT03121, DACO: 4.8,IIA 5.8
1409722	2007, AE 0001789-cyclopropyl-sulfamoybenzamide (tested as AE 0852999 carboxamide) - Salmonella/microsome test plate incorporation and preincubation method TXUBP019, AT03110, DACO: 4.8,IIA 5.8
1409723	2007, AE 0001789-cyclopropyl-sulfamoylbenzamide (tested as AE 0852999 carboxamide) (Project: AE 0001789) - V79/HPRT-test in vitro for the detection of induced forward mutations TXUBP020, AT03164, DACO: 4.8,IIA 5.8

1409724	2007, AE 0001789-sulfamoybenzoic acid (AE 0467398) - (Project: AE 001789) - Salmonella/microsome test plate incorporation and preincubation method TXUBP026, AT03259, DACO: 4.8,IIA 5.8
1409725	2007, AE 0001789-sulfamoylbenzoic acid (AE 0467398) - 90-day toxicity study in the rat by dietary administration TXUBP022, SA 06036, DACO: 4.8,IIA 5.8
1409726	2007, AE 0001789-sulfamoylbenzoic acid (AE 0467398) - Project: AE 0001789 - V79/HPRT-test in vitro for the detection of induced forward mutations TXUBP025, AT03095, DACO: 4.8,IIA 5.8
1409727	2007, AE 0001789-Sulfamoylbenzoic acid - Project: AE 0001789 - In vitro chromosome aberration test with chinese hamster V79 cells TXUBP024, AT03096, DACO: 4.8,IIA 5.8
1409728	2007, AE 0852999 - 28-day toxicity study in the rat by dietary administration, SA 06281, DACO: 4.8,IIA 5.8
1533419	2008, Bayer Cropscience Response to US EPA Request for Historical Control Data in Support of Toxicology Studies Conducted with BYH 18636 and AE 0001789, BCS 07-JZ-06, DACO: 4.4.1,4.4.2,4.4.3,4.4.4
1554040	2008, Bayer CropScience Response to Canada PMRA Request for Historical Control Data in Support of Developmental Toxicity Studies Conducted with AE 0001789, DACO: 4.5.2,4.5.3
1594581	2008, Bayer CropScience Response to Canada PMRA Request for Clarification in Support of Developmental Toxicity Studies Conducted with AE 0001789 (DART #—283510-01-2), DACO: 4.5.1

1409073	2006, Isoxaflutole + AE 0001789 SC 480 - Acute toxicity in the rat after oral administration, T 5076813, DACO: 4.6.1,IIIA 7.1.1
1409074	2006, Isoxaflutole + AE 0001789 SC 480 - Acute toxicity in the rat after dermal application, T 6076814, DACO: 4.6.2,IIIA 7.1.2
1409075	2006, Isoxaflutole & AE 0001789 SC 480 - Activity ID: TXUBP028. Acute inhalation toxicity in rats, T8076807, DACO: 4.6.3,IIIA 7.1.3
1409076	2007, Isoxaflutole + AE 0001789 SC 480 - Acute skin irritation/corrosion on rabbits. Activity ID: TXUBP032, T 9076574, DACO: 4.6.5,IIIA 7.1.4
1409077	2006, Isoxaflutole + AE 0001789 SC 480 - Acute eye irritation on rabbits. Activity ID: TXUBP031, T 0076575, DACO: 4.6.4,IIIA 7.1.5
1409078	2006, Isoxaflutole & AE 0001789 SC 480 - Evaluation of potential dermal sensitization in the local lymph node assay in the mouse, SA 06149, DACO: 4.6.6,IIIA 7.1.6
1596903	2008, Bayer CropScience Response to Canada PMRA Request for Clarification in Support of LLNA Study on IFT + 1789 SC480 (Original Study DART # — 278552-01-2), DACO: 4.6.6

