Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2001-08

Cloransulam-methyl

The active ingredient cloransulam-methyl and the formulated product FirstRate®, for control of specific broadleaf weeds in soybeans (*Glycine max*) in Eastern Canada, have been granted Section 17 temporary registrations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products.

(publié aussi en français)

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for FirstRate®, a herbicide developed by Dow AgroSciences Canada Inc., for use on soybeans. FirstRate®, which contains the active ingredient cloransulam-methyl, is effective against several broadleaf weeds common to soybean growing areas of Eastern Canada.

Methods of analyzing cloransulam-methyl residues in environmental media are available to research and monitoring agencies upon request to the PMRA. The analytical methodology for detection of residues in animal tissue has been requested.

Dow Agrosciences will be carrying out additional studies including analytical methodology, persistence and mobility of transformation products and two short-term toxicity studies as a condition of this temporary registration. Following the review of these new data, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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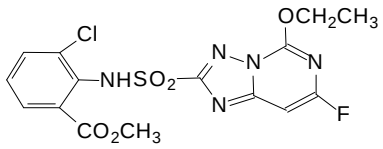
1.0 The active substance, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparation containing it

Active substance:		Cloransulam-methyl
Function:		Herbicide
Chemical name:		
1.	International Union of Pure and Applied Chemistry:	Methyl 3-chloro-2-(5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-*c*]pyrimidin-2-ylsulfonamido)benzoate
2.	Chemical Abstracts Services (CAS):	3-Chloro-2-(((5-ethoxy-7-fluoro(1,2,4)triazolo(1,5-*c*)-pyrimidin-2-yl)sulfonyl)amino)benzoic acid, methyl ester
CAS number:		147150-35-4
Molecular formula:		$C_{15}H_{13}FN_5O_5SCl$
Molecular weight:		430
Structural formula:		
Nominal purity of active:		97.5% nominal (range: 95.1–100%)
Identity of relevant impurities of toxicological, environmental or other significance:		A scientifically sound rationale supporting the waiver request for the absence of hydrazine contamination was accepted. The technical grade cloransulam-methyl does not contain any toxic microcontaminants as identified in Part 2.13.4 of Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, or Toxic Substances Management Policy (TSMP) Track-1 substances as identified in Appendix II, DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

1.2 Physical and chemical properties of active substance

Table 1.1 Technical product: Cloransulam-methyl

Property	Result
Colour and physical state	Off-white powder
Odour	Slight mint odour
Melting point or range	216–218EC (decomposition on melting)
Boiling point or range	Not applicable
Density	1.538 g/mL at 20EC
Vapour pressure	3×10^{-16} mm Hg at 25EC
Henry's Law Constant at 25EC	9.35×10^{-14} Pa m^3/mole
Ultraviolet (UV) – visible spectrum	8_{max} (nm) — Solvent 249 — Methanol 249 — 10% hydrocloric acid (HCl) in methanol 218 — 10% sodium hydroxide (NaOH) in methanol
Solubility in water 20EC	pH — Solubility 5 — 2.96 ppm 7 — 184 ppm 9 — 0.343 g/100 mL
Solubility in organic solvents	Solvent — Solubility (g/100 mL) acetone — 0.436 CH_3CN — 0.550 CH_2Cl_2 — 0.551 ethyl acetate — 0.098 hexane — <10 ppm CH_3OH — 0.047 octanol — <10 ppm toluene — 14.0 ppm
n-Octanol/water partition coefficient (log K_{ow})	pH — log K_{ow} 5 — 1.12 7 — –0.365 8.5 — –1.24 distilled water — –1.88
Dissociation constant (pK_a)	4.81 at 20EC
Stability (metals and temperature)	Stable at room temperature for 28 days and at 50EC alone and with 304 and 316 stainless steel, mild steel, brass, $FeCl_3$ and $MgCl_2$

Property	Result
Storage stability	Not applicable to the technical product

Table 1.2 End-use product: FirstRate®

Property	Result
Colour	Brown
Odour	Sweet odour similar to corn syrup
Physical state	Solid granule at 20EC
Formulation type	Water dispersible granule
Guarantee	84% (nominal) (range: 81.5–86.5%)
Formulants	The product does not contain any United States Environmental Protection Agency (EPA) List 1 or 2 formulants or formulants known to be TSMP Track-1 substances
Container material and description	HDPE water-soluble packets: Monosol 7030 PVA film or Monosol 8030/Aicello/QSA-2004X PVA
Bulk density	0.549 g/mL
pH of 10% dispersion in water	7.05 at 23.3EC
Oxidizing or reducing action	Significant temperature rise when exposed to potassium permanganate ($KMn0_4$)
Storage stability	The product is stable for one year at ambient conditions in PVA packet overpacked in HDPE/Al/PET overpouch
Explodability	Insensitive to impact

1.3 Details of uses and further information

Cloransulam-methyl is a systemic herbicide that must be absorbed by the plant and translocated to the site of action. The primary site of cloransulam-methyl activity is in the meristem. As a pre-emergence application, roots and, to a lesser extent, shoots intercept cloransulam-methyl as they grow through the soil. Soil moisture, texture, organic matter and pH as well as plant growth rate and herbicide dissipation affect the availability and uptake of cloransulam-methyl. Germinating seedlings in direct contact to cloransulam-methyl may not emerge or emerge and quickly stop growing. Cloransulam-methyl applied post-emergence is quickly absorbed by plant foliage and is translocated to shoot meristem. Sensitive seedlings stop growing and competing with the crop and slowly die.

The end-use product (EP), FirstRate®, is a water dispersible granular formulation that contains cloransulam-methyl at a concentration of 84%.

FirstRate® is a selective herbicide that may be applied pre-emergent or post-emergent to soybeans in Eastern Canada for control of specific broadleaf weeds. The pre-emergent application of FirstRate® is effective in controlling common ragweed, velvetleaf and lambsquarters when applied at a rate of 20.8 g/ha (17.5 g active ingredient [a.i.]/ha). The pre-emergent application of FirstRate® is effective in controlling cocklebur and heavy infestations of lambsquarters when applied at a rate of 41.7 g/ha (35 g a.i./ha). The post-emergent application is effective in controlling common ragweed, velvetleaf, cocklebur, jimsonweed and giant ragweed when applied at 20.8 g/ha (17.5 g a.i./ha). When utilized as a post-emergent, FirstRate® must be applied with a non-ionic surfactant at 0.25% v/v and and liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

Winter wheat may be planted four months after application of FirstRate® and field corn may be planted nine months after application of FirstRate®.

FirstRate® may be tankmixed with Broadstrike Dual® at 2.4 L/ha, Pursuit® at 312 mL/ha or Dual® 960 at 2.2 L/ha when applied as a pre-emergent treatment.

FirstRate® may be tankmixed with Pursuit® at 312 mL/ha and a non-ionic surfactant at 0.25% v/v and liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v when applied as a post-emergent treatment.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

An isocratic reverse phase high performance liquid chromatographic (HPLC) method with UV detection at 220 nm and dipropyl phthalate as the internal standard was provided for the determination of the active and all structurally related impurities. The method was found to give good recoveries (for active ingredient, 100%; for impurities, 97–104%), precision (relative standard deviation [RSD] for active ingredient, 0.19%; for impurities, 1.0–10%) and sufficient wide detection range.

2.2 Method for formulation analysis

An isocratic reverse phase HPLC method using UV detection at 249 nm and external standard was provided for the determination of the active ingredient in the formulation. The method has been shown to give good recovery (100 ± 0.95%), precision (RSD = 0.45%) and wide linear detection range. It was assessed to be suitable for use as an enforcement method.

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

A multi-residue method for testing cloransulam-methyl (XDE-565) was conducted according to the Pesticide Analytical Manual Volume I (PAM I), Appendix II I/1994. Gas chromatography (GC) performed isothermally at 230EC, as indicated in the multi-residue method decision tree, separated XDE-565 at an acceptable retention time. However, recoveries of the cloransulam-methyl residues were only 50% in soybean fractions.

2.3.2 Methods for residue analysis of plants and plant products

Soybean grain, forage, hay, hull and meal samples are extracted by homogenizing and shaking with 90% acetone and 10% 0.1 N HCl. An aliquot is evaporated to dryness and the remaining residue is buffered to pH 7.5 with 0.1 M potassium dihydrogen phosphate and partitioned with hexane. The aqueous portion is acidified to pH 2.0 and purified by solid phase extraction. Soybean crude and refined oil samples are dissolved in hexane. The hexane solutions are partitioned with 0.1 M potassium dihydrogen phosphate buffer at pH 7.5. The hexane layers are discarded and the aqueous layers are partitioned a second time with *n*-hexane. The hexane layers are discarded. The aqueous solutions are acidified to pH 2.0 with 2 N HCl and purified by solid phase extraction. For all samples, the eluent is evaporated to dryness and derivatized with trimethyldiazomethane. The resulting samples are evaporated to dryness and the *N*-methyl-XDE-565 derivatives are partitioned into toluene containing *N*-ethyl-XDE-565 as an internal standard. Analysis is by capillary GC with mass spectrometry (GC–MS). Residues of cloransulam-methyl equivalents are calculated as the parent ester. Representative chromatograms of control samples of soybean grain, forage and hay and processed fractions showed no interferences from soybean components or from reagents, solvents and glassware.

The method limit of quantitation (LOQ) and limit of detection (LOD) for cloransulam-methyl equivalents were validated at 0.01 Fg/g and 0.005 Fg/g, respectively. The standard deviation measured with respect to recoveries following spiking at the LOQ was indicative of the method having good repeatability. The response of the detector was linear (correlation coefficient, $r = 0.9998$) within the range of 0.01–0.50 Fg/g for soybean grain, forage and hay and its processed fractions. The interlaboratory validation (ILV) did support the reliability and reproducibility of the proposed methods for the residues of cloransulam-methyl equivalents in soybean matrices (hay, forage and grain). Recoveries were within guideline requirements (70–120%).

2.3.3 Methods for residue analysis of food of animal origin

No methods were submitted for food of animal origin. The results of the animal metabolism studies demonstrated that residues in these fractions were unlikely to be detectable at levels above 0.01 Fg/g, when feeding treated crop at the proposed good agricultural practice.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

In a metabolism study, ^{14}C-XDE-565, uniformly ^{14}C-labelled in the aniline ring (GH-1902-11*a*, Inventory 844), was administered to five Fischer 344 rats/sex/dose by gavage either as a single dose of 5 or 1000 mg ^{14}C-XDE-565/kg body weight (bw) or as 14 daily oral doses of 5 mg/kg bw/d of non-radiolabelled XDE-565 (97.3%), followed by a single 5 mg/kg bw oral dose of ^{14}C-XDE-565 on day 15. Excretion of radioactivity (^{14}C) was followed for 72 h. The rats were then terminated and radioactivity remaining in tissues and carcass was measured. Selected urine and fecal samples were also analyzed by HPLC and DIP–MS. Overall, 91–102% of the ^{14}C administered in each dose was recovered. The overwhelming percentage of the radioactivity was recovered in urine and feces; however, there were both sex and dose differences. After the 5 mg/kg bw doses, males excreted nearly equivalent amounts of ^{14}C in urine and feces (41–52%), while females excreted approximately 3.5 times more ^{14}C in urine than in feces (68–80% versus 21%). A larger percentage of the 1000 than the 5 mg/kg bw dose was eliminated in the feces by both males (83%) and females (78%) and less of this dose was eliminated in the urine (males 10%, females 17%). Half-lives calculated from the elimination of the 5 mg/kg bw doses were 6.5 h for females and 8–8.5 h for males, while the half-lives following the 1000 mg/kg bw dose were 7.9 h for females and 13.2 h for males. Only a small fraction (#2.3%) of the administered ^{14}C remained in the tissues and carcass 72 h post-dosing. Blood, kidney and liver contained the highest concentrations of ^{14}C (i.e., 0.04–0.03% dose/g). The remaining tissues contained #0.018% dose/g. Analysis of urine and fecal samples revealed 10 and 3 peaks, respectively. Females eliminated a greater percentage of the 5 mg/kg bw dose in urine as unchanged XDE-565 than males (-50% in females versus 22% in males). Males eliminated a greater percentage of the 5 mg/kg bw dose in the feces as metabolites (-28% in males versus 10% in females) Both sexes eliminated 15–22% of the 5 mg/kg bw dose in the urine as metabolites. Less than 8% of the 5 mg/kg bw dose was excreted in the feces unchanged but over 70% of the 1000 mg/kg bw dose was excreted as unchanged XDE-565 in the feces. The only metabolite identified had a hydroxyl group in the aromatic ring of XDE-565. In the single high-dose rats, the unchanged parent compound accounted for over 70% of the recovered radioactivity in the feces, indicating that a large portion of the orally administered ^{14}C-XDE-565 might not have been absorbed. Because of the lack of an accurate determination of the absorption of XDE-565, however, estimates for absorption of orally dosed XDE-565 could not be made. Sex-dependent differences in disposition of the 5 mg/kg bw dose were traced to more efficient elimination of unchanged XDE-565 by the female rats. No explanation for this efficiency difference is attempted, nor is the toxicological significance of sex related differences in XDE-565 metabolism and excretion.

In a metabolism study ^{14}C-XDE-565 (99% purity), uniformly ^{14}C-labelled at the 7 and 9 positions on the triazolo-pyrimidine ring, was administered to three Fischer 344 rats of each sex by gavage as a single dose of 5 mg ^{14}C-XDE-565/kg bw. Approximately 94% of the administered dose was recovered in urine, feces, cage wash and tissues. Clear sex-related differences in the routes of elimination were observed. Male rats excreted approximately equal amounts of radioactivity in the urine (37–39%) and feces (48–51%). In females, the principal excretion route was the urine (70–72%), while the feces (20–22%) was the minor excretion route. The tissues and carcass accounted for less than 5% of the dose 72 h post-dosing for both sexes. Comparison of male and female rats administered the triazolo-pyrimidine labelled ^{14}C-XDE-565 indicated a similar qualitative pattern of metabolite distribution. The primary urinary and fecal excretion products were XDE-565 and 4-OH-phenyl-XDE-565. A number of minor metabolites were detected in urine and feces of both sexes. In general, female rats excreted a higher percentage of the administered dose as XDE-565 than did the males. Data from the present study indicated that the excretion and metabolism of ^{14}C-XDE-565 labelled on the triazolo-pyrimidine ring were similar to the excretion and metabolism of ^{14}C-XDE-565 labelled on the aniline ring.

3.1.2 Acute toxicity: technical

In an acute oral toxicity limit test, 10 Fischer 344 rats (five of each sex), aged eight weeks, and fasted overnight prior to treatment, were given a single oral dose (gavage) of XDE-565 (97.3%, 50% solution in 9:1 corn oil and acetone) at 5000 mg/kg bw and observed for two weeks (15 days). No mortality was observed, and the oral mean lethal dose (LD_{50}) was determined to be >5000 mg/kg bw. No treatment-related clinical signs of toxicity were observed, and necropsy findings were negative. All animals gained weight throughout the course of the study. XDE-565 is of low acute oral toxicity based on this limit test in male and female Fischer 344 rats.

In an acute dermal toxicity limit test, 10 New Zealand white (NZW) rabbits (five of each sex), weighing between 2.3 and 2.6 kg were dermally exposed (trunk of each animal, body surface area not specified) to XDE-565 (97.3% purity) for 24 h, at 2000 mg/kg bw and observed for 15 days. No mortality was observed and the dermal LD_{50} was determined to be >2000 mg/kg bw. No treatment-related clinical signs of toxicity were observed, and necropsy findings were negative. All animals gained weight by study termination. XDE-565 is of low acute dermal toxicity based on this limit test in male and female NZW rabbits.

In an acute inhalation toxicity limit test, 10 Fischer 344 rats (five of each sex), aged six weeks were exposed by inhalation (nose-only) to XDE-565 (97.3% purity; jet-milled, aerosol) for 4 h, at a time-weighted average actual concentration of 3.77 mg/L (9.64 mg/L, nominal concentration) and observed for 15 days. No mortality was observed and the inhalation mean lethal concentration (LC_{50}) was determined to be >3.77 mg/L (the highest achievable concentration). No significant treatment-related clinical signs of toxicity were observed, and no necropsy findings were observed. General fur soiling was

noted following exposure. All animals gained weight by study termination. XDE-565 is of low acute inhalation toxicity based on this limit test in male and female Fischer 344 rats.

In a primary eye irritation study, an aliquot of 0.1 g XDE-565 (97.3% purity) was instilled into the conjunctival sac of the right eye of one male and five female NZW rabbits, weighing between 3.2 and 3.9 kg. After dosing, the eyes remained unwashed and were observed for 72 h. Conjuctival redness and chemosis were observed post-instillation. The average irritation scores at 0, 24, 48 and 72 h were 3.0, 0.67, 0 and 0, respectively. The irritation reactions subsided by 24 h post-treatment and no sign of ocular irritation was evident at 48 h. XDE-565 is minimally irritating to the eye based on this assay in NZW rabbits.

In a primary dermal irritation study, an aliquot of 0.5 g XDE-565 (97.3% purity) was applied to the backs (approximate 15 × 15 cm area clipped free of fur) of NZW rabbits (three of each sex), weighing between 3.2 and 4.0 kg. Exposure was maintained for 4 h and animals were observed for 72 h post-treatment (rinsed with damp towel following 4-h administration period). No erythema or edema were observed throughout the course of the study. XDE-565 is not a dermal irritant based on this assay in male and female NZW rabbits.

In a dermal sensitization assay, using a modified Buehler method, groups of 10 male Hartley albino guinea pigs, weighing 306–426 g, were assessed. Animals were subject to three induction applications and a single challenge application of 0.4 g solid XDE-565 (97.3%) or 0.4 g DER-331 epoxy resin in dipropylene glycol monomethyl ether (positive control). The condition of the test skin sites was assessed 24 and 48 h after each application. No erythema or edema was observed over any of the three induction applications, nor following the challenge application in animals exposed to XDE-565. In animals exposed to the positive control, slight erythema was observed following the third induction application in 8 of 10 animals and in all animals following the challenge application. No edema was observed in animals exposed to DER-331. The findings in the positive control animals were considered to be reflective of a hypersensitive response. Deficiency in the induction and challenge applications of XDE-565 without moistening with water or a suitable vehicle rendered the results invalid.

3.1.2.1 Acute toxicity: formulation: FirstRate® Herbicide

In an acute oral toxicity study, a group of overnight fasted Fischer rats (five of each sex) was given a single oral dose of NAF-75 (containing 84.8% XDE-565 as the active ingredient) as a 50% suspension in distilled water at 5000 mg/kg bw and observed for 14 days. All rats survived and gained weight during the two-week observation period. Clinical findings included urine and fecal soiling in the perineal area, loose stool and salivation. There were no treatment-related necropsy findings. The acute oral LD_{50} in males and females rats is >5000 mg/kg bw. Based on the LD_{50} of >5000 mg/kg bw,

NAF-75 is considered as of low acute toxicity via the oral route. No precautionary label hazard statements are required.

In an acute dermal toxicity study, a group of NZW rabbits (five of each sex) was given a single 24-h dermal dose of NAF-75 (containing 84.8% XDE-565 as the active ingredient) moistened with 1.75 mL of distilled water at 2000 mg/kg bw. The animals were observed for 14 days. All rabbits survived and gained weight during the two-week observation period. Erythema was noted at the application sites of all rabbits, but there were no clinical signs indicative of systemic toxicity. There were no treatment-related necropsy findings. The acute dermal LD_{50} for male and female rabbits is >2000 mg/kg bw. Based on the LD_{50} of >2000 mg/kg bw, NAF-75 is considered as of low acute toxicity via the dermal route. No precautionary label hazard statements are required.

No acute inhalation toxicity data on NAF-75 are submitted; however, the Applicant requested a waiver based on the low acute toxicity and low vapour pressure of the technical active as well as the packaging of the formulation in a water soluble pouch. Based on the presented rationale and available information, the waiver request is acceptable. The formulation NAF-75 is estimated to be of low acute inhalation toxicity in view of the following factors: high percentage (84.8%) of the technical active in the formulation, low acute inhalation toxicity of the technical active, low percentages of the non-active ingredients in the formulation, no evidence of significant acute toxicity of the non-active ingredients (most are in U.S. EPA Inert Lists 3, 4A and 4B), packaging of the formulation in water soluble pouches and further dilution of the product prior to use. No precautionary label hazard statements are required.