1409738	2007, Metabolism of [methoxybenzoyl-UL-14C] AE 0001789 in laying hens, MEUBX042, DACO: 6.2,IIA 6.2.2
1409739	2007, Metabolism of [sulfonylbenzamide-UL-14C] AE 0001789 in the laying hen, MEUBX041, DACO: 6.2,IIA 6.2.2
1409740	2007, Metabolism of [methoxybenzoyl-UL-14C] AE 0001789 in the lactating goat, MEUBX044, DACO: 6.2,IIA 6.2.3
1409741	2007, Metabolism of [sulfonylbenzamide-UL-14C] AE 0001789 in the lactating goat, MEUBX043, DACO: 6.2,IIA 6.2.3
1409732	2007, Determination of the total radioactive residue in sorghum raw agricultural commodities after seed treatment with [sulfonylbenzamide-UL-14C] AE 0001789, MEUBP016, DACO: 6.3,IIA 6.2.1
1409733	2007, The metabolism of [methoxybenzoyl-ring-UL-14C]-AE 0001789 in corn (foliar post-emergence application), MEUBX048, DACO: 6.3,IIA 6.2.1
1409734	2007, The metabolism of [sulfonylbenzamide-ring-UL-14C] and [methoxybenzoyl-ring-UL-14C] AE 0001789 in corn (pre-emergence application), MEUBX052, DACO: 6.3,IIA 6.2.1
1409735	2007, The metabolism of [sulfonylbenzamide-ring-UL-14C] and [methoxybenzoyl-ring-UL-14C] AE 0001789 in corn (seed treatment application), MEUBP001, DACO: 6.3,IIA 6.2.1
1409737	2007, The metabolism of [sulfonylbenzamide-ring-UL-14C]-AE 0001789 in corn (foliar post-emergence application), MEUBX047, DACO: 6.3,IIA 6.2.1
1409660	2006, AE0001789: Examination of the applicability of DFG method S 19 (Extended and revised revision) for the determination of residues of AE0001789, P682060586, DACO: 7.2.1,7.2.4,IIA 4.3
1409661	2006, An analytical method for the determination of residue of AE 0001789 in cattle tissues and milk using LC-MS/MS and external matrix matched standard, UB-007-A006-01, DACO: 7.2.1,7.2.4,IIA 4.3
1409662	2006, Analytical method 00961 for the determination of residues of AE 0001789 and its metabolites cyclopropyl-sulfamoylbenzamide, sulfonamide-lactate and sulfonamide-alanine in/on plant matrices by HPLC-MS/MS using stable-labelled internal standards, MR-
1409663	2006, Analytical method 00962 for the determination of residues of BYH18636 and its metabolites BYH18636-N-desmethyl and BYH18636-MMT-glucoside, and of AE 0001789 in/on plant matrices by HPLC-MS/MS, MR-147/05, DACO: 7.2.1,7.2.4,IIA 4.3
1409664	2006, Analytical method 00964 for the determination of residues of AE0001789 in/on plant material by HPLC-MS/MS, MR-149/05, DACO: 7.2.1,7.2.4,IIA 4.3
1409665	2007, Extraction efficiency of AE 0001789, AE 2300002, AE 2300003, and AE 0852999 used in the determination of residues of AE 0001789 in plant matrices, RAUBP031, DACO: 7.2.1,7.2.4,IIA 4.3
1409666	2007, FDA PAM Multiresidue method (MRM) testing for AE 0001789 (cyprosulfamide) and three metabolites, RAUBX010, DACO: 7.2.1,7.2.4,IIA 4.3
1409667	2006, Independent laboratory validation (ILV) of Bayer method no. UB-007-A06-01 for the determination of residues of AE0001789 in materials of animal origin by LC/MS/MS, P1124G, DACO: 7.2.1,7.2.4,IIA 4.3