In a primary eye irritation study, 0.1 g of NAF-75 (contains 84.8% XDE-565 as the active ingredient) was instilled into the conjunctival sac of the right eye of each of six NZW rabbits. The treated eyes remained unwashed and were examined for irritation reaction at 1, 24, 48 and 72 h. Treatment caused slight conjunctival redness and slight to moderate chemosis in all rabbits. Slight to moderate discharge was noted in 5/6 rabbits 1 h post-dosing. Reddening of the iris occurred in 2/6 rabbits 24 h after dosing. All ocular effects were resolved by 48 h. The average irritation scores at 1, 24, 48 and 72 h were 7, 5.6, 0 and 0 (maximum = 110), respectively. Based on the maximum average score (MAS) of 7/110 at 1 h, the test material was considered minimally irritating to the rabbit eye. No irritation hazard warning statements are required.

In a primary dermal irritation study in adult NZW rabbits (four males, two females), an aliquot of 0.5 g of NAF-75 (containing 84.8% XDE-565 as the active ingredient) moistened with distilled water was applied for 4 h to the intact clipped skin on the back of each rabbit. Very slight to well defined erythema was observed on all rabbits within 30 min after patch removal. Irritation was resolved in 5/6 rabbits on day 7 and in 1/6 rabbits by day 11. All rabbits gained weight during the study period. The average irritation scores at 0.5, 24, 48 and 72 h, and on days 7, 8, 9, 10 and 11 were 1.5, 0.5, 0.7 and 0.5, and 0.17, 0.17, 0.17, 0.17 and 0 (maximum = 8), respectively. Based on the MAS

of 1.5/8 at 0.5 h, the test material was considered slightly irritating to the rabbit skin. No irritation hazard warning statements are required.

In a dermal sensitization study based on the Buehler method, 10 male Hartley albino guinea pigs were given three weekly dermal applications of 0.4 g of 100% NAF-75 (containing 84.8% XDE-565 as the active ingredient) in 0.15 mL of distilled water during the three-week induction period. The animals were challenged two weeks later with 0.4 mL of NAF-75 as a 30% suspension in distilled water, which was the highest non-irritating dose. Five naive animals also received the challenge application of the 30% NAF-75. The conditions of the test skin sites were assessed 24 and 48 h after the challenge application. Challenge application did not cause any skin reaction at the test sites, and none of the naive animals showed any evidence of skin reaction. Positive control guinea pigs (10 males) that received three induction doses of 0.4 mL of a 10% solution of DER 331 epoxy resin and were subsequently challenged with a dose of DER 331 identical to the induction dose all showed slight erythema. The naive control guinea pigs that received DER 331 as the challenged dose did not show any skin reaction. Thus, under the conditions of this study, NAF-75 was not a dermal sensitizer in guinea pigs.

3.1.3 Genotoxicity

XDE-565 (97.3%) was evaluated in the *Salmonella* – mammalian-microsomal bacterial mutagenicity assay (Ames test). The test was conducted in the presence and absence of metabolic activation (S-9) using *Salmonella typhimurium* tester strains TA98, TA100, TA1535 and TA1537. The concentrations of the test material in dimethylsulfoxide (DMSO) ranged from 5 to 5000 Fg/plate in the dose-setting assay with TA 100. Concentrations of 5 Fg/plate or higher without activation or 15 Fg/plate or higher with activation resulted in toxicity, as determined by a reduction in the number of bacterial colonies. In the main assay, 0.05, 0.15, 0.5, 1.5 and 5.0 Fg/plate without activation and 0.15, 0.5, 1.5, 5.0 and 15.0 Fg/plate with activation were tested. Two independent assays were conducted in each tester strain. The test material did not induce a mutagenic response in any of the tester strains, as judged by the frequency of histidine-independent revertants. The positive controls induced the appropriate response in the corresponding strains. Therefore, the test material was classified as negative in the Ames test under the experimental conditions used.

In a mammalian cell gene mutation assay (HGPRT forward mutation assay) Chinese hamster ovary (CHO) cells cultured in vitro were exposed to XDE-565 (98.2%) in DMSO at concentrations of 50, 100, 200, 400, 600 and 800 Fg/mL in the presence and absence of mammalian metabolic activation (rat liver S-9). Two independent assays were performed and two cultures per dose were initiated. In DMSO, precipitate was observed at $600 Fg/mL. A preliminary cytotoxicity test showed that XDE-565 at up to 800 Fg/mL was minimally toxic to cultured CHO cells with and without metabolic activation. Without activation, the mutant frequencies of treated CHO cultures varied randomly and were within the acceptable range for background levels ($0–5 \times 10^{-6}$). None of the test

groups showed mutant frequencies that were statistically elevated over that of the concurrent vehicle control cultures. With metabolic activation, except for the 400 Fg/mL concentration in Trial II, findings were similar, showing no elevation of mutant frequencies. The 400 Fg/mL in Trial II exhibited a significant increase in mutant frequency; however, no dose-dependent trend was observed and the results at the 400 Fg/mL concentration were considered consistent with random variation. The positive controls induced large and significant increased in mutation frequency. XDE-565 was therefore considered negative for inducing forward mutations at the HGPRT locus in CHO cells under the S-9 metabolic activation and non-activation conditions of the assay.

The clastogenic potential of XDE-565 (97.3% purity) was evaluated in an in vitro chromosome aberration assay utilizing rat lymphocytes. About 48 h after initiation of culture, the cells were treated with XDE-565 for 4 h at doses of 0, 6, 20, 60, 200 or 600 Fg/mL, with and without S-9 metabolic activation. Cells were harvested 24 and 48 h after treatment and evaluated for the incidence of chromosomal aberrations. Positive controls, mitomycin C and cyclophosphamide, induced a significantly higher incidence of cells with chromosomal aberrations. There was no evidence of an increase in the incidence of chromosomal aberrations in cells treated with XDE-565 when compared with negative controls with and without metabolic activation.

In a bone marrow micronucleus assay, groups of CD-1/(ICR)BR mice (five mice/sex/group), aged 9–10 weeks, were treated with a single oral dose (gavage) of XDE-565 (97.3% purity, in corn oil) at 0, 500, 1667 and 5000 mg/kg bw. Bone marrow cells were harvested at 24, 48 and 72 h post-treatment. No mortality or treatment-related clinical findings were observed in XDE-565 treated mice. One thousand polychromatic erythrocytes were evaluated from each mouse. There were no significant differences in the frequencies of micro-nucleated polychromatic erythrocytes (MN-PCE) between the treated and negative control groups. The positive control, cyclophosphamide, induced a significant increase in MN-PCE. Hence, under the experimental conditions used, XDE-565 was considered to be negative in the mouse bone marrow micronucleus test.

3.1.4 Subchronic and chronic toxicity

3.1.4.1 Subchronic and chronic toxicity in the mouse

In a 90-day dietary toxicity study in B6C3F1 mice, XDE-565 (97.3% purity) was administered to 10 mice/sex/dose at 0, 50, 100, 500 and 1000 mg/kg bw/d. There were no treatment-related effects in clinical signs, body weight, feed consumption, feed efficiency, gross pathology or hematology. The liver was the primary target organ for XDE-565. Treatment-related liver alteration consisted of slightly increased in size centrilobular and midzonal hepatocytes often accompanied by altered tinctorial properties. Electron microscopy further characterized the alteration as decreased cytoplasmic glycogen and increased rough endoplasmic reticulum. These treatment-related effects were seen in males at $100 mg/kg bw/d and in females at 1000 mg/kg bw/d. The liver alteration was accompanied by increased liver weights and/or increased serum alkaline phosphatase in

mid- and high-dose animals. There was no indication of hepatocellular degeneration or necrosis in mice at any dose levels. A treatment-related kidney alteration was noted in male mice only, at $100 mg/kg bw/d. The alteration was characterized as decreased vacuolation of renal tubules, consistent with decreased cytoplasmic fat, and was accompanied by lower kidney weights at 500 and 1000 mg/kg bw/d. Reduction in kidney weight was also observed in high-dose females. No significant treatment-related effects were observed in any other measured parameters. The no observable adverse effect level (NOAEL) for male mice is 50 mg XDE-565/kg bw/d. The NOAEL for female mice is 100 mg XDE-565/kg bw/d.

In a two-year carcinogenicity study, XDE-565 (98.2% purity) was administered to 60 B6C3F1 mice/sex/dose at dose levels of 0, 10, 100 or 1000 mg/kg bw/d in the diet for 24 months (with an interim sacrifice of 10 mice/sex/dose at 12 months). No treatment-related clinical signs were observed throughout the study duration. A treatment-related effect on mean body-weight gain was observed. On average, body-weight gains in high-dose males and mid- and high-dose females were suppressed relative to controls. No treatment-related findings in mortality, feed consumption, feed efficiency or hematology were observed. Treatment-related increase in liver weights (mid- and high-dose males and high-dose females) and decrease in kidney weights (high-dose males and mid- and high-dose females) were observed. An increase in the incidences of centrilobular hypertrophy in the liver was observed in mid- and high-dose males and females. There was however, no evidence of hepatocellular degeneration or necrosis in any dose group. A decrease in the incidence of normal cytoplasmic vacuoles and a decrease in the incidence of renal mineralization and renal tubular degeneration were observed in mid- and high-dose males. The histopathologic changes that were observed in the liver and kidneys were considered not to be of toxicological significance. Based on decreased body-weight gain in females at $100 mg/kg bw/d, the NOAEL in male and female mice was determined to be 10 mg/kg bw/d. At the doses tested, a treatment-related increase in tumour incidence was not observed when compared with controls. XDE-565 was concluded not to be oncogenic, based on this study in male and female B6C3F1 mice.

3.1.4.2 Chronic toxicity in the rat

In a combined chronic and carcinogenicity study, XDE-565 (98.2% purity) was administered to 60 Fischer 344 rats/sex/dose at 0, 10, 75 or 325 mg/kg bw/d in the diet for 24 months (with an interim sacrifice of 10 rats/sex/dose at 12 months). Aside from an increase in the incidence of perineal soiling in female rats at 75 and 325 mg/kg bw/d, no other treatment-related clinical findings were observed. A treatment-related effect on mean body weight and body-weight gain was observed. Relative to controls, body weight and body-weight gain were suppressed in high-dose males and females for a good portion of the dosing period. No treatment-related findings in mortality, feed consumption and feed efficiency were observed. Minor changes in hematology, clinical chemistry and urinalysis were observed in high-dose males and females. The kidneys were the target organ. Treatment-related effects on the kidneys included higher absolute and relative weights (mid- and high-dose males), hypertrophy of collecting duct epithelial cells (high-

dose males and females), tubular vacuolation consistent with fatty changes in renal proximal tubules (high-dose males and females, mid-dose females) and/or mineralization of the renal pelvis (high-dose males and females, mid-dose males). An apparent treatment-related hyperplasia and hypertrophy of thyroid follicles were observed in high-dose males. Based on kidney histopathology in male rats at 75 mg/kg bw/d, the lowest observable adverse effect level (LOAEL) and NOAEL in male and female rats were determined to be 75 and 10 mg/kg bw/d, respectively. At dose levels up to 325 mg/kg bw/d, a treatment-related increase in tumour incidence was not observed when compared with controls. XDE-565 was concluded not to be oncogenic, based on this study in male and female Fischer 344 rats.

3.1.4.3 Subchronic toxicity in the dog

XDE-565 (99% purity) was fed to Beagle dogs (one dog/sex/group) in the diet at 50, 100, 200 or 500 mg/kg bw/d for two weeks. In addition, one male and two female Beagle dogs were similarly dosed at 1000 mg/kg bw/d for two weeks. Parameters evaluated were: general health status, body weight, food consumption, hematology, urinalysis, pathology and gross histopathology. At 1000 mg/kg bw/d, one dog of each sex exhibited lower food consumption and lower body weight. The male dogs at 500 or 1000 mg/kg bw/d showed gross pathologic changes involving multiple hemorrhages in numerous organs and tissues. Lower platelet counts were noted in one dog of each sex at 1000 mg/kg bw/d and might have contributed to the hemorrhages. Treatment-related histopathologic liver alterations were present in four dogs that received dietary doses of XDE-565 at 500 or 1000 mg/kg bw/d. The liver alterations were characterized by aggregates of inflammatory cells frequently adjacent to degenerative or necrotic hepatocytes in three of the dogs and inflammation of hepatic blood vessels in the other dog. There were no treatment-related effects at 100 or 200 mg/kg bw/d.

In a one-year study, XDE-565 (98.2% purity) was administered to four Beagle dogs/sex/dose in the diet at dose levels of 0, 5, 10 or 50 mg/kg bw/d. Parameters evaluated comprised clinical observations, body weight, body-weight gain, hematology, clinical chemistry, urinalysis, organ absolute and relative weights, gross pathology and histopathology. Food consumption was reported as was feed efficiency, but these parameters were of restricted use, since dogs were paired in each cage and food consumption was measured by cage. The administered dose over the course of the study was calculated to be within 2–3% of target values. No adverse effects were seen on any parameters except for clinical chemistry and for histopathology. Histopathological changes comprised centrilobular and midzonal hepatocellular hypertrophy and accumulation (dose related in severity) of golden-brown pigment (possibly hemosiderin) in Kupffer cells and hepatocytes at 10 and 50 mg/kg bw/d. The clinical chemistry changes were elevated alkaline phosphatase and alanine aminotransferase (10 and 50 mg/kg bw/d, both sexes) and decreased albumin (50 mg/kg bw/d, both sexes) and protein (females at 50 mg/kg bw/d). Based on the evaluated data, the NOAEL for systemic toxicity was 5 mg/kg bw/d for both male and female dogs; the LOAEL was 10 mg/kg bw/d, based on liver toxicity at 50 mg/kg bw/d.

3.1.4.4 Subchronic toxicity in the rabbit

In a 21-day dermal toxicity study, XDE-565 (98.2% purity), moistened with water, was applied to the shaved skin of five NZW rabbits/sex/dose at dose levels of 0, 100, 500 or 1000 mg/kg bw/d, 6 h/day, five days per week during a 21-day period. For males, there were no compound related effects on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights or gross and histopathology. The NOAEL for male rabbits is 1000 mg/kg bw/d. For female rabbits at the 1000 mg/kg bw/d dose level, there were significant hematologic findings, relative to controls, in red blood cell count (RBC), hemoglobin concentration (Hb) and hematocrit values (Hct), all of which were lower than concurrent controls. These differences were consistent with slight anemia. Corresponding to this, histologic changes were observed in the red blood cells of some of the 1000 mg/kg bw/d rabbits; specifically, their red blood cells exhibited anisocytosis and macrocytosis, conditions consistent with a compensatory response to increase red blood cell mass. The bone marrow of female rabbits given 1000 mg/kg bw/d was normal and comparable to the bone marrow of control female rabbits. There were no differences in RBC, Hb or Hct among the 0, 100 or 500 mg/kg bw/d dose groups. Apart from the aforementioned, there were no compound related differences on mortality, clinical signs, body weight, food consumption, other hematologic parameters, clinical chemistry, organ weights or gross and histologic pathology. For female rabbits, the NOAEL is 500 mg/kg bw/d.

NAF-75 (containing 83.6% XDE-565 as the active ingredient) was evaluated for systemic toxicity following repeated dermal applications. Five NZW rabbits/sex/dose received 15 daily dermal applications (6 h/day exposure) of 0, 100, 500 or 1000 mg/kg bw/d over a 21-day period. Parameters evaluated included mortality, clinical appearance, ophthalmic examination, body weight, clinical chemistry and hematologic parameters, selected organ weights and gross and histopathology. Repeated dermal application of NAF-75 resulted in no significant dermal irritation in male and female rabbits or systemic toxicity in male rabbits. Statistically significantly different values from the control females on erythrocyte (lower) and leucocyte (higher) counts, as well as on the hematocrit (lower) values were evident for the high-dose females. These findings were considered treatment induced and biologically relevant. Therefore, under the conditions of this study and based on the hematological effects in females at 1000 mg/kg bw/d, the NOAELs for the male and female rabbits are 1000 and 500 mg/kg bw/d, respectively. The LOAELs for the male and female rabbits are >1000 and 1000 mg/kg bw/d, respectively.

3.1.5 Reproductive and developmental toxicity

In a two-generation, one litter per generation reproductive toxicity study, cloransulam-methyl (98.2% purity) was administered to 30 Sprague–Dawley (SD) rats/sex/dose level per generation in the diet at dose levels of 0, 10, 100 or 500 mg/kg bw/d. For parental animals, treatment-related systemic toxicity involved lower body weight and body-weight gains in P_1 males (pre-mating period) and females (pre-mating and gestation periods) at 500 mg/kg bw/d. Organ and tissue pathology was evident in the kidneys and possibly the

thyroid. The relative kidney weights were higher in male rats at 100 (P_2 generation) and 500 (P_1 and P_2) mg/kg bw/d when compared with concurrent control values. In females, kidney weights were unaffected. Treatment-induced renal changes included hypertrophy of the collecting ducts and vacuolation consistent with fatty changes of proximal tubules in mid- and high-dose males and females. Diffuse hypertrophy of thyroid follicular epithelial cells was observed in high-dose males and females. There were no treatment-related gross or histopathological alterations in P_1 and P_2 generation male or female rats at 10 mg/kg bw/d. The LOAEL for systemic toxicity was 100 mg/kg bw/d, based on kidney histology, and the NOAEL was 10 mg/kg bw/d for both sexes. There were no treatment-related effects on fertility, gestation, time to mating, litter size or gross and histopathology of the reproductive organs at any dose level tested. Thus, for reproductive toxicity, the NOAEL was 500 mg/kg bw/d. For offspring toxicity, cloransulam-methyl at dietary concentration of 500 mg/kg bw/d resulted in smaller litter size and reduced survival of F_1 pups during days 0–4 of lactation. The effects, probably related to parental toxicity at this dose level, were marginal and are within normal biological variations. The viability indices are also within historical range. There were no treatment-related effects on pup body weight, sex ratio or gross pathological alterations at any dose level tested in either the F_1 or the F_2 generation. Thus, the LOAEL for offspring toxicity was 500 mg/kg bw/d and the NOAEL for offspring toxicity was 100 mg/kg bw/d.

Groups of 10 mated female SD rats were administered XDE-565 (97.4% purity) via gavage at dose levels of 0, 100, 500 or 1000 mg/kg bw/d from gestation day 6 to 15. During the study period, the rats were evaluated for clinical signs of systemic toxicity, feed and water consumption, body weight, body-weight gain and various reproductive toxicity parameters. On gestation day 16, the rats were sacrificed and examined for gross pathological changes. Liver and kidney weights were recorded. The ovaries were examined for corpora lutea and the uterus for implantations and resorptions. The fetuses were not examined. The results indicated that there were no treatment-related effects on clinical observations, food and water consumption, body weight, body-weight gain, absolute and relative organ weights or gross pathology or on reproductive or embryonal or fetal parameters at any dose level. The number of corpora lutea in the 500 and 1000 mg/kg bw/d dams were statistically significantly lower than the control dams; the finding was not considered to be related to treatment, as ovulation and luteinization occurred prior to dosing. In conclusion, under the conditions of this study, the highest dose level of 1000 mg/kg bw/d did not induce maternal toxicity.

In a developmental study, cloransulam-methyl (97.4% purity) was administered to groups of 30 female SD rats per dose in 0.5% Methocel A4M suspension by gavage at dose levels of 0, 100, 500 or 1000 mg/kg bw/d from day 6 through 15 of gestation. The rats were sacrificed on day 21 of gestation. There were no treatment-related effects in mortality, clinical signs, body weight, food consumption or caesarian parameters. The maternal LOAEL is >1000 mg/kg bw/d and the maternal NOAEL is 1000 mg/kg bw/d. There were no treatment-related effects in developmental parameters. The developmental LOAEL is >1000 mg/kg bw/d and the developmental NOAEL is 1000 mg/kg bw/d.

In a teratology range-finding study, groups of seven artificially inseminated female NZW rabbits were administered XDE-565 (97.4% purity) via gavage at targeted dose levels of 0, 100, 500 or 1000 mg/kg bw/d from gestation day 7 to 19. The rabbits were evaluated for clinical signs of systemic toxicity, feed consumption, body weight and body-weight gain. On gestation day 20, the rabbits were sacrificed and examined for gross pathological changes. Liver and kidney weights were recorded. The ovaries were examined for corpora lutea and the uterus for implantations and resorptions. The fetuses were not examined for gross or histopathological changes. The results indicated maternal toxicity at dose levels of 500 and 1000 mg/kg bw/d. The toxic effects in maternal animals included lower fecal output, food consumption, body weight and body-weight gain. The marked effects on body weight, including weight loss, in the high-dose dams led to an early sacrifice of these animals on gestation day 14. Similarly, due to marked effects on body weight, 2/7 dams at the mid-dose level were sacrificed on gestation day 17. All other rabbits survived to scheduled necropsy on gestation day 20. There were no significant maternal effects at 100 mg/kg bw/d.

In a developmental toxicity study, XDE 565 (98.2% purity) was administered to 20 female NZW rabbits per dose in 0.5% aqueous Methocel A4M suspension by gavage at dose levels of 0, 30, 100 or 300 mg/kg bw/d from day 7 through 19 of gestation with sacrifice on day 28 of gestation. At 300 mg/kg bw/d, body-weight gain was depressed on days 7–10 and 7–20 compared with controls. Feed consumption was also depressed during dosing. Fecal output was reduced. Two out of 20 rabbits aborted at 300 mg/kg bw/d, probably due to anorexia. The LOAEL for maternal toxicity is 300 mg/kg bw/d based on the body weight and food intake effects. The NOAEL for maternal toxicity is 100 mg/kg bw/d. There were no treatment-related effects on developmental parameters. Thus, the LOAEL and NOAEL for developmental toxicity are >300 and 300 mg/kg bw/d, respectively.

3.1.6 Neurotoxicity (acute and subchronic)

The acute neurotoxicity potential of cloransulam-methyl was assessed in rats that were given single oral doses of up to 2000 mg/kg bw. After dosing, the rats were assessed for mortality, clinical toxic signs, body weight, motor activity and functional observational battery. There were no treatment-related effects on the parameters assessed. Thus, the NOAEL for acute neurotoxicity is 2000 mg/kg bw/d.

3.1.7 Weight of evidence regarding the carcinogenic potential of cloransulam-methyl

Cloransulan-methyl was not found to be genotoxic in a battery of in vitro and in vivo tests. Long-term dietary toxicity and oncogenicity studies in rats and mice did not demonstrate a carcinogenic potential of cloransulam-methyl.

3.2 Determination of acceptable daily intake

Short-term and long-term toxicity data on cloransulam-methyl did not demonstrate significant toxicity concerns on oncogenicity, genotoxicity, teratogenicity, reproductive toxicity or neurotoxicity. There were no indications of a quantitative or qualitative sensitivity of the young. The most sensitive species tested was the dog. Based on the NOAEL of 5 mg/kg bw/d established in the one-year dog dietary toxicity study, and the standard 100-fold safety factor, the recommended acceptable daily intake (ADI) for dietary risk assessment is 0.05 mg/kg bw/d.

3.3 Acute reference dose

Toxicological data assessed indicated the lack of acute toxicity hazards for cloransulam-methyl. Therefore, there is no need to establish an acute reference dose (ARfD) for acute risk assessment.

3.4 Toxicology end-point selection for occupational and bystander risk assessment

Occupational exposure is expected to be primarily via the dermal route. Application of product would take place over a short period of time (maximum exposure over two weeks for custom applicators).

Short-term dermal toxicity data are most relevant for the assessment of possible occupational risk. Adequate dermal toxicity data are available for both the technical active cloransulam-methyl and the formulation FirstRate®. After 21 days of dermal exposure to FirstRate® herbicide at doses up to 1000 mg/kg bw/d in rabbits, the only treatment-related effect observed was anemia in the females at the highest dose tested. Treatment had no effect on mortality, clinical signs, food consumption, body weight, clinical chemistry, organ weights or gross and histopathology. The NOAEL established in these data is 500 mg/kg bw/d, which can be used for the assessment of occupational risks.

As cloransulam-methyl did not demonstrate toxicity concerns on oncogenicity, genotoxicity, teratogenicity, reproductive toxicity or neurotoxicity, the target margin of exposure is 100, the standard acceptable value that is considered adequate in the assessment of occupational risk.

3.5 Drinking water limit

Will be addressed in Section 4.2.

3.6 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

3.6.1 Operator exposure assessment

FirstRate® Herbicide, containing 84% cloransulam-methyl is proposed for pre-emergence or post-emergence control of broadleaved weeds in soybeans. FirstRate® is a water dispersible granular formulation and is packaged in water soluble packaging. There is the potential for exposure during the open mixing, loading, application and possible repairs and cleanup of the application equipment. A single application, using ground equipment only, would be made in a growing season.

Personal protective equipment on the draft label includes: “Applicators and other handlers must wear: long-sleeved shirt and long pants and chemical resistant gloves.”

A Pesticide Handler’s Exposure Database (PHED) version 1.1 assessment was conducted to quantify exposure to herbicide during mixing, loading and application of product to soybeans using ground boom equipment. Mixer, loader and applicator exposure estimates are based on the maximum application rate of 0.035 kg a.i./ha (pre-emergence) and the respective number of hectares treated. In a typical day, a farmer applying cloransulam-methyl by ground boom application equipment to 50 ha of soybeans would handle 1.75 kg a.i. A custom applicator could treat 120 ha, thereby handling 4.2 kg a.i. per day.

Mixer, loader and applicator exposure
Potential worker exposure estimates were generated from the generic database (PHED, version 1.1). There were appropriate PHED data for mixing and loading a dry flowable formulation (equivalent to water dispersible granules) and ground boom application. A protection factor of 90% was applied to the mixer and loader dermal and inhalation unit exposure values to account for water soluble packaging. The PHED estimates generated otherwise conformed with North American Free Trade Agreement Guidelines for using and reporting PHED data.

The PHED exposure estimates were normalized for kilograms of cloransulam-methyl handled, based on the maximum application rate of 0.035 kg a.i./ha and the respective number of hectares treated by a farmer and a commercial applicator using ground boom equipment. An exposure of 1.27 Fg a.i./kg bw/d was estimated for farmers mixing, loading and applying 1.75 kg of cloransulam-methyl. For commercial applicators, an exposure of 3.05 Fg a.i./kg bw/d was estimated for mixing, loading and applying 4.2 kg of cloransulam-methyl.

All assessments were conducted with one layer of clothing and gloves as protective equipment with the exception of the applicators, in whom exposure was estimated without gloves. For all scenarios, the primary route of exposure was dermal and 3% was by inhalation. In the absence of dermal absorption data, dermal absorption was assumed

to be equivalent to oral absorption. From these scenarios, the custom ground boom applicator had the greatest exposure potential.

For the risk assessment, the exposure estimates were compared with the NOAELs of 500 mg/kg bw/d with the technical grade of active ingredient (TGAI) and the EP, from the 21-day dermal studies in the rabbit. The margins of exposure (MOEs) for the farmer and the custom applicator are in excess of 390,000 and 160,000, respectively. These MOEs are considered acceptable to the Health Evaluation Division.

3.6.2 Bystanders

Given that application is by ground boom equipment only to an agricultural crop, exposure and risk to bystanders would be minimal.

3.6.3 Re-entry workers

As product would be applied pre-emergence or post-emergence, prior to the flowering stage of soybean, re-entry activities should be minimal. As such, exposure and risk to re-entry workers would be minimal. A restricted entry interval is not required for the soybean use.

4.0 Residues

4.1 Definition of the residues relevant to maximum residue limits

4.1.1 Definition of the residues in field corn relevant to maximum residue limits

Plant metabolism

In the metabolism study, XDE-565(99+%) formulated as the 84% WDG formulation, labelled as either the [aniline-UL]-XDE-565 (‘A’) or the [triazolopyrimidine-7,9]-XDE-565 (‘TP’), was applied post-emergent to soybean in the V5 growth (stage 43 days) after planting at approximately 88 g a.i./ha (5X the Canadian recommended label rate for post-emergence use). Soybean forage samples were harvested at 0 days after application (DAA), 1 DAA and 20 DAA. The soybeans were harvested at maturity (98 DAA). Immediately after application, several of the soybean plants were covered to yield ‘dark-grown’ plants harvested 1 DAA to examine the effect of light on the metabolism. Residues in the 0-day forage were similar (7.4 and 10.4 ppm) but declined after 20 days (0.71 and 1.05 ppm) in the ‘A’ and ‘TP’ labels, respectively. The major metabolites, in addition to the parent compound, identified in plants one day after treatment were 565-homoglutathione, 565-cysteine (565-CYS), triazolopyrimidine sulfonic acid (TPSA) and TP-cysteine (TP-CYS). Residues in the harvested beans were 0.019 and 0.007 ppm for the ‘A’ and ‘TP’ labels, respectively. The bound residues characterized in the bean samples consisted of a series of protein, whey and polysaccharide fractions. Therefore, no further extraction and fractionation were conducted on seeds for identification of metabolites. The proposed metabolic pathway in plants, following a post-emergent

application, consisted of homoglutathione adduct formation and photolysis. The major photolysis products observed in the 'light-grown' plants were sulfonamide and sulfonic acid derivatives, demonstrating that cleavage of the sulfonamide bridge and opening of the pyrimidine ring occurred.

In the metabolism study (MRID no. 436689-23), XDE-565 (99+% a.i. formulated as an acetonitrile water solution) labelled as either 'A' or 'TP', was applied to soil at a rate equivalent to 477 g a.i./ha, which was approximately 13.6X the recommended label rate for pre-emergent application in Canada (35 g a.i./ha). Following application, the test material was incorporated into the soil at a depth of 4–6 cm and the soybeans were planted immediately following incorporation. Plant specimens were taken at early forage (27 DAA), bloom-stage forage (61 DAA) and mature-harvest beans (140 DAA). The proposed metabolic pathway for cloransulam-methyl following preplant incorporation to the soil suggests that the parent compound is metabolized in the soil. After the metabolites from the soil containing only the triazolopyrimidine ring system were taken up by the soybean plant, further metabolism occurred. Metabolism and/or conjugation via the homoglutathione pathway resulted in the formation of minor metabolites including (7*S*-[3-aminosulfonyl-5-methoxy-[1,2,4]triazolo[1,5-*c*]-pyrimidinyl]cysteine (methyl-ASTP-CYS). All other soluble metabolites were products containing both the 'A' and 'TP' ring systems. Bound residues were associated with cellulose and lignin fractions (forage) and with proteins (soybean seed).

Overall, the profiles of the post-emergent treatment plants were dominated by components derived from photolysis with minor contributions by components derived from the metabolism of soil-deposited cloransulam-methyl in contrast to pre-plant incorporated treatment. The residue of concern (ROC) in plant may be defined as cloransulam-methyl and its acid, cloransulam, calculated as parent ester.

Confined crop rotation studies

In the confined crop rotation study, cloransulam-methyl (XDE-565), 99% a.i., WDG labelled as either 'A' or 'TP', was applied to sandy loam soil at 55 g a.i./ha (1.6X the recommended Canadian label rate for pre-emergent treatment; 3.2X the recommended Canadian label rate for post-emergent treatment). Wheat, lettuce and potatoes were planted at 120 days post-treatment. Lettuce, potato tuber, wheat forage, straw and grain were harvested and analyzed for total radioactive residues (TRRs). The harvested wheat grain and straw had higher TRRs and were further extracted for identification and characterization. The majority of the residues were bio-incurred and associated with starch (grain), lignin and cellulose (straw). No metabolites were found at concentrations greater than 0.01 Fg/g (10% of the TRRs) following the 120-day plant-back interval. The only identifiable metabolite in wheat straw was XDE-565 TPSA in the 'TP' label at levels of 6.6% of the TRRs (0.004 Fg/g). The label has a plant-back restriction of no month (soybeans), four months (wheat) and nine months (corn). All other crops will require a field bioassay. The confined crop rotation study supports the definition of the ROC as defined in the plant and animal metabolism studies.

Storage stability

In the freezer storage stability study, samples of soybean grain, forage and hay were spiked with cloransulam-methyl, 99.2% a.i., at a level of 0.20 Fg/g and stored at –20EC for a duration of 375, 188 and 174 days, respectively. Residues of cloransulam-methyl were found to be stable over the time periods studied. The freezer storage stability study will not impact on the ROC.

4.1.2 Definition of the residue in food of animal origin relevant to maximum residue limits

Animal metabolism

In the laying hen metabolism study, XDE-565, 99+% a.i., labelled as either 'A' or 'TP', was administered separately to five white leghorn hens (*Gallus domesticus*) at dose levels of 0.90 or 0.86 mg/kg bw/d, respectively. The animals were dosed twice daily with capsules for five consecutive days. Excreta and eggs were collected daily. At sacrifice, samples of muscle, fat and liver were isolated. Radioactivity recovered in the feces and urine accounted for 99.7% of the administered dose. Metabolites identified by mass spectral analysis from excreta in the 'A' and 'TP' labels were the parent compound and its 4- and 5-hydroxy metabolites; however, these metabolites were not detected in any of the tissues or eggs. Eggs, liver and muscle tissues were further extracted for identification and characterization of metabolites. Differences in the level and distribution of the radioactive residues were observed for the two labels indicating that bridge cleavage was occurring between the 'A' and 'TP' rings. The major organic soluble component identified was 5-ethoxy-7-fluoro(1,2,4)triazolo[1,5-*c*] pyrimidine-2-sulfonamide (ASTP) in liver (50% of TRRs; 0.07 Fg/g) and muscle (60% of TRRs; 0.021 Fg/g). Treatment of the insoluble residues with buffer, enzymes and acid hydrolysis released approximately 64% of the TRRs (0.102 Fg/g) and 35% of the TRRs (0.05 Fg/g) in the 'A' and 'TP' labels, respectively. The remaining aqueous fractions from both 'A' and 'TP' label contained multiple components. Only the parent compound (approximately 40% of TRRs; 0.006 Fg/g) was identified in eggs. Soybean grain can be used as an animal feed item for laying hens. Since the feeding levels were highly exaggerated (3600X), it is unlikely that hens fed treated crop would have residue levels detectable in any tissue or eggs above 0.01 Fg/g.

In the goat metabolism study, XDE-565, 99+%, labelled as either 'A' or 'TP', was administered orally to two goats, species *carpa* (one per treatment group), at a dose level of 0.3 mg/kg bw/d (equivalent to 10 ppm in feed), once daily for five consecutive days using a balling gun. The dosing level represented approximately 190X the expected dietary exposure in the ruminant diets. Samples of milk, urine and feces were collected throughout the study. Approximately 24 h after the final dose, the animals were sacrificed and tissues collected.

The majority of the radioactivity was readily excreted in the urine and feces (99.9%). The radioactivity in the samples collected was approximately 93% of the total dose administered for the ('A') label and 81% for the ('TP') label. The highest average

concentration of cloransulam-methyl equivalent residues were found in the kidney (0.12 Fg/g), followed by the liver (0.045 Fg/g), blood (0.035 Fg/g), muscle (0.002 Fg/g), milk (<0.001 Fg/g) and fat (0.002 Fg/g). Kidney and liver tissues were further extracted and fractionated for possible metabolite identification and characterization. In kidney, for both labels, the majority of the residues were identified as parent (51% of TRRs), with a small amount of XDE-565 acid (1.3% of TRRs). In liver, XDE-565 acid represented approximately 9.5% of the TRRs (0.005 Fg/g). The remainder of the liver and kidney residues consisted of multiple minor fractions, each representing less than 10% of the TRRs (0.05 Fg/g). The TRRs were comparable between labelling positions indicating no significant levels of bridge cleavage.

Based on the ruminant and laying hen metabolism studies, the ROC is defined as cloransulam-methyl and its acid, cloransulam, calculated as parent ester.

4.2 Residues relevant to consumer safety

Supervised residue trial studies

Supervised crop field trial studies in soybeans were conducted in the U.S. in Canadian representative zones. The proposed use patterns are pre-emergent application (35 g a.i./ha) and early post-emergent application (17.5 g a.i./ha), with a preharvest interval (PHI) of 65 days. Cloransulam-methyl residues in soybean following the pre-emergent treatment of NAF-75, 84.4% a.i. (XDE-565) formulation at 36.4–45.9 g a.i./ha (1.04–1.3X the recommended Canadian label rate), were less than the LOQ (0.01 ppm) in samples collected 102–149 days following the last application. Cloransulam-methyl residues following the post-emergent application at 17.0–17.9 g a.i./ha (0.97–1.02X the recommended Canadian label rate) for grain (65–224 days) after the last treatment were less than LOQ (0.01 ppm). In the majority of the trials, the post-emergent application included the non-ionic surfactant Ortho X-77 and the presence of the liquid fertilizer UAN. The use of different adjuvants did not impact on the residue profile. Consequently, a maximum residue limit (MRL) of 0.01 ppm should be established to cover residues of XDE-565 equivalents in soybean.

Processing study

In the processed food and feed study, XDE-565 formulated as NAF-75 (84.4% a.i.), was applied to soybeans as a post-emergent spray in the 6–7 leaf stage at 87.5 g a.i./ha (5X the recommended post-emergent label rate). The soybean grain harvested 76 DAA was processed into hulls, dust, meal, crude oil and refined oil. The processing procedures reflected those of a commercial processing operation. Cloransulam-methyl residues were not detected in the grain or any of its processed fraction indicating no concentration. Therefore, the theoretical concentration factor of up to 12X for conversion into oil is not applicable. Several of the processed fractions including hulls, meal and aspirated grain fractions (dust) are used as animal feed (85–92% dry matter). Maximum residue limits will not need to be established to cover residues of XDE-565 in soybean processed fractions: hulls, dust, meal, crude oil and refined oil.

Dietary risk assessment

For the chronic dietary risk assessment, the potential daily intake (PDI) was determined using the proposed MRLs in or on soybeans and the Dietary Exposure Evaluation Model™ (DEEM™) Software. The assessment was conducted using the 1994–1996 Continuing Survey of Food Intake for Individuals. The PDI, including a 10% water allocation, was less than 10% of the ADI (0.05 mg/kg bw) for the total population, including infants and children. Consequently, the proposed domestic use of cloransulam-methyl on soybean does not pose an unacceptable dietary (both food and water) risk to any segment of the population including infants, children and adults.

4.3 Residue relevant to worker safety

Has been addressed in Section 3.6.3.

4.4 Proposed MRLs and compliance with existing MRLs

4.4.1 Compliance with existing MRLs in Canada

Since this active ingredient is a new chemical, there are no existing MRLs.

4.4.2 Proposed MRLs

The proposed MRL is 0.01 ppm for soybean seed. The U.S. has also established tolerances for soybean seed, forage and hay at 0.02, 0.1 and 0.2 ppm, respectively. The Canadian label prohibits the feeding of treated forage or hay to animals.

4.5 Proposed import tolerances

Import tolerances have not been petitioned in Canada.

4.6 Basis for differences, if any, established or proposed MRLs

CODEX has not established MRLs for residues of cloransulam-methyl in or on plant or animal commodities.

4.7 Integrated residue summary

Plant and animal metabolism studies were conducted using cloransulam-methyl radiolabelled in both the‘A’ and the ‘TP’ portions of the molecule. The main degradation products resulted from the cleavage of the sulfonamide bridge and the opening of the pyrimidine ring in plant and animal. When cloransulam-methyl was applied post-emergent to soybeans (5X the proposed application rate of 17.5 g a.i./ha), the parent compound and the metabolites were not detected in soybean seed at levels greater than 0.005 Fg/g. The proposed pathway involved the formation of homoglutathione adducts and photolysis derived products. In hen and goat metabolism studies, the major route of

elimination was via excretion (>99.7% of the TRRs). Degradation occurred rapidly to form cloransulam, 5-hydroxycloransulam, 5-hydroxycloransulam-methyl, sulfonamides and sulfonic acid derivatives. The residues in milk and tissues were identified as cloransulam-methyl and its acid metabolite. Residues in eggs and tissues consisted of cloransulam-methyl and triazolopyrimidine derived products. Based on plant and animal metabolism studies, the ROC is defined as cloransulam-methyl and its acid, cloransulam, calculated as parent ester.

Residues of cloransulam-methyl and its acid, cloransulam, calculated as parent ester were quantitated by capillary GC–MS. The method LOQ and LOD were validated at 0.01 Fg/g and 0.005 Fg/g, respectively. The standard deviation measured with respect to recoveries following spiking at the LOQ was indicative of the method having good repeatability. The detector response was linear (r = 0.9998) in the range of 0.01–0.50 Fg/g for soybean grain, forage and hay and processed fractions. The ILV did support the reliability and reproducibility of the proposed method for the quantitation of cloransulam-methyl residues in soybean matrices (hay, forage and grain).