1409668	2006, Independent Laboratory Validation of Bayer CropScience Method No. 00964 for the Determination of Residues of AE0001789 in Plant Material by LC/MS/MS, P612065522, DACO: 7.2.1,7.2.4,IIA 4.3
1409669	2007, Independent laboratory validation of Bayer method UB-008-P06-01 - An analytical method for the determination of residues of AE 0001789 in crop matrices using LC/MS/MS, RAUBP022, DACO: 7.2.1,7.2.4,IIA 4.3
1409670	2007, Radiovalidation of Bayer method UB-006-A-06-01 - An analytical method for the determination of AE 0001789 and AE 0852999 in cattle and biota using LC-MS/MS and stable isotopic internal standards, RAUBP028, DACO: 7.2.1,7.2.4,IIA 4.3
1409671	2007, Validation of Bayer CropScience method UB-006-A-06-01 - Analytical method for the determination of AE 0001789 and AE 0852999 in cattle and biota using LC-MS/MS and stable isotopic internal standards, RAUBP020, DACO: 7.2.1,7.2.4,IIA 4.3
1409672	2007, Validation of Bayer CropScience method UB-007-A06-01 - Analytical method for the determination of AE 0001789 in cattle tissues and milk using LC-MS/MS and external matrix matched standard, RAUBP024, DACO: 7.2.1,7.2.4,IIA 4.3
1409673	2007, Validation of Bayer CropScience method UB-008-P06-01 - An analytical method for the determination of residues of AE 0001789 in crop matrices using LC/MS/MS, RAUBP046, DACO: 7.2.1,7.2.4,IIA 4.3
1409729	2007, Storage stability of AE 0001789 in plant matrices for 18 months - results for an interval of up to 12 months, P642055517, DACO: 7.3,IIA 6.1.1
1409730	2006, Storage stability of cyclopropyl-sulfamoylbenzamide, sulfonamide-lactate and sulfonamide-alanine (metabolites of AE 0001789) in plant matrices for 18 months - Results for an interval of 0 to 12 months, P642050579, DACO: 7.3,IIA 6.1.1
1409742	2007, AE 0001789 500 SC and 500 FS - Magnitude of the residue in/on field corn, sweet corn, and pop corn, RAUBX012, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.10
1409753	2007, Magnitude of residues in/on corn treated with one application of the herbicide IFT/1789 480 SC with a 110 day phi for grain, RAUBO011, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.10
1409755	2007, AE 0001789 - Magnitude of the residue in lactating cows, RAUBP019, DACO: 7.5,7.6,IIA 6.4.2
1409756	2007, AE 0001789 500 SC - Request for waiver of the study of the magnitude of the residue in/on field corn processed commodities, RAUBP010, DACO: 7.4.5,IIA 6.5.4
1409757	2007, The accumulation of [14C] AE 0001789 residues in confined rotational crops, MEUBX049 MEUBX 050, DACO: 7.3,7.8,IIA 6.6.2
1409758	2007, AE0001789 500 FS - Magnitude of the residue in field rotational crops - soybeans, turnips, and wheat (1-month plant-back interval) - Limited rotational crop, RAUBP017, DACO: 7.3,7.8,IIA 6.6.3
1409760	2007, AE0001789 500 SC - Magnitude of the residue in field rotational crops - soybeans, turnips, and wheat (2-month plantback interval) - Limited rotational crop, RAUBP001, DACO: 7.3,7.8,IIA 6.6.3

1409674	2006, An analytical method for the determination of AE 0001789 and AE 0852999 in cattle and biota using LC-MS/MS and stable isotopic internal standards, UB-006-A06-01, DACO: 8.2.2.4,IIA 4.3,IIA 4.8
1409675	2007, Independent laboratory validation of Bayer method no. UB-006-A06-01 - AE 0001789: An analytical method for the determination of AE 0001789 and AE 0852999 in cattle and biota using LC-MS/MS and stable isotopic internal standards, ADPEN-2K6-982-1003,

4.0 Value

1409072 102000014305 SC herbicide - New safener in formulation with isoxaflutole herbicide on field corn- Canadian Value Package. 509pp. DACOs 10.2.33, 10.3.2, 10.3.3, 10.4, 10.5.1, 10.5.2, 10.5.3, 10.5.4

B. ADDITIONAL INFORMATION CONSIDERED

I) Published Information

1.0 Impact on the Environment

1175731 RPA201772 determination of effects on seed germination, seedling emergence and vegetative vigor of ten plant species. Final report. 17 november 1994.(94-4-5234;10566.0194.6326.610) (isoxaflutole technical, subn#97-0653), DACO: 9.8.4

1175732 RPA201772 technical-toxicity to duckweed, Lemna gibba. Final report. 1 july 1994.(94-6-5319;10566.0194.6325.410) (isoxaflutole technical, subn#97-0653) [*note-page#64 missing], DACO: 9.8.5

2.0 Impact on Human and Animal Health

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