Residues of cloransulam-methyl in soybean seed following the pre-emergent treatment of FirstRate®, 84.4% a.i. (XDE-565) WDG formulation at 36.4–45.9 g a.i./ha (1.04–1.3X the recommended Canadian label rate), were less than the LOQ (0.01 ppm) in samples collected 102–149 days following the last application. Residues of cloransulam-methyl following the post-emergent application of FirstRate® at 17.0–17.9 g a.i./ha (0.97–1.02X the recommended Canadian label rate) were less than the LOQ (0.01 ppm) in the seeds (65–224 days after harvest). The use of different adjuvants indicated no effect on the residue levels in soybeans. Soybean processing studies indicated that cloransulam-methyl residues were less than LOQ in the soybean meal, hulls, grain dust fractions, crude oil and refined oil. Consequently, an MRL of 0.01 ppm should be established to cover cloransulam-methyl residues in soybean seed. The Canadian label prohibits the feeding of treated forage or hay to animals.

For the chronic dietary risk assessment, the PDI was determined using the proposed MRLs on plant and animal commodities and the DEEM™ Software. The assessment was conducted using the U.S. Department of Agriculture 1994–1996 Continuing Survey of Food Intake for Individuals (CSFII). The PDI, including a 10% water allocation, was less than 10% of the ADI (0.05 mg/kg bw) for the total population, including infants, children and seniors.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

5.2 Abiotic transformation

Cloransulam-methyl hydrolyzes very slowly at acidic and neutral pH; however, it hydrolyzes rapidly at pH 9 with a half-life of 3 days. The major hydrolysis transformation products at pH 9 were XDE-565-imidate and XDE-565-acetic acid. Phototransformation on soil is not a principal route of transformation (half-life of 30–70 days.) Although the UV-visible absorption spectrum indicates that there is a low potential for phototransformation, photolysis in water is a principal route of transformation (half-life of 22 min). The major phototransformation products in water are XDE-565-sulfonic acid (TPSA) and XDE-565-sulfonamide (ASTP).

5.3 Biotic transformation

In aerobic soil, the time required for 50% dissipation (DT_{50}) for XDE-565 ranged from 13 to 28 days. The major transformation products were XDE-565 acid, 5-OH-XDE-565 and 5-OH-XDE-565-acid. Under aerobic aquatic conditions, the half-life of XDE-565 is 25.6 days in water. After 31 days, 76–82% of the radiolabel remained in the water column. The major transformation product was XDE-565-acid. Under anaerobic aquatic conditions, the half-life of the parent compound is approximately 16 days in water. The major transformation products in water and sediment were XDE-565-acid and *N*-(2-carboxy-phenyl-6-chloro)-{1-methyl-5-(2-fluoroethenyl)-1,2,4-triazol-3-sulfonamide}. In the aqueous phase, 5-OH-XDE-565 acid was also detected as a major transformation products. At 5EC, the half-life of the parent compound was 237 days and no major transformation products were detected.

5.4 Mobility

The results from the adsorption study indicated that XDE-565 is not strongly adsorbed to soil and has a high to very high mobility classification. The results from the aged partitioning study indicated that the mobility of the transformation products would be equal to or greater than that of the parent compound. Under laboratory conditions, no volatile transformation products other than CO_2 were detected following application of cloransulam-methyl to a clay loam soil and a silt loam soil.

5.5 Dissipation and accumulation under field conditions

Under field conditions in Wisconsin, cloransulam-methyl had a DT_{50} value of 6.6 days in sandy loam soil. The time required for 90% dissipation (DT_{90}) was 59.1 days. The maximum concentration of XDE-565-acid was 25% of applied parent compound and was <10% at 100 days post-application. The residues of cloransulam-methyl and XDE-565-

acid, the only major transformation product monitored during the study, were primarily detected in the 0–30 cm soil layer (5.7% of applied).

5.6 Bioaccumulation

The range of log K_{ow} values (1.12 to –1.24) indicates a low potential for bioaccumulation of cloransulam-methyl and does not trigger a bioaccumulation study with fish.

5.7 Summary of fate and behaviour in the terrestrial environment

Cloransulam-methyl hydrolyzes very slowly at acidic and neutral pH; however, it hydrolyzes rapidly at pH 9 with a half-life of 3 days. Phototransformation on soil is not a principal route of transformation (half-life of 30–70 days). In laboratory studies with aerobic soil, the DT_{50} for XDE565 ranged from 13 to 28 days. The major transformation products were XDE-565 acid, 5-OH-XDE-565 and 5-OH-XDE-565-acid.

The results from the adsorption study indicated that XDE-565 and the transformation product XDE-565-acid are not strongly adsorbed in most soils. Under laboratory conditions, no volatile transformation products other than CO_2 were detected from a clay loam soil and a silt loam soil.

Under field conditions in Wisconsin, cloransulam-methyl had a DT_{50} value of 6.6 days in sandy loam soil. The DT_{90} was 59.1 days. The maximum concentration of XDE-565-acid was 25% of applied parent compound and was <10% at 100 days post-application. The residues of cloransulam-methyl and the transformation product, XDE-565-acid, were primarily detected in the 0–30 cm soil layer (5.7% of applied).

5.8 Summary of fate and behaviour in the aquatic environment

Cloransulam-methyl hydrolyzes very slowly at acidic and neutral pH; however, it hydrolyzes rapidly at pH 9 with a half-life of 3 days. The UV-visible absorption spectrum indicates that there is a low potential for phototransformation. Phototransformation on soil will not be an important, route of transformation; however, photolysis in water is a principal route of transformation (half-life of 22 min). The major phototransformation products in water are TPSA and ASTP. Under aerobic aquatic conditions, the half-life of XDE-565 is 25.6 days in water. After 31 days, 76–82% of the radiolabel remained in the water column. The major transformation product was XDE-565-acid. Under anaerobic aquatic conditions, the half-life of the parent compound is approximately 16 days (total system). The major transformation products in water and sediment were XDE-565-acid and *N*-(2-carboxy-phenyl-6-chloro)-{1-methyl-5-(2-fluoroethenyl)-1,2,4-triazol-3-sulfonamide}. In the aqueous phase, 5-OH-XDE-565 acid was also detected as a major transformation product. At 5EC, the half-life of the parent compound was 237 days.

5.9 Expected environmental concentrations

5.9.1 Soil

The concentration of cloransulam-methyl in 15 cm depth of soil immediately after application to the soil surface at the maximum label rate of 35 g a.i./ha will be 0.016 mg a.i./kg soil.

5.9.2 Aquatic systems

Direct overspray: The concentration of cloransulam-methyl in 30 cm depth of water immediately after a direct overspray at the maximum label rate will be 0.012 mg a.i./L.

6.0 Effects on non-target species

6.1 Effects on biological methods of sewage treatment

Not applicable for the proposed use.

6.2 Risk characterization

6.2.1 Environmental behaviour

Cloransulam-methyl is slightly persistent in soil and water. It is not expected to volatilize from water or moist soils. The principal routes of routes transformation are biotransformation in soil and phototransformation and biotransformation in aquatic environments. There is a high potential for the parent compound and major transformation products to leach in soil. The relatively short half-life in soil would partially mitigate the potential for leaching of the parent compound.

6.2.2 Terrestrial organisms

The risk to non-target organisms was calculated using expected environmental concentration (EEC) values of 0.016 mg/kg in 15 cm depth of soil and 0.012 mg/L in 30 cm depth in water. The EEC in wildlife food sources will be 4.20, 1.18, 17.66, 17.55 and 23.19 mg a.i./kg dry weight (dw) for the bobwhite quail, mallard ducks, rats, mice and rabbits, respectively. Margins of safety (MOS) were calculated using the no observable effect concentration (NOEC), or an estimated NOEC equivalent to 1/10 of the mean effective concentration (EC_{50}) or LC_{50}, or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50} for the most sensitive species per group.

Terrestrial invertebrates
The major route of exposure for earthworms is through ingested soil in treated soybean fields. The MOS based on a 14-day NOEC of 116 mg a.i./kg soil was calculated as 7.25×10^3; thus, earthworms are not expected to be at risk from the proposed use of FirstRate®.

The major route of exposure to honeybees is through contact with contaminated flowering plants. Cloransulam-methyl is classified as relatively non-toxic to honey bees on an acute contact basis. Using the assumptions of Atkins et al. (1981),[1] an LD_{50} > 25 Fg a.i./bee would be equivalent to an application rate >30 kg a.i./ha would kill 50% of bees foraging in treated fields at the time of application or shortly afterwards. The MOS, therefore, is >857. As the rate of application is 0.035 kg a.i./ha, bees are not expected to be at risk from the proposed use of FirstRate®.

Avian species

The major risk to avian species is through ingestion of food sources contaminated by exposure to cloransulam-methyl during application. The MOS for dietary and reproductive effects, based on an 8-day dietary NOEC for bobwhite quail of 5620 mg a.i./kg diet and a reproductive NOEC for the mallard duck of 125 mg a.i./kg diet, are 1.34×10^3 and 1.06×10^2, respectively. There is no risk from the acute oral route. Therefore, birds are not considered to be at risk from the proposed use of FirstRate®.

Terrestrial plants

The most sensitive species tested was the radish. Based on the effective concentration for 25% of the population (EC_{25}) value of 0.099 g a.i./ha for the radish, the MOS is 2.83×10^{-3}. Therefore, there is a risk to non-target terrestrial plants.

Aquatic species

The major source of contamination of aquatic environments is through a direct overspray. Based on a 48-h NOEC of 64.3 mg a.i./L for daphnids, a 96-h NOEC of 121 mg a.i./L for shrimp and a 96-h NOEC for rainbow trout of 86 mg a.i./L, the MOS for daphnids, shrimp and rainbow trout are 5.36×10^3, 1.01×10^4 and 7.17×10^3, respectively. Therefore, these species are not considered to be at risk from the proposed use of FirstRate®.

Based on the 96-h NOEC for the green alga (*Selenastrum capricornutum*) of 0.9 Fg a.i./L and a 14-day NOEC for duckweed of 0.78 Fg a.i./L, the MOS for algae and duckweed are 7.5×10^{-2} and 6.50×10^{-2}, respectively. Therefore, the use of FirstRate® poses a risk to these species.

Small wild mammals

The major risk to small mammals is through ingestion of food sources contaminated by exposure to cloransulam-methyl during application. For acute oral toxicity (rat) the MOS is expressed as 5660 days of intake required to produce the equivalent of the dose administered to kill 50% of the laboratory population. The MOS for dietary toxicity (mouse) is 2.85, based on the NOAEL for the males of 50 mg/kg bw/d. Based on a

[1] Atkins, E.L., Kellum, D., and Atkins, K.W. 1981. Reducing pesticide hazards to honey bees: Mortality prediction techniques and integrated management strategies. Univ. Calif., Div. Agric. Sci., Leaflet 2883. 22 pp.

NOAEL of 500 mg/kg bw/d, the MOS for reproductive toxicity (rat) is 28.3. Therefore, the use of FirstRate® does not pose a risk to small wild mammals.

6.3 Risk mitigation

Laboratory studies indicate a potential for mobility of cloransulam-methyl and its major transformation products in soil. The lack of persistence of the parent compound, as indicated by the results of laboratory studies may mitigate the potential for cloransulam-methyl to contaminate ground water. The fate of the major transformation products, 5-OH-XDE-565 and 5-OH-XDE-565-acid, in soil was not adequately addressed in terrestrial field studies in soybean growing areas in Ecoregion 8.1.

Based on a first approximation of EEC, there is a risk to terrestrial and aquatic non-target plants in the absence of mitigation. These risks can be mitigated by the establishment of terrestrial and aquatic buffer zones.

A buffer zone of 35 m is required to protect non-target plant species for ground application. This value is based on the phytotoxicity to radish. A buffer zone of 7 m around all open bodies of water, e.g., rivers, lakes, streams and ponds, is required to protect non-target aquatic species. This value is based on the NOEC for duckweed, the most sensitive aquatic species.

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended use

FirstRate® is a selective herbicide that may be applied pre-emergent or post-emergent to soybeans in Eastern Canada for control of specific broadleaf weeds. The pre-emergent application of FirstRate® is effective in controlling common ragweed, velvetleaf and lambsquarters when applied at a rate of 20.8 g/ha (17.5 g a.i./ha). The pre-emergent application of FirstRate® is effective in controlling cocklebur and heavy infestations of lambsquarters when applied at a rate of 41.7 g/ha (35 g a.i./ha). The post-emergent application is effective in controlling common ragweed, velvetleaf, cocklebur, jimsonweed and giant ragweed when applied at 20.8 g/ha (17.5 g a.i./ha). When utilized as a post-emergent, FirstRate® must be applied with a non-ionic surfactant at 0.25% v/v and and liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

Winter wheat may be planted four months after application of FirstRate® and field corn may be planted nine months after application of FirstRate®.

FirstRate® may be tankmixed with Broadstrike Dual® at 2.4 L/ha, Pursuit® at 312 mL/ha or Dual® 960 at 2.2 L/ha when applied as a pre-emergent treatment.

FirstRate® may be tankmixed with Pursuit® at 312 mL/ha and a non-ionic surfactant at 0.25% v/v and liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v when applied as a post-emergent treatment.

7.1.2 Mode of action

Cloransulam-methyl is a systemic herbicide that must be absorbed by the plant and translocated to the site of action. The primary site of cloransulam-methyl activity is in the meristem. As a pre-emergence application, roots, and to a lesser extent shoots, intercept cloransulam-methyl as they grow through the soil. Soil moisture, texture, organic matter and pH as well as plant growth rate and herbicide dissipation affect the availability and uptake of cloransulam-methyl. Germinating seedlings in direct contact to cloransulam-methyl may not emerge or emerge and quickly stop growing. Cloransulam-methyl applied post-emergence is quickly absorbed by plant foliage and is translocated to shoot meristem. Sensitive seedlings stop growing and competing with the crop and slowly die.

Cloransulam-methyl and other sulfonanilide herbicides act on the acetolactate synthase (ALS) enzyme. The ALS enzyme plays a central role in plant production of three amino acids necessary for cell division and growth, namely: valine, leucine and isoleucine. Once in the cells, cloransulam-methyl inactivates the ALS enzyme, thus prohibiting the production of these three amino acids. After a toxic amount of cloransulam-methyl accumulates in meristem, cell division in roots and shoots quickly slows or stops.

Other herbicide families that act on this same pathway are the sulfonylurea herbicides and the imidazolinone herbicides.

7.1.3 Crops

Soybean is the only crop for which data was submitted and for which a label claim was made.

7.1.4 Effectiveness against pests

7.1.4.1 Pre-emergent application

7.1.4.1.1 Pre-emergent application of FirstRate®

Common ragweed (*Ambrosia artemisiifolia*): Control of common ragweed with FirstRate® at 17.5 g a.i./ha was reported in 20 trials conducted over three years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 88% (n = 21) at 14–40 DAA and 87% (n = 25) at 41 or more DAA. The data supports a claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*): Control of velvetleaf with FirstRate® at 17.5 g a.i./ha was reported in seven trials conducted over three years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 95% (*n* = 6) at 14–40 DAA and 91% (*n* = 5) at 41 or more DAA. The data supports a claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Lambsquarters (*Chenopodium album*): Control of lambsquarters with FirstRate® at 17.5 g a.i./ha was reported in 21 trials conducted over four years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 84% (*n* = 24) at 14–40 DAA and 82% (*n* = 20) at 41 or more DAA. The data supports a claim of lambsquarters control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*): Control of cocklebur with FirstRate® at 17.5 g a.i./ha was reported in four trials conducted over three years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 70% (*n* = 5) at 14–40 DAA and 59% (*n* = 3) at 41 or more DAA. The data indicate the level of control provided by FirstRate® at 17.5 g a.i./ha is not acceptable.

Control of cocklebur with FirstRate® at 35 g a.i./ha was reported in six trials conducted over four years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 89% (*n* = 5) at 14–40 DAA and 89% (*n* = 4) at 41 or more DAA. The data supports a claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

7.1.4.1.2 Pre-emergent application of FirstRate® + Broadstrike Dual®

Common ragweed (*Ambrosia artemisiifolia*): Control of common ragweed with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was reported in 14 trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 91% (*n* = 18) at 14–40 DAA and 91% (*n* = 20) at 41 or more DAA. The data indicates the level of control of common ragweed is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha The data supports the claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*): Control of velvetleaf with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was reported in three trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 88% (*n* = 5) at 14–40 DAA and 86% (*n* = 4) at 41 or more DAA. The data indicates the level of control of velvetleaf is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha The data supports the claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Lambsquarters (*Chenopodium album*): Control of lambsquarters with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was reported in 13 trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 93% (*n* = 18) at 14–40 DAA and 89% (*n* = 15) at 41 or more DAA. The data indicates the level of control of lambsquarters is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha. The data supports the claim of lambsquarters control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*): Control of cocklebur with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was reported in two trials conducted in one year in Ontario under conventional and minimum tillage practices. Mean control was 88% (*n* = 2) at 14–40 DAA and no data reported at 41 or more DAA. The data indicates the level of control of cocklebur is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha. The data supports the claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

Redroot pigweed (*Amaranthus retroflexus*): Four side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of redroot pigweed following an application of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha and Broadstrike Dual® at 2.4 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 98% (*n* = 4) at 14–40 DAA and 96% (*n* = 7) at 41 or more DAA. Mean control for Broadstrike Dual® at 2.4 L/ha was 93% (*n* = 4) at 14–40 DAA and 96% (*n* = 7) at 41 or more DAA. The level of redroot pigweed control provided by Broadstrike Dual® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of redroot pigweed control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha.

Barnyard grass (*Echinochloa crusgalli*): Two side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of barnyard grass following an application of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha and Broadstrike Dual® at 2.4 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 91% (*n* = 2) at 14–40 DAA and 84% (*n* = 3) at 41 or more DAA. Mean control for Broadstrike Dual® at 2.4 L/ha was 90% (*n* = 2) at 14–40 DAA and 75% (*n* = 3) at 41 or more DAA. The level of barnyard grass control provided by Broadstrike Dual® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of barnyard grass control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha.

Green foxtail (*Setaria viridis*): Three side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of green foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at

2.4 L/ha and Broadstrike Dual® at 2.4 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 99% (*n* = 1) at 14–40 DAA and 85% (*n* = 4) at 41 or more DAA. Mean control for Broadstrike Dual® at 2.4 L/ha was 99% (*n* = 1) at 14–40 DAA and 80% (*n* = 4) at 41 or more DAA. The level of green foxtail control provided by Broadstrike Dual® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of green foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha.

Yellow foxtail (*Setaria glauca*): Five side-by-side trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices reported control of yellow foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha and Broadstrike Dual® at 2.4 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 86% (*n* = 4) at 14–40 DAA and 85% (*n* = 5) at 41 or more DAA. Mean control for Broadstrike Dual® at 2.4 L/ha was 78% (*n* = 4) at 14–40 DAA and 80% (*n* = 5) at 41 or more DAA. The level of yellow foxtail control provided by Broadstrike Dual® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of yellow foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha.

7.1.4.1.3 Pre-emergent application of FirstRate® + Pursuit®

Common ragweed (*Ambrosia artemisiifolia*): Control of common ragweed with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was reported in 14 trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 92% (*n* = 19) at 14–40 DAA and 89% (*n* = 19) at 41 or more DAA. The data indicates the level of control of common ragweed is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha. The data supports the claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*): Control of velvetleaf with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was reported in three trials conducted over two years in Ontario under conventional and minimum tillage practices. Mean control was 98% (*n* = 3) at 14–40 DAA and 96% (*n* = 2) at 41 or more DAA. The data indicates the level of control of velvetleaf is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha. The data supports the claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Lambsquarters (*Chenopodium album*): Control of lambsquarters with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was reported in 13 trials conducted over two years in Ontario under conventional and minimum tillage practices. Mean control was 91% (*n* = 18) at 14–40 DAA and 88% (*n* = 14) at 41 or more DAA. The data indicates the level of control of lambsquarters is acceptable when treated with the tankmix of

FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha. The data supports the claim of lambsquarters control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*): Control of cocklebur with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was reported in one trial conducted in Ontario under conventional and minimum tillage practices. Mean control was 99% (n = 2) at 14–40 DAA and 80% (n = 2) at 41 or more DAA. The data indicates the level of control of cocklebur is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha. The data supports the claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

Redroot pigweed (*Amaranthus retroflexus*): Four side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of redroot pigweed following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha and Pursuit® at 312 mL/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 99% (n = 2) at 14–40 DAA and 99% (n = 5) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha was 98% (n = 2) at 14–40 DAA and 98% (n = 5) at 41 or more DAA. The level of redroot pigweed control provided by Pursuit® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of redroot pigweed control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha.

Barnyard grass (*Echinochloa crusgalli*): Three side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of barnyard grass following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha and Pursuit® at 312 mL/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 80% (n = 3) at 14–40 DAA and 85% (n = 4) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha was 92% (n = 3) at 14–40 DAA and 83% (n = 3) at 41 or more DAA. The level of barnyard grass control provided by Pursuit® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of barnyard grass control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha.

Green foxtail (*Setaria viridis*): Three side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of green foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha and Pursuit® at 312 mL/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 96% (n = 2) at 14–40 DAA and 79% (n = 2) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha was 98% (n = 2) at 14–40 DAA and 80% (n = 2) at 41 or more DAA. The level of green foxtail control provided by Pursuit® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of green foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha.

Yellow foxtail (*Setaria glauca*): Three side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of yellow foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha and Pursuit® at 312 mL/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 76% (*n* = 3) at 14–40 DAA and 73% (*n* = 4) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha was 72% (*n* = 3) at 14–40 DAA and 74% (*n* = 4) at 41 or more DAA. The level of yellow foxtail control provided by Pursuit® was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of yellow foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha.

7.1.4.1.4 Pre-emergent application of FirstRate® + Dual® 960

Common ragweed (*Ambrosia artemisiifolia*): Control of common ragweed with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was reported in 12 trials conducted over three years in Ontario, Quebec and U.S. border states under conventional and minimum tillage practices. Mean control was 91% (*n* = 7) at 14–40 DAA and 93% (*n* = 11) at 41 or more DAA. The data indicates the level of control of common ragweed is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha. The data supports the claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*): Control of velvetleaf with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was reported in seven trials conducted over three years in Ontario and U.S. border states under conventional and minimum tillage practices. Mean control was 91% (*n* = 6) at 14–40 DAA and 96% (*n* = 7) at 41 or more DAA. The data indicates the level of control of velvetleaf is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha. The data supports the claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Lambsquarters (*Chenopodium album*): Control of lambsquarters with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was reported in 10 trials conducted over three years in Ontario under conventional and minimum tillage practices. Mean control was 94% (*n* = 8) at 14–40 DAA and 86% (*n* = 8) at 41 or more DAA. The data indicates the level of control of lambsquarters is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha. The data supports the claim of lambsquarters control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*): Control of cocklebur with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was reported in four trials conducted in U.S. border states over four years under conventional tillage practices. Mean control was 82% (*n* = 4) at 14–40 DAA and 85% (*n* = 4) at 41 or more DAA. The data indicates the level of control of cocklebur is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha. The data supports the claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

Redroot pigweed (*Amaranthus retroflexus*): Nine side-by-side trials conducted over four years in Ontario and U.S. border states under conventional and minimum tillage practices reported control of redroot pigweed following an application of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha and Dual® 960 at 2.2 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 98% (*n* = 6) at 14–40 DAA and 97% (*n* = 9) at 41 or more DAA. Mean control for Dual® 960 at 2.2 L/ha was 75% (*n* = 6) at 14–40 DAA and 88% (*n* = 9) at 41 or more DAA. The level of redroot pigweed control provided by Dual® 960 was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of redroot pigweed control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha.

Eastern black nightshade (*Solanum ptycanthum*): Three side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of eastern black nightshade following an application of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha and Dual® 960 at 2.2 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 87% (*n* = 3) at 14–40 DAA and 99% (*n* = 2) at 41 or more DAA. Mean control for Dual® 960 at 2.2 L/ha was 96% (*n* = 3) at 14–40 DAA and 96% (*n* = 2) at 41 or more DAA. The level of eastern black nightshade control provided by Dual® 960 was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of eastern black nightshade control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha.

Green foxtail (*Setaria viridis*): Two side-by-side trials conducted in one year in Ontario under conventional tillage practices reported control of green foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha and Dual® 960 at 2.2 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 98% (*n* = 1) at 14–40 DAA and 95% (*n* = 2) at 41 or more DAA. Mean control for Dual® 960 at 2.2 L/ha was 99% (*n* = 1) at 14–40 DAA and 94% (*n* = 2) at 41 or more DAA. The level of green foxtail control provided by Dual® 960 was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of green foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha.

Giant foxtail (*Setaria faberii*): Four side-by-side trials conducted over three years in Ontario and U.S. border states under conventional and minimum tillage practices reported control of giant foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha and Dual® 960 at 2.2 L/ha alone. Mean control for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 93% (*n* = 3) at 14–40 DAA and 94% (*n* = 4) at 41 or more DAA. Mean control for Dual® 960 at 2.2 L/ha was 91% (*n* = 3) at 14–40 DAA and 94% (*n* = 4) at 41 or more DAA. The level of giant foxtail control provided by Dual® 960 was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of giant foxtail control in soybeans grown in

conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha.

7.1.4.2 Post-emergent application

7.1.4.2.1 Post-emergent application of FirstRate® + non-ionic surfactant + fertilizer

Common ragweed (*Ambrosia artemisiifolia*) 4–8 leaf stage: Control of common ragweed with FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 55 trials conducted over four years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 82% (n = 32) at 7–14 DAA, 95% (n = 48) at 14–40 DAA and 97% (n = 57) at 41 or more DAA. The data supports a claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*) 2–4 leaf stage: Control of velvetleaf with FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 12 trials conducted over four years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 80% (n = 3) at 7–14 DAA, 98% (n = 9) at 14–40 DAA and 97% (n = 11) at 41 or more DAA. The data supports a claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*) 4–8 leaf stage: Control of cocklebur with FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 13 trials conducted over three years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 63% (n = 6) at 7–14 DAA, 97% (n = 4) at 14–40 DAA and 96% (n = 14) at 41 or more DAA. The data supports a claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

Jimsonweed (*Datura stramonium*) 2–4 leaf stage: Control of jimsonweed with FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 13 trials conducted over four years in U.S. border states under conventional tillage practices. Mean control was 93% (n = 5) at 7–14 DAA, 90% (n =12) at 14–40 DAA and 90% (n = 4) at 41 or more DAA. The data supports a claim of jimsonweed control in soybeans grown in conventional or minimum tillage practices.

Giant ragweed (*Ambrosia trifida*) 4–6 leaf: Control of giant ragweed with FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 19 trials conducted over seven years in U.S. border states under conventional and minimum tillage practices. Mean control was 89% (n = 6) at 7–14 DAA, 94% (n = 15) at 14–40 DAA and 88% (n = 12) at 41 or more DAA. The

data supports a claim of giant ragweed control in soybeans grown in conventional or minimum tillage practices.

7.1.4.2.2 Post-emergent application of FirstRate® plus Pursuit® + non-ionic surfactant + fertilizer

Common ragweed (*Ambrosia artemisiifolia*): Control of common ragweed with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in 18 trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices. Mean control was 85% (n = 11) at 7–14 DAA, 96% (n = 15) at 14–40 DAA and 96% (n = 17) at 41 or more DAA. The data indicates the level of control of common ragweed is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. The data supports the claim of common ragweed control in soybeans grown in conventional or minimum tillage practices.

Velvetleaf (*Abutilon theophrasti*): Control of velvetleaf with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in four trials conducted over two years in Ontario and Quebec under conventional tillage practices. Mean control was 92% (n = 1) at 7–14 DAA, 99% (n = 2) at 14–40 DAA and 98% (n = 3) at 41 or more DAA. The data indicates the level of control of velvetleaf is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. The data supports the claim of velvetleaf control in soybeans grown in conventional or minimum tillage practices.

Cocklebur (*Xanthium strumarium*): Control of cocklebur with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was reported in five trials conducted over two years in Ontario under conventional tillage practices. Mean control was 67% (n = 3) at 7–14 DAA, 95% (n = 2) at 14–40 DAA and 96% (n = 5) at 41 or more DAA. The data indicates the level of control of cocklebur is acceptable when treated with the tankmix of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. The data supports the claim of cocklebur control in soybeans grown in conventional or minimum tillage practices.

Redroot pigweed (*Amaranthus retroflexus*): Ten side-by-side trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices reported control of redroot pigweed following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v and Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. Mean control for FirstRate® at

17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was at 93% (*n* = 5) at 7–14 DAA, 89% (*n* = 7) at 14–40 DAA and 90% (*n* = 7) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 98% (*n* = 5) at 7–14 DAA, 97% (*n* = 7) at 14–40 DAA and 98% (*n* = 7) at 41 or more DAA. The level of redroot pigweed control provided by Pursuit® at 312 mlLha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of redroot pigweed control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

Barnyard grass (*Echinochloa crusgalli*): Five side-by-side trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices reported control of barnyard grass following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v and Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was at 96% (*n* = 4) at 7–14 DAA, 95% (*n* = 4) at 14–40 DAA and 96% (*n* = 4) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 95% (*n* = 4) at 7–14 DAA, 94% (*n* = 4) at 14–40 DAA and 88% (*n* = 4) at 41 or more DAA. The level of barnyard grass control provided by Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of barnyard grass control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5 v/v.

Green foxtail (*Setaria viridis*): Three side-by-side trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices reported control of green foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v and Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 92% (*n* = 1) at 7–14 DAA, 89% (*n* = 3) at 14–40 DAA and 99% (*n* = 2) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 87% (*n* = 1) at 7–14 DAA, 88% (*n* = 3) at 14–40 DAA and 98% (*n* = 2) at 41 or more DAA. The level of green foxtail control provided by Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the

claim of green foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

Yellow foxtail (*Setaria glauca*): Four side-by-side trials conducted over two years in Ontario under conventional and minimum tillage practices reported control of yellow foxtail following an application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v and Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. Mean control for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 91% (n = 2) at 7–14 DAA, 97% (n = 3) at 14–40 DAA and 97% (n = 3) at 41 or more DAA. Mean control for Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 89% (n = 2) at 7–14 DAA, 96% (n = 3) at 14–40 DAA and 96% (n = 3) at 41 or more DAA. The level of yellow foxtail control provided by Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was not compromised when tankmixed with FirstRate® at 17.5 g a.i./ha. The data supports the claim of yellow foxtail control in soybeans grown in conventional or minimum tillage practices with FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

7.2 Information on the occurrence or possible occurrence of the development of resistance

To address the issue of development of herbicide resistance, the following information will be included on the FirstRate® label:

"FirstRate® is a Group 2 herbicide. Any weed population may contain plants naturally resistant to FirstRate® and other Group 2 herbicides. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by FirstRate® or other Group 2 herbicides. To delay herbicide resistance:

- Avoid the exclusive, repeated use of FirstRate® or other herbicides in the same herbicide group.
- Rotate with herbicides from a different herbicide group that control the same weeds as FirstRate®.
- Use tankmixes with herbicides from different groups when a use is permitted.
- Integrate tillage or other mechanical cultural control methods into weed control programs whenever practical.
- Prevent movement of resistant weeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.
- Keep accurate records of crop rotation and herbicides used in each of your fields.

For further information, contact your local DowAgroScience representative."

7.3 Effects on the yield of treated plants or plant products in terms of quantity and quality

7.3.1 Pre-emergent application

7.3.1.1 Pre-emergent application of FirstRate®

Six trials conducted over two years in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at the maximum requested use rate of 35 g a.i./ha. One trial reported yield following application of the product at 44 g a.i./ha (1.25 × maximum requested rate), two trials reported yield following application of the product at 52 g a.i./ha (1.5 × maximum requested rate), one trial reported yield following application of the product at 70 g a.i./ha (2 × maximum requested rate) and one trial reported yield following application of the product at 104 g a.i./ha (3 × maximum requested rate).

Mean reported yield, expressed as a percentage of the untreated checks, was 203% (n = 6) for the 1× rate, 157% (n = 1) for the 1.25× rate, 335% (n = 2) for the 1.5× rate, 536% (n = 1) for the 2× rate and 472% (n = 1) for the 3× rate.

7.3.1.2 Pre-emergent application of FirstRate® + Broadstrike Dual®

Five trials conducted over two years in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha and three trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha.

Mean reported yield, expressed as a percentage of the untreated checks, for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 139% (n = 7) and for FirstRate® at 35 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 127% (n = 3).

7.3.1.3 Pre-emergent application of FirstRate® + Pursuit®

Three trials conducted over two years in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha and one trial reported tolerance following application of FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha.

Mean reported yield, expressed as a percentage of the untreated checks, for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 150% (n = 5) and for FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha was 178% (n = 1).

7.3.1.4 Pre-emergent application of FirstRate® + Dual® 960

Five trials conducted in one year in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha and five trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Dual® 960 at 2.2 L/ha.

Mean reported yield, expressed as a percentage of the untreated checks, for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 135% (n = 5) and for FirstRate® at 35 g a.i./ha plus Dual® 960 at 2.2 L/ha was 138% (n = 5).

7.3.2 Post-emergent application

7.3.2.1 Post-emergent application of FirstRate® + non-ionic surfactant + fertilizer

Twenty trials conducted over two years in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at the maximum requested use rate of 17.5 g a.i./ha. Nine trials reported yield following application of the product at 35 g a.i./ha (2 × maximum requested rate), one trial reported yield following application of the product at 44 g a.i./ha (2.5 × maximum requested rate), three trials reported yield following application of the product at 52 g a.i./ha (3 × maximum requested rate), two trials reported yield following application of the product at 70 g a.i./ha (4 × maximum requested rate) and two trials reported yield following application of the product at 104 g a.i./ha (6 × maximum requested rate).

Mean reported yield, expressed as a percentage of the untreated checks, was 143% (n = 23) for the 1× rate, 165% (n = 9) for the 2× rate, 181% (n = 1) for the 2.5× rate, 192% (n = 3) for the 3× rate, 105% (n = 2) for the 4× rate and 149% (n = 2) for the 6× rate.

7.3.2.2 Post-emergent application of FirstRate® + Pursuit® + non-ionic surfactant + fertilizer

Eight trials conducted over two years in Ontario under conventional and minimum tillage practices reported soybean yield following application of FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v and three trials reported yield following application of FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v.

Mean reported yield, expressed as a percentage of the untreated checks, for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 162% (n = 8) and for FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 144% (n = 3).

7.4 Phytotoxicity to target plants (including different varieties) or target plant products

7.4.1 Pre-emergent application

7.4.1.1 Pre-emergent application of FirstRate®

Tolerance of soybeans to the maximum proposed rate of FirstRate® at 35 g a.i./ha was evaluated in 23 field trials conducted over three years in Ontario and Quebec under conventional and minimum tillage practices and represented 17 soybean varieties. Nine trials reported tolerance following application of the product at 44 g a.i./ha (1.25 × maximum requested rate), 11 trials reported tolerance following application of the product at 52 g a.i./ha (1.5 × maximum requested rate), three trials reported tolerance following application of the product at 70 g a.i./ha (2 × maximum requested rate) and two trials reported tolerance following application of the product at 104 g a.i./ha (3 × maximum requested rate). Tolerance was assessed visually relative to an untreated check.

Tolerance differences between soil organic matter (1.7–4.7%) and variety selection was not detected. The product label includes a statement advising that extended cold, wet conditions (soil temperatures below 10EC for extended periods) or abnormally high soil moisture conditions during emergence and early crop development may cause injury symptoms on soybeans such as temporary yellowing of the leaves and crop stunting. Soybeans will quickly outgrow these symptoms once normal growing conditions resume. Data submitted for review support these statements.

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (35 g a.i./ha) was 1.6% (*n* = 10) at 7–14 DAA, 0.4% (*n* = 23) at 14–40 DAA and 0% (*n* = 23) at 41 or more DAA.

Mean reported tolerance for the 1.25× rate (44 g a.i./ha) was 0% (*n* = 4) at 7–14 DAA, 0.1% (*n* = 9) at 14–40 DAA and 0% (*n* = 4) at 41 or more DAA. Mean reported tolerance for the 1.5× rate (52 g a.i./ha) was 0% (*n* = 4) at 7–14 DAA, 0.1% (*n* = 9) at 14–40 DAA and 0% (*n* = 8) at 41 or more DAA. Mean reported tolerance for the 2× rate (70 g a.i./ha) was 0.8% (*n* = 2) at 7–14 DAA and 0% (*n* = 4) at 41 or more DAA. Mean reported tolerance for the 3× rate (104 g a.i./ha) was 0% (*n* = 2) at 41 or more DAA.

7.4.1.2 Pre-emergent application of FirstRate® + Broadstrike Dual®

Tolerance of soybeans to FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was evaluated in 16 field trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices and represented 14 soybean varieties. Nine trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha. Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for FirstRate® at 17.5 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 3.3% (*n* = 8) at 7–14 DAA, 0.5% (*n* = 20) at 14–40 DAA and 0% (*n* = 16) at 41 or more DAA and for FirstRate® at 35 g a.i./ha plus Broadstrike Dual® at 2.4 L/ha was 0.6% (*n* = 6) at 7–14 DAA, 1.4% (*n* = 8) at 14–40 DAA and 0% (*n* = 6) at 41 or more DAA.

7.4.1.3 Pre-emergent application of FirstRate® + Pursuit®

Tolerance of soybeans to FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was evaluated in 15 field trials conducted over two years in Ontario under conventional and minimum tillage practices and represented 13 soybean varieties. Seven trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha. Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha was 1.6% (*n* = 8) at 7–14 DAA, 0.1% (*n* = 20) at 14–40 DAA and 0% (*n* = 17) at 41 or more DAA and for FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha was 0% (*n* = 4) at 7–14 DAA, 0% (*n* = 8) at 14–40 DAA and 0% (*n* = 4) at 41 or more DAA.

7.4.1.4 Pre-emergent application of FirstRate® + Dual® 960

Tolerance of soybeans to FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was evaluated in 12 field trials conducted over two years in Ontario under conventional and minimum tillage practices and represented 9 soybean varieties. Fifteen trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Dual® 960 at 2.2 L/ha. Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for FirstRate® at 17.5 g a.i./ha plus Dual® 960 at 2.2 L/ha was 0.2% (*n* = 4) at 7–14 DAA, 0.8% (*n* = 9) at 14–40 DAA and 0% (*n* = 8) at 41 or more DAA and for FirstRate® at 35 g a.i./ha plus Dual® 960 at 2.2 L/ha was 0.3% (*n* = 5) at 7–14 DAA, 1.6% (*n* = 12) at 14–40 DAA and 0.7% (*n* = 10) at 41 or more DAA.

7.4.2 Post-emergent application

7.4.2.1 Post-emergent application of FirstRate® + non-ionic surfactant + fertilizer

Tolerance of soybeans to FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was evaluated in 75 field trials conducted over four years in Ontario and Quebec under conventional and minimum tillage practices and represented 22 soybean varieties. Tolerance was assessed visually relative to an untreated check.

Thirty-nine trials reported tolerance following application of the product at 35 g a.i./ha (2 × maximum requested rate), 8 trials reported tolerance following application of the product at 44 g a.i./ha (2.5 × maximum requested rate), 10 trials reported tolerance following application of the product at 52 g a.i./ha (3 × maximum requested rate), 4 trials reported tolerance following application of the product at 70 g a.i./ha (4 × maximum requested rate) and 4 trials reported tolerance following application of the product at 104 g a.i./ha (6 × maximum requested rate).

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (17.5 g a.i./ha) was 1.7% (*n* = 64) at 7–14 DAA, 0.6% (*n* = 67) at 14–40 DAA and 0% (*n* = 34) at 41 or more DAA.

Mean reported tolerance for the 2× rate (35 g a.i./ha) was 1.5% (*n* = 32) at 7–14 DAA, 0.2% (*n* = 29) at 14–40 DAA and 0% (*n* = 17) at 41 or more DAA. Mean reported tolerance for the 2.5× rate (44 g a.i./ha) was 0.5% (*n* = 6) at 7–14 DAA, 0.1% (*n* = 6) at 14–40 DAA and 0% (*n* = 3) at 41 or more DAA. Mean reported tolerance for the 3× rate (52 g a.i./ha) was 0.6% (*n* = 5) at 7–14 DAA, 0.1% (*n* = 4) at 14–40 DAA and 0% (*n* = 7) at 41 or more DAA. Mean reported tolerance for the 4× rate (70 g a.i./ha) was 0% (*n* = 4) at 41 or more DAA. Mean reported tolerance for the 6× rate (104 g a.i./ha) was 0% (*n* = 4) at 41 or more DAA.

7.4.2.2 Post-emergent application of FirstRate® + Pursuit® + non-ionic surfactant + fertilizer

Tolerance of soybeans to FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was evaluated in 21 field trials conducted over two years in Ontario and Quebec under conventional and minimum tillage practices and represented 15 soybean varieties. Eight trials reported tolerance following application of FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v. Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for FirstRate® at 17.5 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 3.5% (*n* = 20) at 7–14 DAA, 1.5% (*n* = 18) at 14–40 DAA and 0% (*n* = 7) at 41 or more DAA and for FirstRate® at 35 g a.i./ha plus Pursuit® at 312 mL/ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was 0.2% (*n* = 8) at 7–14 DAA, 0.2% (*n* = 6) at 14–40 DAA and 0% (*n* = 4) at 41 or more DAA.

7.5 Observation on undesirable or unintended side effects

7.5.1 Impact on succeeding crops

7.5.1.1 Pre-emergent application

7.5.1.1.1 Field corn

Tolerance of field corn planted the year following a pre-emergent application of FirstRate® at 35 g a.i./ha was evaluated in nine trials conducted over four growing seasons testing 12 varieties with a soil organic matter range of 1.3–4.0% in Ontario, Quebec and U.S. border states.

Four trials reported tolerance following application of the product at 52 g a.i./ha (1.5 × maximum requested rate), four trials reported tolerance following application of the product at 70 g a.i./ha (2 × maximum requested rate) and four trials reported tolerance following application of the product at 104 g a.i./ha (3 × maximum requested rate). Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (35 g a.i./ha) was 0.1% (n = 23) early in the growing season and 0% (n = 20) late in the growing season.

Mean reported tolerance for the 1.5× rate (52 g a.i./ha) was 0% (n = 18) early in the growing season and 0% (n = 18) late in the growing season. Mean reported tolerance for the 2× rate (70 g a.i./ha) was 0% (n = 18) early in the growing season and 0% (n = 18) late in the growing season. Mean reported tolerance for the 3× rate (104 g a.i./ha) was 0% (n = 18) early in the growing season and 0% (n = 18) late in the growing season.

7.5.1.1.2 Winter wheat

Tolerance of winter wheat planted the fall of the same year as a pre-emergent application of FirstRate® at 35 g a.i./ha was evaluated in six trials conducted over two growing seasons testing 2 varieties with a soil organic matter range of 1.5–2.7% in Ontario.

Five trials reported tolerance following application of the product 52 g a.i./ha (1.5 × maximum requested rate), three trials reported tolerance following application of the product at 70 g a.i./ha (2 × maximum requested rate) and three trials reported tolerance following application of the product at 104 g a.i./ha (3 × maximum requested rate). Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (35 g a.i./ha) was 0% (n = 6) early in the growing season and 0% (n = 4) late in the growing season.

Mean reported tolerance for the 1.5× rate (52 g a.i./ha) was 0% (*n* = 5) early in the growing season and 0% (*n* = 4) late in the growing season. Mean reported tolerance for the 2× rate (70 g a.i./ha) was 0% (*n* = 3) early in the growing season and 0% (*n* = 2) late in the growing season. Mean reported tolerance for the 3× rate (104 g a.i./ha) was 0% (*n* = 3) early in the growing season and 0% (*n* = 2) late in the growing season.

7.5.1.2 Post-emergent application

7.5.1.2.1 Field corn

Tolerance of field corn planted the year following a post-emergent application of FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was evaluated in 12 trials conducted over three growing seasons testing 13 varieties with a soil organic matter range of 1.5–4.4% in Ontario and U.S. border states.

Twelve trials reported tolerance following application of the product at 35 g a.i./ha (2 × requested rate), four trials reported tolerance following application of the product at 52 g a.i./ha (3 × requested rate), eight trials reported tolerance following application of the product at 70 g a.i./ha (4 × requested rate) and four trials reported tolerance following application of the product at 104 g a.i./ha (6 × requested rate). Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (17.5 g a.i./ha) was 0% (*n* =24) early in the growing season and 0% (*n* = 22) late in the growing season. Mean reported tolerance for the 2× rate (35 g a.i./ha) was 0.6% (*n* = 21) early in the growing season and 0.4% (*n* = 25) late in the growing season. Mean reported tolerance for the 3× rate (52 g a.i./ha) was 0% (*n* = 19) early in the growing season and 0% (*n* = 18) late in the growing season. Mean reported tolerance for the 4× rate (70 g a.i./ha) was 0.1% (*n* = 19) early in the growing season and 0.4% (*n* = 22) late in the growing season. Mean reported tolerance for the 6× rate (104 g a.i./ha) was 0% (*n* = 18) early in the growing season and 0% (*n* = 18) late in the growing season.

7.5.1.2.2 Winter wheat

Tolerance of winter wheat planted in the fall of the same year as a post-emergent application of FirstRate® at 17.5 g a.i./ha plus non-ionic surfactant at 0.25% v/v plus liquid fertilizer (28-0-0 or 32-0-0) at 2.5% v/v was evaluated in 10 trials conducted over four growing seasons testing 13 varieties with a soil organic matter range of 1.5–4.4% in Ontario and U.S. border states.

Six trials reported tolerance following application of the product at 35 g a.i./ha (2 × requested rate), three trials reported tolerance following application of the product at 52 g a.i./ha (3 × requested rate), four trials reported tolerance following application of the product at 70 g a.i./ha (4 × requested rate) and three trials reported tolerance following

application of the product at 104 g a.i./ha (6 × requested rate). Tolerance was assessed visually relative to an untreated check.

Mean reported tolerance, expressed as percent crop injury, for the 1× rate (17.5 g a.i./ha) was 0% (*n* = 8) early in the growing season and 0% (*n* = 10) late in the growing season.

Mean reported tolerance for the 2× rate (35 g a.i./ha) was 0% (*n* = 6) early in the growing season and 0% (*n* = 6) late in the growing season. Mean reported tolerance for the 3× rate (52 g a.i./ha) was 0% (*n* = 3) early in the growing season and 0% (*n* = 3) late in the growing season. Mean reported tolerance for the 4× rate (70 g a.i./ha) was 0% (*n* = 5) early in the growing season and 0% (*n* = 4) late in the growing season. Mean reported tolerance for the 6× rate (104 g a.i./ha) was 0% (*n* = 3) early in the growing season and 0% (*n* = 4) late in the growing season.

7.6 Economics

Soybeans are one of Canada's most important agricultural crops. In the 1999 growing season, 999,000 ha were seeded to produce a total of 2.77 million tonnes with an average yield of 2.80 tonnes/ha. Ontario accounted for about 85% of Canada's 1999 production by seeding 860,000 ha to produce a total of 2.34 million tonnes with an average yield of 2.70 tonnes/ha.

The majority of soybeans produced are crushed to be utilized in making soybean oil products. Soybeans may also be utilized in whole soybean products and soybean protein products.

Weed control is essential for successful soybean production. Unchecked weed growth can reduce soybean growth and yield owing to competition for nutrients, water and light. Crop loss as a result of weed competition is directly related to weed pressure. Harvest operations can also be more difficult and costly because of weed presence.

Data submitted for the use of FirstRate® has demonstrated that acceptable control of certain weeds common in soybean producing areas of Eastern Canada will be provided by the product when used according to label directions. The product will provide soybean producers with the option of pre-emergent or post-emergent control of weeds that could reduce yield and quality of soybeans and contribute to increased harvest costs.

7.7 Sustainability

7.7.1 Survey of alternatives

Several herbicides that may be used alone or in various tankmix combinations are registered for weed control in soybeans. Such products include acifluorfen, metribuzin, bentazon, clorimuron-ethyl, clomazone, ethalfluralin, flumetsulam, glyphosate,

imazethapyr, imazamox, linuron, thifensulfuron-methyl, metolachlor, pendimethalin and trifluralin.

7.7.2 Compatibility with current management practices including integrated pest management

Application of FirstRate® would not exclude the sequential use of other herbicides with different modes of action for control of annual and perennial species not controlled by the product alone or when tankmixed.

Nonchemical means of weed control include cultivation and crop rotation. The pre-emergent use of FirstRate® in conventionally tilled soybeans would not exclude the use of cultivation. Recropping data indicates winter wheat may be planted in the fall of the year of application of FirstRate® and field corn may be planted the year following application of FirstRate®.

7.7.3 Contribution to risk reduction

FirstRate® alone will provide control of certain broadleaf weeds in soybeans at a low amount of active ingredient per hectare. The residual control provided by FirstRate® may reduce the need for sequential treatment for the control of weed escapes. Broad-spectrum weed control, including grass weeds, can be obtained with a single application by utilizing the approved tankmixes.

The use of water soluble packets will reduce the risk of exposure to mixers, handlers and applicators.

7.8 Conclusions

The data made available indicate that soybeans grown in Eastern Canada are expected to be acceptably tolerant to a pre-emergent application of 17.5–35 g a.i./ha when applied according to label directions. Control of common ragweed, velvetleaf and lambsquarters can be expected following application of 17.5 g a.i./ha. Control of cocklebur and heavy infestations of lambsquarters can be expected following application of 35 g a.i./ha. FirstRate® may be tankmixed with Broadstrike Dual®, Pursuit® or Dual® 960 to provide additional broadleaf and grass control.

The data made available indicate that soybeans grown in Eastern Canada are expected to be acceptably tolerant to a post-emergent application of 17.5 g a.i./ha plus non-ionic surfactant and fertilizer when applied according to label directions. Control of common ragweed, velvetleaf, giant ragweed, cocklebur and jimsonweed can be expected following application of 17.5 g a.i./ha. FirstRate® may be tankmixed with Pursuit® to provide additional broadleaf and grass control.

Winter wheat may be sown the fall of the year of application and field corn may be sown in the spring following an application of FirstRate®.

7.8.1 Summary

Crop:	soybeans (*Glycine max*), conventional and minimum tillage
Varieties:	all (no restrictions)
Product:	FirstRate®
Application timing:	pre-emergent or post-emergent to soybeans and weeds
Application method:	ground equipment only do not apply by air
Number of applications per year:	one
Rates of application:	pre-emergent: 17.5–35 g a.i./ha post-emergent: 17.5 g a.i./ha + non-ionic surfactant + fertilizer
Spray volume:	100–300 L/ha
Spray pressure:	135–270 kPa
Weed species controlled:	**pre-emergent at 17.5 g a.i./ha** common ragweed velvetleaf lambsquarters **pre-emergent at 35 g a.i./ha** cocklebur heavy infestations of lambsquarters **post-emergent at 17.5 g a.i./ha + non-ionic surfactant + fertilizer** common ragweed velvetleaf lambsquarters giant ragweed jimsonweed
Tankmix option:	**pre-emergent**

Broadstrike Dual® at 2.4 L/ha
Pursuit® at 312 mL/ha
Dual® 960 at 2.2. L/ha

post-emergent
Pursuit® at 312 mL/ha

Rotational crops: Winter wheat (fall of the year of application)
Field corn (spring of the year following application)

8.0 Toxic Substances Management Policy

During the review of cloransulam-methyl and FirstRate®, the PMRA has taken into account the federal TSMP[2] and has followed DIR99-03.[3] It has been determined that this product does not meet TSMP Track-1 criteria because of the following.

- Cloransulam-methyl does not meet the criteria for persistence. Its values for half-life in water (25.6 days), soil (14–22 days) and sediment (16 days, in a water and sediment system) are below the TSMP Track-1 cut-off criteria for water (≥182 days), soil (≥182 days) and sediment (≥365 days). Persistence in air, although not known, is not a concern because there is a low potential for volatilization; the low volatility did not trigger a phototransformation study in air.
- Cloransulam-methyl is not bioaccumulative. Studies have shown that log K_{ow} is 1.12 at pH 5, which is below the TSMP Track-1 cut-off criterion of ≥5.0, so a fish bioaccumulation study was not triggered. The mammalian toxicology and livestock and poultry metabolism studies support the conclusion that cloransulam-methyl does not bioaccumulate.
- The toxicity of cloransulam-methyl is discussed in Chapters 3 and 6.
- Cloransulam-methyl (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.
- The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

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2 The federal Toxic Substances Management Policy is available through Environment Canada's web site at www.ec.gc.ca/toxics.

3 The PMRA's *Strategy for Implementing the Toxic Substances Management Policy*, DIR99-03, is available through the PMRA web site at www.hc-sc.gc.ca/pmra-arla.

9.0 Overall Conclusions

The product chemistry data for cloransulam-methyl technical material and the end-use product, FirstRate®, are complete. The technical material was fully characterized and the specifications were supported by the analysis of five batches of the technical product for active and impurities using a specific validated method of analysis. The technical material does not contain any impurities known to be toxic microcontaminants as identified in Part 2.13.4 of DIR98-04 or any impurities which meet the TSMP Track-1 criteria. The required physical and chemical properties of technical material and of the end-use products were determined using acceptable methods. A fully validated HPLC method for the determination of active in the formulation was submitted. The end-use product is not known to contain any U.S. EPA inert List 1 or 2 formulants or any known TSMP Track-1 substances.

In rats, orally administered cloransulam-methyl is rapidly absorbed and eliminated. At single oral doses of 5 or 1000 mg/kg bw, or repeat oral doses of 5 mg/kg bw/d for 15 days, the overall recovery of the administered dose in 72 h in the excreta is over 90%. There are sexual differences in the metabolism of orally administered cloransulam-methyl. Female rats appear to eliminate orally administered cloransulam-methyl more efficiently, with half-lives of elimination of 6.5–7.9 h, while those for males were 8–13.2 h. With a single low dose of 5 mg/kg bw, urinary elimination predominated in female rats (68–80%), while fecal excretion accounted for only about 21%. For the males, elimination in the urine and feces was similar (41–52%). With a single high dose of 1000 mg/kg bw, elimination was mainly fecal, at 78–83% in both male and female rats. Urinary excretion accounted for 10–17% of the administered dose. Residues in tissues and the carcass were low, <5% of the administered doses, and the highest levels were found in the blood, kidneys and liver (0.03–0.04% of administered dose/g tissue). Analyses of metabolite profiles revealed up to 11 and 8 peaks in the urine and feces, respectively. The metabolites identified were unchanged parent, 4-OH-phenyl-XDE-565, OH-pyrimidine-XDE-565, XDE-565-7-*N*-acetylcysteine in the urine, and unchanged parent compound and 4-OH-phenyl-XDE-565 in the feces. The unchanged parent compound accounted for over 70% of the fecal metabolites in both male and female rats that were dosed with cloransulam-methyl at 1000 mg/kg bw. The unchanged parent compound also accounted for a high percentage of the urinary metabolites in female rats given the low dose (5 mg/kg bw/d) of cloransulam-methyl, but accounted for only 22% of the urinary metabolites in the males. Metabolism of cloransulam-methyl is similar after a single oral dose of 5 mg/kg bw or after 15 daily oral doses of 5 mg/kg bw/d.

Technical cloransulam-methyl is of low acute toxicity by the oral (rat), dermal (rabbit) and inhalation (rat) routes of exposure and the respective acute LD_{50} or LC_{50} are >5000 mg/kg bw, >2000 mg/kg bw and >3.77 mg/L (actual). When tested in rabbits, cloransulam-methyl was minimally irritating to the eye and not a skin irritant. The dermal sensitization potential of cloransulam-methyl could not be assessed due to a deficient study. However, the dermal sensitization data generated with an end-use formulation of cloransulam-methyl (FirstRate® Herbicide) demonstrated the lack of dermal sensitization

potential and, because of the high percentage (86%) of cloransulam-methyl in the formulation, the data could be used to fill the deficient toxicological database of the technical active. It is therefore estimated that technical cloransulam-methyl is unlikely to be a dermal sensitizer.

FirstRate® Herbicide is also of low acute toxicity by the oral (LD_{50} in rats >5000 mg/kg bw) and dermal (LD_{50} in rabbits >2000 mg/kg bw) routes of exposure. It is not an eye or skin irritant when tested in rabbits, nor is it a dermal sensitizer when tested in the guinea pig. No acute inhalation toxicity data are available for FirstRate® Herbicide. However, based on the high percentage of cloransulam-methyl in the formulation and no evidence of inhalation toxicity of other formulant ingredients in the formulation, the acute inhalation toxicity of FirstRate® Herbicide is considered to be similar to that of the technical active, i.e., low acute inhalation toxicity. After 21 days of dermal exposure to FirstRate® Herbicide at doses up to 1000 mg/kg bw/d in rabbits, the only treatment-related effect observed was anemia in the females at the highest dose tested. Treatment had no effects on mortality, clinical signs, food consumption, body weight, clinical chemistry, organ weight or gross and histopathology.

Short-term toxicity data are available after dietary exposure to the mouse (90-day) and dog (two-week and one-year), as well as to rabbits after dermal exposure (21-day). In both the mouse and dog, dietary exposure to cloransulam-methyl resulted in liver pathology and effects on a few clinical chemistry parameters that are related to liver pathology (e.g., higher serum levels of lower enzymes such as alkaline phosphatase and SGPT). Based on liver pathology, the LOAEL and NOAEL for male mice are 100 and 50 mg/kg bw/d, respectively, and those for female mice are 500 and 100 mg/kg bw/d, respectively. Also based on liver pathology, the LOAEL and NOAEL for male and female dogs are 10 and 5 mg/kg bw/d, respectively. The findings of the 21-day dermal toxicity study of cloransulam-methyl in rabbits mimic those of the study with FirstRate®, i.e., the only effect observed was anemia in female rabbits at the highest dose level tested (1000 mg/kg bw/d). Thus, the short-term dermal toxicity LOAEL and NOAEL for female rabbits are 1000 and 500 mg/kg bw/d, respectively, and the NOAEL for male rabbits is 1000 mg/kg bw/d, the highest dose level tested.

Long-term toxicity data in mice and rats did not demonstrate any oncogenic potential for cloransulam-methyl. The treatment-related toxic effects were perineal staining (rats), reduction in body weight and body-weight gains (male and female mice at 1000 mg/kg bw/d, female mice at 100 mg/kg bw/d, male and female rats at 325 mg/kg bw/d) and pathology of the liver, kidneys and possibly the thyroids. Liver pathology was evident in mice only and was in the form of hypertrophy of centrilobular and mid-zonal hepatocytes (male and female mice at 1000 mg/kg bw/d, male mice at 100 mg/kg bw/d) and increased cytoplasmic eosinophilia (male and female mice at 1000 mg/kg bw/d, male mice at 100 mg/kg bw/d). Kidney changes in mice differed from those in rats. In the mouse, the changes involving lower kidney weight (male and female mice at 1000 mg/kg bw/d) and decreased renal tubular vacuolation and cytoplasmic fat (male mice at 1000 mg/kg bw/d) were unlikely to be of toxicological concern. In the rat, kidney changes were

toxicologically significant and included hypertrophy of collecting ducts (male and female rats at 325 mg/kg bw/d), tubular vacuolation (male and female rats at 75 and 325 mg/kg bw/d) and mineralization (male and female rats at 325 mg/kg bw/d, male rats at 75 mg/kg bw/d). Thyroid effects, in the form of follicular hyperplasia and hypertrophy, were observed in male rats only and only at the highest dose level tested. Based on effects on body weight and liver pathology, the LOAEL and NOAEL in the mouse are 100 and 10 mg/kg bw/d, respectively. In the rats, based on body-weight effects and kidney pathology, the LOAEL and NOAEL are 75 and 10 mg/kg bw/d, respectively.

Mutagenicity data assessing gene mutation in microbial and mammalian cell systems, as well as in vitro and in vivo chromosome aberration did not demonstrate genotoxic effects for cloransulam-methyl. DNA damage and repair end points were not assessed.

A two-generation reproductive toxicity study in rats showed that cloransulam-methyl at dietary levels of up to 500 mg/kg bw/d had no effects on reproductive parameters. But, this dietary level caused a slight increase in F_1 pup mortality during lactation days 0–4. The viability indices of the F_1 pups are still within the historical range. The toxic effect observed in the F_1 offspring was probably related to systemic toxicity exhibited by the parental animals: lower body weight and body-weight gains in P_1 males (pre-mating period) and females (pre-mating and gestation periods) at 500 mg/kg bw/d. In parental animals, organ and tissue pathology was evident in the kidneys and possibly the thyroid. Kidney changes included higher relative kidney weight (male rats at 100 and 500 mg/kg bw/d), hypertrophy of the collecting tubules and vacuolation consistent with fatty changes of proximal tubules (mid- and high-dose males and females). Diffuse hypertrophy of thyroid follicular epithelial cells was observed in high-dose males and females. Based on the kidney effect, the LOAEL and NOAEL for parental toxicity are 100 and 10 mg/kg bw/d, respectively. The LOAEL and NOAEL for offspring toxicity are 500 and 100 mg/kg bw/d, respectively. The NOAEL for reproductive toxicity is 500 mg/kg bw/d, the highest dose level tested. Since the offspring viability effect in the F_1 was within historical control range, the effect was not considered to indicate a quantitative sensitivity of the young.

Teratogenicity of cloransulam-methyl was assessed in the rat and rabbit. In the rat, oral doses of up to 1000 mg/kg bw/d, administered during gestation days 6–15, did not elicit any maternal or developmental toxicity. Thus, the NOAEL for maternal and developmental toxicity is 1000 mg/kg bw/d. In the rabbit, cloransulam-methyl at an oral dose of 300 mg/kg bw/d, administered during gestation days 7–19, led to maternal toxicity, manifested as reduced food intake, lower body weight, lower fecal output and two dams aborted. Thus, the LOAEL and NOAEL for maternal toxicity are 300 and 100 mg/kg bw/d, respectively. There were no effects on developmental toxicity, and the NOAEL for developmental toxicity is 300 mg/kg bw/d, the highest dose level tested.

The acute neurotoxicity potential of cloransulam-methyl was assessed in rats that were given single oral doses of up to 2000 mg/kg bw. After dosing, the rats were assessed for mortality, clinical toxic signs, body-weight, motor activity and functional observational

battery. There were no treatment-related effects on the parameters assessed. Thus, the NOAEL for acute neurotoxicity is 2000 mg/kg bw/d.

At this time, there is no evidence in the animal data to suggest an alteration of endocrine function as a result of exposure to cloransulam.

Cloransulam-methyl provides commercially acceptable crop tolerance to soybeans in conventional and minimum tillage practices when applied pre-emergent or post-emergent according to label directions. FirstRate® will control common ragweed, velvetleaf and lambsquarters when applied pre-emergent at 17.5 g a.i./ha. Pre-emergent application at 35 g a.i./ha will provide control of cocklebur and heavy infestations of lambsquarters. When applied as a pre-emergent treatment, FirstRate® may be tankmixed with Broadstrike Dual® at 2.4 L/ha, Pursuit® at 312 mL/ha or Dual® 960 at 2.2 L/ha. FirstRate® will control common ragweed, velvetleaf, giant ragweed, cocklebur and jimsonweed when applied post-emergent at 17.5 g a.i./ha plus non-ionic surfactant and fertilizer. When applied as a post-emergent treatment, FirstRate® may be tankmixed with Pursuit®. Winter wheat may be planted in the fall of the year of application and field corn may be planted in the spring of the year following an application of FirstRate®.

The nature of the residue in plants and animals is adequately understood. The ROC in plant and animal products is the parent compound, cloransulam-methyl and its acid, cloransulam, calculated as parent ester. The data gathering and enforcement analytical methodology (GC – thermionic specific detector) is valid for the quantitation of cloransulam-methyl equivalent residues in food matrices. The residues of cloransulam-methyl equivalents are stable under freezer storage. Processing of the raw agricultural commodities indicates no concentration of the cloransulam-methyl equivalent residues in the soybean seed or in the oil fractions. Supervised residue trials conducted throughout the U.S. and Canada using the end-use product containing cloransulam-methyl at the registered rate in or on soybean are sufficient to establish an MRL.

The DEEM™ Software, which utilized data from the 1994–1996 CSFII, was used for purposes of assessing the potential chronic dietary exposure to residues of cloransulam-methyl. It was estimated that chronic dietary exposure to cloransulam-methyl from food and water will utilize 10% of the ADI (0.05 mg/kg/d) for the total population, including infants, children, adults and seniors.

Based on our evaluation, it is concluded that the following MRL should be promulgated in Table II of Division 15 of the *Food and Drugs Act* and Regulations: residues of cloransulam-methyl (methyl 3-chloro-2-(5-ethoxy-7-fluoro[1,2,4]triazolo[1,5-*c*]pyrimidin-2-ylsulfonamido)benzoate and its acid, cloransulam, calculated as parent ester in or on soybeans at 0.01 ppm.

Acceptable MOEs were determined for the farmer and the custom applicator applying FirstRate® herbicide to soybeans.

As the product would be applied pre-emergence or post-emergence prior to the flowering stage of soybean, re-entry activities should be minimal. As such, exposure and risk to re-entry workers would be minimal. A restricted entry interval is not required for the soybean use.

Cloransulam-methyl is not persistent in soil and water, and it will not volatilize from water or moist soil. Microbial-mediated transformation and phototransformation in water are the principal routes of transformation. The major transformation products were XDE-565 acid, 5-OH-XDE-565 and 5-OH-XDE-565-acid. CO_2 is the only volatile transformation product. Based on the results of adsorption studies, cloransulam-methyl and its transformation products in soil have a potential for leaching to ground water. The relatively short half-life of cloransulam-methyl should partially mitigate its leaching. The use of FirstRate® will result in a risk to non-target terrestrial and aquatic plants. Buffer zones have been proposed to mitigate this risk. Other non-target species are not considered to be at risk from the use of FirstRate®.

10.0 Regulatory Decision

Cloransulam-methyl and end-use product FirstRate® have been granted temporary registrations for use on soybeans in Eastern Canada, pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation and review of the following:

- analytical methodologies for animal tissues;
- a description of the persistence and mobility of the major soil transformation products; and
- two short-term toxicity studies.

List of abbreviations

'A'	[aniline-UL]XDE-565
ADI	acceptable daily intake
a.i.	active ingredient
ALS	acetolactate synthase
ARfD	acute reference dose
ASTP	XDE-565-sulfonamide
bw	body weight
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CSFII	Continuing Survey of Food Intake by Individuals
d	day(s)
DAA	days after application
DEEM™	Dietary Exposure Evaluation Model™
DIP–MS	direct insertion probe
DMSO	dimethylsulfoxide
DT_{50}	time required for 50% dissipation
DT_{90}	time required for 90% dissipation
dw	dry weight
EC_{25}	effective concentration for 25% of the population
EC_{50}	mean effective concentration
EEC	expected environmental concentration
EP	end-use product
F_1	first generation offspring
F_2	second generation offspring
GAP	good agricultural practices
GC	gas chromatograghy
GSD	geometrical standard deviation
h	hour(s)
Hb	hemoglobin concentration
Hct	hematocrit value
HDPE	high-density polyethylene
HDT	highest dose tested
HGPRT	hypoxanthine-guanine phosphoribosyl
HPLC	high performance liquid chromatography
ILV	interlaboratory validation
LC_{50}	mean lethal concentration
LD_{50}	mean lethal dose
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEL	lowest observable effect level
LOQ	limit of quantitation
min	minute(s)
MMAD	mass mediam aerodynamic diameter
MN-PCE	micro-nucleated polychromatic erythrocytes

MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MS	mass spectrometry
NOAEL	no observable adverse effect level
NOEC	no observable effect concentration
NZW	New Zealand white
P_1	first generation parents
P_2	second generation parents
PAM I	Pesticide Analytical Manual Volume I
PDI	potential daily intake
PET	polyethylene terphthalate
PHED	Pesticide Handler's Exposure Database
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
r	correlation coefficient
RBC	red blood cell count
ROC	residue of concern
RSD	relative standard deviation
SD	Sprague–Dawley
SGPT	serum glutamate pyruvate traisaminase
TGAI	technical grade of active ingredient
'TP'	[triazolopyrimidine-7,9]XDE-565
TPSA	triazolopyrimidine sulfonic acid (XDE-565-sulfonic acid)
TRR	total radioactive residues
TSMP	Toxic Substances Management Policy
UV	ultraviolet
v/v	volume per volume
WDG	water dispersable granule

Appendix I Residue summary table

PARAMETER	PERTINENT INFORMATION
Chemical	Cloransulam-methyl (XDE-565)
Formulation	FirstRate® Herbicide Water Dispersible Granules
Crop	Soybean (seed)
Type of application	Ground
No. of applications	One
Timing	Pre-emergent **or** early post-emergent in Eastern Canada
Rate and application and season	Pre-emergent: 35 g a.i./ha; Early post-emergent: 17.5 g a.i./ha
Label restrictions	Do not harvest soybeans for forage or hay. Do not apply by air. Do not harvest before 65 days after the last application.
Plant metabolism ***Crop*** ***Radiolabel positions*** ***Proposed metabolic pathway***	Soybean Aniline 'A' and triazolopyrimidine 'TP' label Homoglutathione adducts and photolysis ('A' fragments and 'TP' derived products) Post-emergent: [5X proposed GAP for post-emergent application] Soybean seed: no parent or metabolites detected Forage: 'TP' derived metabolite; sulfonic acid (TPSA) ROC: cloransulam-methyl and its acid, cloransulam, calculated as parent ester
Animal metabolism ***Goat*** ***Hen***	Major route of elimination via excretion (>99.7% of TRRs) Residues in milk and tissues were mainly the parent compound and its acid metabolite (XDE-acid). Residues in eggs and tissues were mainly the parent compound and 'TP' derived products (ASTP). ROC: cloransulam-methyl and its acid, cloransulam, calculated as parent ester

Analytical methodology: plant ***Data gathering method*** ***Confirmation method*** ***Enforcement method*** ***ILV***	ROC: cloransulam-methyl and its acid, cloransulam, calculated as parent ester GC–MS; XDE-565 derivatized to *N*-methyl-XDE-565; internal standard *N*-ethyl-XDE-565 LOQ: 0.01 ppm LOD: 0.005 ppm Soybean grain: 85±6% Forage: 87±7% Hay: 89±9% GC–MS can detect and quantitate analytes as confirmatory method Equivalent to data gathering method: ILV indicated good reliability and reproducibility
Supervised residue trials	[1.0–1.9X proposed GAP] Soybean seed: pre-emergent: <LOQ (0.01 ppm); post-ermergent: <LOQ (0.01 ppm) Forage: post-emergent: maximum residues 0.321 ppm Hay: post-emergent: maximum residues 0.121 ppm
Residue decline	Forage: 0-d PHI: 0.9 ppm; 14-d PHI: 0.01 ppm; 21/28/35-d PHI: <0.01 ppm Hay: 0-d PHI: 3.3 ppm; 14-d PHI: 0.03 ppm; 21/28/35-d PHI: <0.02 ppm
Storage stability	At –20EC, residues of cloransulam-methyl are stable up to 6 months (forage and hay) and up to 1 year in soybean seeds.
Confined rotational crops	Soybean: 0 month Wheat: 4 months Corn: 9 months
Processing studies	Soybean from residue trials treated at 5X the post-emergent recommended label rate were processed into meal, hulls, grain dust fractions, crude oil and refined oil. Residues of XDE-565 in the soybeans and all fractions were below the LOD of 0.005 ppm.
Dietary exposure	The PDI, including a 10% water allocation, was less than 10% of the ADI (0.05 mg/kg bw) for the total population, including infants, children and seniors.
Proposed MRLs	Soybean seed: 0.01 ppm

Appendix II Summary table of toxicology studies on cloransulam-methyl (TGAI) and FirstRate® herbicide (EP)

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
METABOLISM			
In a metabolism study ^{14}C-XDE-565, uniformly ^{14}C-labeled in the aniline ring (purity of unlabeled XDE-565 = 97.3%) was administered to 5 Fischer 344 rats/sex/dose by gavage either as a single dose of 5 or 1000 mg ^{14}C-XDE-565/kg bw or as 14 daily oral dose of 5 mg/kg bw/d of non-radiolabeled XDE-565 followed by a single 5 mg/kg bw oral dose of ^{14}C-XDE-565 on day 15. Excretion of radioactivity (^{14}C) was followed for 72 h post-dosing. The rats were then terminated and radioactivity in tissues and carcass were measured. Urine and fecal samples were analyzed by HPLC and DIP–MS. Overall 91–102% of the administered radioactivity in each dose regiment was recovered. The overwhelming percentage of the radioactivity was recovered in urine and feces. However, there were both sex and dose differences. At the low dose of 5 mg/kg bw, males excreted nearly equivalent amounts of radioactivity in urine and feces (41–52%) while females excreted approximately 3.5 times more radioactivity in urine than in feces (68–80% versus 21%). At the high dose of 1000 mg/kg bw, fecal excretion of radioactivity predominated, 83% of the administered radioactivity was eliminated in the feces of males and 78% in females. Urinary elimination was 10 and 17% in males and females, respectively. Half-lives calculated from the elimination of the 5 mg/kg bw doses were 6.5 h for females and 8–8.5 h for males, while the half-lives following the 1000 mg/kg bw dose were 7.9 h for females and 13.2 h for males. Only a small fraction (#2.3%) of the administered radioactivity remained in the tissues and carcass 72 h post-dosing. Blood, kidneys and liver contained the highest concentrations of radioactivity (i.e., 0.04–0.03% dose/g). The remaining tissues contained #0.018% dose/g. Analysis of metabolite profile using HPLC indicated up to 10 peaks found in urine and 3 in feces. Females eliminated a greater percentage of the 5 mg/kg bw dose in urine as unchanged XDE-565 than males (-50% versus 22%). Males eliminated a greater percentage of the 5 mg/kg bw dose in the feces as metabolites (-28% versus 10%). Both sexes eliminated 15–22% of the 5 mg/kg bw dose in the urine as metabolites. Less than 8% of the 5 mg/kg bw dose was excreted in the feces unchanged but over 70% of the 1000 mg/kg bw dose was excreted as unchanged XDE-565 in the feces. The only metabolite identified had a hydroxyl group in the aromatic ring of XDE-565. Incomplete absorption of the 1000 mg/kg dose is used to account for the dose dependent differences observed in the disposition of XDE-565. Sex dependent differences in disposition of the 5 mg/kg bw dose were traced to more efficient elimination of unchanged XDE-565 by the female kidneys.			
In a second metabolism study, ^{14}C-XDE-565 (99% purity), uniformly labelled at the 7 and 9 positions on the triazolo-pyrimidine ring, was administered to 3 Fischer 344 rats/sex by gavage as a single dose of 5 mg/kg bw/d. Approximately 94% of the administered dose was recovered in urine, feces, cage wash and tissues and carcass. Clear sex-related differences in the routes of elimination were observed. Male rats excreted about equal amounts of radioactivity in the urine (37–39%) and feces (48–51%). In females, the principal excretion route was the urine (70–72%) while the feces (20–22%) was the minor excretion route. The tissues and carcass accounted for less than 5% of the administered dose at 72 h post-dosing for both sexes. Characterization of metabolites by HPLC indicated up to 11 separate radiolabelled peaks in the urine and up to 8 peaks in fecal samples. The identified urinary metabolites were the unchanged parent compound, 4-OH-phenyl-XDE-565, OH-pyrimidine-XDE-565 and XDE-565-7-*N*-acetylcysteine. The identified fecal metabolites were the unchanged parent compound and 4-OH-phenyl-XDE-565. The metabolism data indicated that the excretion and metabolism of ^{14}C-XDE-565 labeled on the triazolo-pyrimidine ring were similar to the excretion and metabolism of ^{14}C-XDE-565 labeled on the aniline ring.			

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
ACUTE STUDIES: Technical active			
Oral	**Cloransulam-methyl** 97.3%, AGR 293032 rat, Fischer 344; 5/sex 5000 mg/kg bw in 50% solution (9:1 corn oil: acetone) by gavage	LD_{50}: **%** + **&** > 5000 mg/kg bw	No mortality, clinical signs, gross pathology; all rats gained weight **Low toxicity**
Dermal	**Cloransulam-methyl** 97.3%, AGR 293032 rabbit, NZW 2000 mg/kg bw; 5/sex	LD_{50}: **%** + **&** > 2000 mg/kg bw	No mortality, clinical signs, gross pathology, all animals gained weight; skin reaction was apparently not assessed **Low toxicity**
Inhalation (4-h nose-only)	**Cloransulam-methyl** 97.3%, AGR 293032 rat, Fischer 344; 5/sex 3.77 mg/L (actual) 9.64 mg/L (nominal) MMAD ± GSD = 1.86 Fm ± 2.63	LC_{50}: **%** + **&** > 3.77 mg/L (actual)	No mortality, clinical signs, gross pathology, all animals lost weight initially but gained weight by day 8 **Low toxicity**
Eye irritation	**Cloransulam-methyl** 97.3%, AGR 293032 0.1 g/eye rabbit, NZW; 1 **%** + 5 **&**	MAS at 1 h = 3/110	Maximum average irritation scores at 1, 24, 48 and 72 h = 3.0, 0.67, 0, 0 of 110, respectively **Minimally irritating**
Skin irritation	**Cloransulam-methyl** 97.3%, AGR 293032 0.5 g/rabbit rabbit, NZW	Maximum irritation score (MIS) = 0/8	No skin reactions at 0.5, 24, 48 and 72 h post-dosing **Non-irritating**
Skin sensitization (Buehler method)	**Cloransulam-methyl** 97.3%, AGR 293032 guinea pig, Hartley albino induction: 0.4 g, 100% challenge: 0.4 g, 100%		Study is rejected because the test article was not moistened with a vehicle such as water. Based on the dermal sensitization data on FirstRate®, cloransulam-methyl is not expected to be a dermal sensitizer.
ACUTE STUDIES: EP (NAF-75)			
Oral	**NAF-75** A946-23 rat, Fischer 344; 5/sex 5000 mg/kg bw in distilled water	LD_{50}: **%** + **&** > 5000 mg/kg bw	No mortality or gross pathology; all rats gained weight; clinical findings included urine and fecal soiling in perineal area, loose stool and salivation **Low toxicity**
Dermal	**NAF-75** A946-23 rabbit, NZW, 5/sex 2000 mg/kg bw moistened with distilled water	LD_{50}: **%** + **&** > 2000 mg/kg bw	No mortality, clinical signs, gross pathology, all animals gained weight; erythema noted at all test skin sites **Low toxicity**

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
Inhalation			No data; based on high % of technical active in EP, low acute inhalation toxicity of technical active and no evidence of active toxicity of non-active ingredients, NAF-75 is estimated to be of **Low toxicity**
Eye irritation	**NAF-75** A946-23 0.1 g/eye rabbit, NZW; 3/sex	MIS = 7/110 at 1 h	**Minimally irritating**
Skin irritation	**NAF-75** A946-23 0.5 g/rabbit, moistened with water rabbit, NZW, 4**%** + 2**&**	MIS = 1.5/8 at 0.5 h	**Slightly irritating**
Skin sensitization (Buehler method)	**NAF-75** A946-23 guinea pig, Hartley albino induction: 0.4 mL, 100% challenge: 0.4 mL, 30% vehicle = distilled water		Negative **Not a dermal sensitizer**
SHORT-TERM TOXICITY: EP (NAF-75)			
21-d dermal rabbit	**NAF-75** A946-23 rabbit, NZW 0, 100, 500, 1000 mg/kg bw/d; 5/sex/group	NOAEL: **%** = 1000 **&** = 500 LOAEL: **%** > 1000 **&** = 1000 mg/kg bw/d	No effects on mortality, clinical signs, food intake, bw, clinical chemistry, organ weight, gross and histopathology 1000 mg/kg bw/d: **&** anemic, 9 RBC, Hct, 8 white blood cell count
SHORT-TERM TOXICITY: Technical active			
90-d dietary mouse	**Cloransulam-methyl** 97.3%, AGR 0293032 dietary at 0, 50, 100, 500, 1000 mg/kg bw/d mouse, B6C3F1, 10/sex	NOAEL: **%** = 50 **&** = 100 lowest observable effect level (LOEL): **%** = 100 **&** = 500 mg/kg bw/d	No effects on mortality, clinical signs of toxicity, ophthalmoscopy, bw, bw gain, food intake, gross pathology $100: **%** liver pathology (histologic changes) $500: **&** liver pathology (histologic changes) **%** + **&** 8 alkaline phosphatase activity Terminal bw of control mice: **%** = 30.9 ± 2.5, **&** = 25.5 ± 1.4 g (*n* = 10/sex) Terminal food intake of control mice: **%** = 5.4 ± 1.2 (*n* = 10), **&** = 7.3 ± 1.4 g/mouse/d (*n* = 6)
2-week palatability and toxicity dog	**Cloransulam-methyl** 99%, ACPR-353-12 dietary at 0, 50, 100, 200, 500, 1000 mg/kg bw/d dog, beagle, 1/sex/group	No effects at #200 mg/kg bw/d	1000: 9 bw, food intake, platelet counts $500: gross pathology (multiple hemorrhages in various organs and tissues) liver pathology: infiltration of inflammatory cells and degenerative hepatocytes #200: no effects

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
1-year dietary dog	**Cloransulam-methyl** 98.2%, TSN100049 dog, beagle, 4/sex/group 0, 5, 10, 50 mg/kg bw/d	NOAEL = 5 mg/kg bw/d LOEL = 10 mg/kg bw/d	No effects on mortality, clinical signs, food intake, bw, bw gain, ophthalmoscopy, hematology, urinalysis, organ weight, gross pathology 50: **%** + **&** 9 albumin, 8 AP, SGPT, liver histopathology 10: **%** + **&** 8 AP, SGPT, liver histopathology
21-d dermal rabbit	**Cloransulam-methyl** 98.2%, TSN100049 rabbit, NZW 0, 100, 500, 1000 mg/kg bw/d; 5/sex/group	NOAEL: **%** = 1000 **&** = 500 LOEL: **%** > 1000 **&** = 1000 mg/kg bw/d	No effects on mortality, clinical signs, dermal findings, food intake, bw, clinical chemistry, organ weight, gross and histopathology 1000: **&** anemic, 9 RBC, Hb, Hct RBC: anisocytosis and macrocytosis
LONG-TERM CHRONIC TOXICITY AND ONCOGENICITY			
2-year dietary oncogenicity mouse	**Cloransulam-methyl** 98.2%, DECO-343-6 mouse, B6C3F1 0, 10, 100, 1000 mg/kg bw/d 60/sex/group (10/sex/group sacrificed at 12 months)	NOAEL = 10 mg/kg bw/d LOEL = 100 mg/kg bw/d No evidence of oncogenic potential	Mortality (week 104, based on 50/sex/group): **%** = 5, 7, 8, 9; **&** = 12, 8, 14, 8 at 0, 10, 100 and 1000 mg/kg bw/d, respectively) No effects on mortality, clinical signs, food intake, feed efficiency, ophthalmoscopy or hematology 1000: **%** + **&** 9 bw gain 100: **&** 9 bw gain 10: no effects
2-year dietary chronic and oncogenicity rat	**Cloransulam-methyl,** 98.2%, DECO-343-6 rat, Fischer 344 0, 10, 75, 325 mg/kg bw/d 60/sex/group (10/sex/group for interim sacrifice at 52 weeks)	NOAEL = 10 mg/kg bw/d LOEL = 75 mg/kg bw/d No evidence of oncogenic potential	Mortality (week 104, based on 50/sex/group): **%** = 20, 27, 16, 8; **&** = 7, 12, 8, 13 at 0, 10, 75 and 325 mg/kg bw/d, respectively) No effects on mortality, food intake, feed efficiency, ophthalmoscopy, hematology, clinical chemistry, organ weights, gross pathology 325: **%** + **&** perineal soiling at 12 and 24 months, 9 bw and bw gain, kidney histopathology 75: **%** + **&** perineal soiling at 12 and 24 months, kidney histopathology 10: **%** + **&** perineal soiling at 24 months
MUTAGENICITY			
Study	**Species, Strain or Cell Type**	**Doses Employed**	**Significant Effects and Comments**
In vitro *Salmonella* and Ames test	**Cloransulam-methyl** 97.3%, AGR 0293032 *S. typhimurium*: TA98, TA100, TA1535, TA1537	–S9: 0, 0.05, 0.15, 0.5, 1.5, 5 Fg/plate +S9: 0, 0.15, 0.5, 1.5, 5, 15 Fg/plate	Negative
In vitro CHO HGPRT gene mutation	**Cloransulam-methyl** 98.2%, TSN100049 CHO-K1-BH_4	±S9: 50, 100, 200, 400, 600, 800 Fg/mL	Negative

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
In vitro chromosome aberration in rat lymphocytes	**Cloransulam-methyl** 97.3%, AGR 0293032 primary rat peripheral blood lymphocytes SD rats 2 independent assays	±S9: 4-h exposure assay 1: 0, 6, 20, 60, 200, 600 Fg/mL assay 2: 0, 53, 183, 6000 Fg/mL Positive controls: –S9: Mitomycin C +S9: cyclophosphamide cells harvested at 24 and 48 h	Negative
Micronucleus assay (in vivo)	**Cloransulam-methyl** 97.3%, AGR 0293032 mouse CD-1, **%** + **&**, 5/sex/group bone marrow	0, 500, 1667, 5000 mg/kg bw 1000 polychromatic RBC/mouse assessed at 24, 48, 72 h	Negative
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
2-generation dietary reproductive toxicity (rat), 1 litter per generation	**Cloransulam-methyl** 98.2%, TSN100049 rat, SD, 30/sex/group at 0, 10, 100, 500 mg/kg bw/d (ppm equivalent: mean of all time intervals: **%** = 0, 165, 1695, 8813, **&** = 0, 123, 1410, 6263)	Parental systemic toxicity LOEL = 100 mg/kg bw/d NOAEL = 10 mg/kg bw/d Reproductive toxicity NOAEL = 500 mg/kg bw/d, HDT Offspring toxicity LOEL = 500 mg/kg bw/d NOAEL = 100 mg/kg bw/d	Reproductive performance: no treatment-related effects Parental effects: 500: P_1 **%** + **&**: 9 bw and bw gain (pre-mating and gestation periods) $100: **%** kidney pathology (8 weight, histopathology) **&** kidney patholgy (histopathology) Offspring toxicity: 500: 8 F1 pup death during lactation d 0–4, viability indices within historical range
Teratology probe (rat)	**Cloransulam-methyl** 97.4%, AGR 293032 rat, SD, 10 mated **&**/group 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by gavage from gestation d 6–15; sacrifice on gestation d 16	No treatment related effects	No treatment-related effects on maternal toxicity; embryotoxicity was not assessed.
Teratology (rat)	**Cloransulam-methyl** 97.4%, AGR 293032 rat, SD, 30 mated **&**/group 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by gavage from gestation d 6–15; sacrifice on gestation d 21	LOAEL for maternal and developmental toxicity > 1000 mg/kg bw/d NOAEL for maternal and developmental toxicity = 1000 mg/kg bw/d No evidence of teratogenicity	Number of litters assessed: 28, 29, 27, 29, respectively for 0, 100, 500, 1000 mg/kg bw/d Maternal toxicity: none Fetotoxicity: none

Study	TGAI, Purity, Species, Strain and Doses	NOAEL or LOAEL (mg/kg bw/d)	Target Organ and Significant Effects and Comments
Teratology probe (rabbit)	**Cloransulam-methyl** 98.2%, TSN100049 rabbit, NZW; 7 inseminated &/group at 0, 100, 500, 1000 mg/kg bw/d in 0.5% aqueous Methocel A4M by oral gavage on gestation d 7–19; sacrifice on gestation d 20	No effects at 100 mg/kg bw/d	Maternal toxicity: $500: 9 food intake, bw, bw gain, fecal output 100: no treatment-related effects Embryotoxicity was not assessed
Teratology (rabbit)	**Cloransulam-methyl** 98.2%, TSN100049 rabbit, NZW; 20 inseminated &/group 0, 30, 100, 300 mg/kg bw/d in 0.5% aqueous Methocel A4M by oral gavage on gestation d 7–19; sacrifice on gestation d 28	LOAEL (mg/kg bw/d): maternal toxicity = 300 developmental toxicity > 300 NOAEL (mg/kg bw/d) maternal toxicity = 100 developmental toxicity = 300 Not teratogenic	Litters assessed: 18, 17, 16, 14 respectively for 0, 30, 100, 300 mg/kg bw/d Maternal toxicity: 300: 9 bw, food intake, fecal output; 2 dams aborted due to anorexia Developmental toxicity: no treatment-related effects
SPECIAL STUDIES			
Acute neurotoxicity	**Cloransulam-methyl** 97.3%, TSN100049 rat, Fischer; 10/sex/group 0, 200, 1000, 2000 mg/kg bw in 0.5% aqueous methylcelluose	NOAEL for acute neurotoxicity >2000 mg/kg bw	No deaths, clinical signs, bw, bw gain, motor activity, FOB assessment, no histopathological findings in nervous tissues (5/sex of control and high-dose group examined)
Compound-Induced Mortality: Not evident as demonstrated below: acute oral toxicity in rats: at 5000 mg/kg bw; acute dermal toxicity in rabbits: at 2000 mg/kg bw acute inhalation toxicity in rats: at 3.77 mg/L (actual, 4-h nose only exposure) short-term (90-d) dietary toxicity in mice: at up to 1000 mg/kg bw/d short-term (2-week) dietary toxicity in dogs: at up to 1000 mg/kg bw/d short-term (1-year) dietary toxicity in dogs: at up to 50 mg/kg bw/d short-term (21-d) dermal toxicity in rabbits: at up to 1000 mg/kg bw/d long-term (2-year) dietary toxicity in mice: at up to 1000 mg/kg bw/d long-term (2-year) dietary toxicity in rats: at up to 325 mg/kg bw/d			
Recommended ARfD: None; no acute toxicity hazards are expected			
Recommended ADI: 0.05 mg/kg bw/d, based on the NOAEL of 5 mg/kg bw/d established in the 1-year dog study and the standard safety factor of 100			
Recommended NOAEL for occupational risk assessment: 500 mg/kg bw/d established in the 21-d dermal toxicity studies of cloransulam-methyl and FirstRate® Herbicide (EP) in rabbits			

Appendix III Environmental summaries

Table 1 Physical and chemical properties relevant to the environment

Property	Test substance	Value	Comments
Water solubility (at 20EC)	Cloransulam-methyl	pH 5 = 2.96 mg/L pH 7 = 184 mg/L pH 9 = 3430 mg/L	Low solubility to high solubility with increasing pH in water in the environmentally relevant pH range; increasing potential for mobility with increasing pH
Vapour pressure	Cloransulam-methyl	3×10^{-16} mm Hg at 25EC (4×10^{-17} kPa at 25EC)	Low potential for volatilization
Henry's Law Constant 1/H (at 25EC and solubility at pH 7)	Cloransulam-methyl	9.35×10^{-14} Pa m^3/mole 2.65×10^{16}	Very low potential for volatilisation from water or moist soil
log K_{ow}	Cloransulam-methyl	pH 5 = 1.12 pH 7 = –0.365 pH 9 = –1.240	Low potential for bioaccumulation in the environmental relevant pH range
pK_a	Cloransulam-methyl	4.81 at 20EC	Negative charge in the environmentally relevant pH range; leaching potential will not be pH dependent
UV–visible absorption	Cloransulam-methyl	8_{max} methanol = 249 nm No absorption observed at wavelength range of 300–800 nm	Not expected to phototransform

Table 2 Fate and behavior in the terrestrial environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	XDE-565	Half-lives pH 5 > 365 d pH 7 = 231 d pH 9 = 3 d	Not a principal route at acidic and neutral pH: parent compound rapidly transforms at basic pH
Phototransformation on soil	XDE-565	Half-life = 30–70 d	Not a principal route of transformation
Phototransformation in air	Study not triggered	—	Not expected to volatilize from water or moist soil
Biotransformation			
Biotransformation in aerobic soil	XDE-565	Half-life = 14–22 d	Slightly persistent

Property	Test material	Value	Comments
Mobility			
Adsorption/desorption	XDE-565 XDE-565-acid	Values from batch equilibrium study K_{oc} parent = 15.8–87.1 K_{oc} XDE-565-acid = 57.0–135.3	High potential for mobility for the parent and transformation products
Volatilization	XDE-565 (from soil)	—	CO_2 was the only volatile product
Field studies			
Field dissipation		DT_{50} < 1 week	Non-persistent

Table 3 Fate and behavior in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	XDE-565	DT_{50} pH 5 > 365 d pH 7 = 231 d pH 9 = 3 d	Not a principal route at acidic and neutral pH: parent compound rapidly transforms at basic pH
Phototransformation in water	XDE-565	Half-life = 22 min	A principal route of transformation
Biotransformation			
Biotransformation in aerobic water systems	XDE-565	Half-life = 25.6 d in water	Slightly persistent in water
Biotransformation in anaerobic water systems	XDE-565	Half-life = 16 d in water	Slightly persistent
Partitioning			
Adsorption/desorption	X DE-565 XDE-565-acid	K_{oc} values for adsorption ranged from 15.8 to 87.1 for XDE-565 and from 57.0 to 135.3 for XDE-565-acid	Will remain primarily in aqueous phase
Field studies			
Field dissipation	Study not submitted	—	—

Table 4 Maximum EEC in vegetation and insects after a direct overspray

Matrix	EEC (mg a.i./kg fresh weight)[a]	Fresh to dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	7	3.3[b]	25
Leaves and leafy crops	4	11[b]	43
Long grass	3	4.4[b]	15
Forage crops	22	5.4[b]	10
Small insects	2	3.8[c]	7
Pods with seeds	0	3.9[c]	1
Large insects	0	3.8[c]	1
Grain and seeds	0	3.8[c]	1
Fruit	0.2	7.6[c]	2

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

[b] Fresh to dry weight ratios from Harris (1975)

[c] Fresh to dry weight ratios from Spector (1956)

Table 5 Maximum EEC in diets of birds and mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	4.2
Mallard duck	30% large insects 70% grain	1.18
Rat	70% short grass 20% grain and seeds 10% large insects	17.66
Mouse	25% short grass 50% grain and seeds 25% leaves and leafy crops	17.55
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	23.19

Appendix IV Effects on non-target organisms

Table 1 Summary of effects on terrestrial organisms

Organism	Exposure	Test substance	End point value	Degree of toxicity
Invertebrates				
Earthworm	Acute	XDE-565	14-d LC_{50} > 859 mg a.i./kg soil 14-d NOEC = 116 mg a.i./kg soil	N.A.
Bee	Oral	Not submitted	—	—
	Contact	XDE-565	48-h LD_{50} > 25 Fg a.i./bee 48-h NOEC = 3.1 Fg a.i./bee	Relatively non-toxic
Birds				
Bobwhite quail	Acute	XDE-565	14-d LD_{50} > 2250 mg a.i./kg bw 14-d NOEC = 2250 mg a.i./kg bw	Practically non-toxic
	Dietary	XDE-565	8-d LC_{50} > 5620mg a.i./kg diet 8-d NOEC = 5620 mg a.i./kg diet	Practically non-toxic
	Reproduction	XDE-565	NOEC egg reproduction and quality = 500 mg a.i./kg diet	N.A.
Mallard duck	Dietary	XDE-565	8-d LC_{50} > 5620mg a.i./kg diet 8-d NOEC = 5620 mg a.i./kg diet	Practically non-toxic
	Reproduction	XDE-565	NOEC egg shell thickness = 125 mg a.i./kg diet	N.A.
Mammals				
Rat	Acute oral	XDE-565	LD_{50} > 5000 mg a.i./kg bw	Low toxicity
	Acute oral	NAF-75	LD_{50} > 5000 mg a.i./kg bw	Low toxicity
	Reproductive and developmental toxicity	XDE-565	Reproductive toxicity NOAEL = 500 mg a.i./kg bw/d	—
Mouse	90-d dietary	XDE-565	NOAEL % = 50 mg a.i./kg bw/d	—
Vascular plants				
Vascular plant	Post-emergence (vegetative vigour: shoot length)	XDE-565	EC_{25} = 0.099 g a.i./ha NOEC = 0.025 g a.i./ha	N.A.

Table 2 Effects on aquatic organisms

Organism	Exposure	Test substance	End point value	Degree of toxicity
Freshwater species				
Daphnia magna	Acute	XDE-565	48-h LC_{50} = 97.5 mg a.i./L 48-h NOEC = 64.3 mg a.i./L	Slightly toxic
	Chronic	XDE-565	NOEC progeny per adult = 11.3 mg a.i./L	N.A.
Rainbow trout	Acute	XDE-565	96-h LC_{50} > 86 mg a.i./L 96-h NOEC = 86 mg a.i./L	Slightly toxic
Bluegill sunfish	Acute	XDE-565	96-h LC_{50} > 154 mg a.i./L 96-h NOEC = 154 mg a.i./L	Practically non-toxic
Freshwater algae diatom blue-green green	Acute	XDE-565	 5-d EC_{25} = 1.10 mg a.i./L 5-d EC_{50} = 1.79 mg a.i./L 5-d NOEC < 0.43 mg a.i./L 5-d EC_{25} = 7.3 Fg a.i./L 5-d EC_{50} = 12.4 Fg a.i./L 5-d NOEC < 5.64 Fg a.i./L 5-d EC_{50} = 2.7 Fg a.i./L 5-d NOEC = 0.9 Fg a.i./L	 N.A. N.A. N.A.
Vascular plant	Dissolved in test medium	XDE-565	14-d EC_{25} = 0.91 Fg a.i./L 14-d EC_{50} = 2.91 Fg a.i./L 14-d NOEC frond no./plant growth = 0.78 Fg a.i./L	N.A.
Marine species				
Crustacean (*Palaemonetes pugio*)	Acute	XDE-565	96-h LC_{50} > 121 mg a.i./L 96-h NOEC = 121 mg a.i./L	Practically non-toxic
Mollusk (oyster)	Acute	XDE-565	96-h EC_{50} = 111 mg a.i./L 96-h NOEC = 111 mg a.i./L	Practically non-toxic
Fish (*Menidia beryllina*)	Acute	XDE-565	96-h LC_{50} > 121 mg a.i./L 96-h NOEC = 121 mg a.i./L	Practically non-toxic
Marine algae	Acute	XDE-565	5-d EC_{25} = 1.64 mg a.i./L 5-d EC_{50} = 3.55 mg a.i./L 5-d NOEC = 0.44 mg a.i./L	N.A.

Table 3 Risk to terrestrial organisms

Organism	Exposure	End point value	EEC	MOS	Risk
Invertebrates					
Earthworm	Acute	14-d NOEC = 116 mg a.i./kg soil	0.016 mg a.i./L	7.25×10^3	No risk
Bee	Contact	LD_{50} > 25 Fg a.i./ha	35 mg a.i./ha	>857	No risk
Birds					
Bobwhite quail	Acute	14-d NOEC = 2250 mg a.i./kg bw	4.20 mg a.i./kg dw	4.22×10^3 d equivalent dose administered to reach NOEC in laboratory population	No risk
	Dietary	8-d NOEC = 6520 mg a.i./kg diet	4.20 mg a.i./kg dw	1.34×10^3	No risk
Mallard duck	Reproduction	NOEC egg shell thickness = 125 mg a.i./kg diet	1.18 mg a.i./kg dw	1.06×10^2	No risk
Mammals					
Rat	Acute	LD_{50} > 5000 mg/kg bw	17.66 mg a.i./kg dw	>5.66×10^3 d of daily intake to reach equivalent to kill 50% laboratory population	No risk
Mouse	Dietary	90-d NOAEL = 50 mg/kg bw/d	17.55 mg a.i./kg dw	2.85	Low risk
Vascular plants					
Vascular plant	Post-emergence	NOEC = 0.99 g a.i./ha	35 g a.i./ha	2.83×10^{-3}	Very high risk

Table 4 Aquatic organisms

Organism	Exposure	End point value	EEC	MOS	Risk
Freshwater species					
Daphnia magna	Acute	48-h NOEC = 63.3 mg a.i./L	0.012 mg a.i./L	5.36×10^3	No risk
Rainbow trout	Acute	96-h NOEC = 86 mg a.i./L	0.012 mg a.i./L	7.17×10^3	No risk
Freshwater algae	Acute	96-h NOEC = 0.9 Fg a.i./L	0.012 mg a.i./L	7.5×10^{-2}	High risk
Vascular plants	Dissolved	14-d NOEC = 0.78 Fg a.i./L	0.012 mg a.i./L	6.5×10^{-2}	High risk