Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision PRDD98-01

Sulfosulfuron

The active ingredient sulfosulfuron and the formulated product Sundance, for control of wild oats and specific broadleaf weeds in wheat, are proposed for registration.

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

This document has been prepared in keeping with the ongoing efforts of the Pest Management Regulatory Agency (PMRA) to regulate pest control products in an open and transparent manner.

The PMRA will accept written comments on this proposal up to 45 days from the date of this document. Please forward all comments to:

Sulfosulfuron Working Group
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Foreword

This regulatory document proposes to register Sundance (sulfosulfuron) herbicide, a Monsanto product for control of wild oats and certain broadleaf weeds in wheat and details the supporting scientific rationale.

Sulfosulfuron is noteworthy in that:

- it is the first chemical jointly reviewed on an international basis. Canada, the United States, Australia and European Union, with Ireland as competent authority, cooperated in this pilot project that built on previous North American experience and international harmonization activities focused through the Organisation for Economic Co-operation and Development (OECD).

- the assessment and regulatory process is well advanced in all participating countries and in the OECD infrastructure. Canada and Ireland are the first countries to propose registration.

- it reflects a worldwide approach by the manufacturer and regulatory agencies and a commitment to flexibility and cooperation essential to the success of international harmonization.

- the use pattern for the product, for example, rates, timing, frequency of application and tank mixes is parallel, with a view to providing a level playing field for growers in all countries.

- the parallel use pattern allows for harmonized maximum residue limits (MRLs) or tolerances, which are key to avoiding trade irritants.

- the product was assessed within the PMRA 25% faster than the established standard for a new active ingredient. This saving reflects efficiencies gained through international cooperation and exchange and utilization of each other's reviews. While relatively modest, it is nevertheless significant for an initial pilot, and is particularly important since it positions the product to be available for the 1999 growing season.

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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

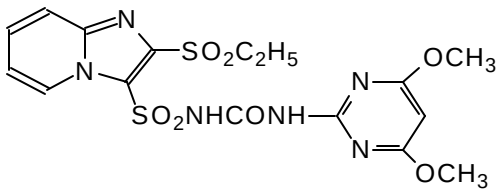
Active substance:	Sulfosulfuron
Function:	Herbicide
Chemical name (International Union of Pure and Applied Chemistry):	1-(4,6-dimethoxypyrimidin-2-yl)-3-[(2-ethanesulfonylimidazo[1,2-a]pyridine)sulfonyl]urea
Chemical name (Chemical Abstracts Service (CAS)):	N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-2-(ethylsulfonyl)imidazo [1,2,a]pyridine-3-sulfonamide
CAS Number:	141776-32-1
Nominal purity of active:	98%

Identity of relevant impurities of toxicological, environmental and/or other significance:

Nitrosamines were analyzed but were not detected at a limit of detection of 0.1 ppm for non-polar nitrosamines or 1.0 ppm for polar nitrosamines. Compounds such as chlorinated dibenzodioxins, chlorinated dibenzofurans and hexachlorobenzene would not form in this product, given the absence of precursors in the manufacturing process.

Molecular Formula:	$C_{16}H_{18}N_6O_7S_2$
Molecular Mass:	470.47

Structural Formula:



1.2 Physical and chemical properties of active substance

Table 1 Technical product: Sulfosulfuron

Property	Result	Comment
Colour and physical state	White powder	N/A
Odour	Odourless	N/A
Melting point/range	201.1 - 201.7/C	N/A
Boiling point/range	Not applicable	N/A
Density	1.5185 g/cm^3 at 20/C	N/A
Vapour pressure	/C Vapour pressure 20 2.29×10^{-10} mmHg (3.05×10^{-08} Pa) 25 6.61×10^{-10} mmHg (8.81×10^{-08} Pa)	Low potential for residues to decrease as a result of volatilization.
Ultraviolet (UV)/visible spectrum at 26/C	λ_{max} at 208, no absorption at λ >320 nm	Potential to absorb sunlight in UV/visible range of 280-320 nm.
Solubility in water at 20/C	pH Solubility (ppm) 5 17.60 ± 2.71 7 1626.8 ± 39.8 9 482.44 ± 8.35	Soluble at pH 5, very soluble at pH 7 and 9
Solubility in organic solvents at 20/C	Solvent Solubility (g/L) MeOH 0.33 Xylene 0.16 $C_2H_4Cl_2$ 4.35 Acetone 0.71 Ethyl acetate 1.01 Heptane < 0.001	In general, solubility appears to increase with increasing organic solvent polarity.
n-Octanol/water partition coefficient	pH log K_{ow} 5 <1 7 <1 9 <1	Low potential for bioaccumulation in milk fat and fatty tissues.
Dissociation constant	pKa = 3.51 at 20/C	Dissociates and exists as negatively charged ion at environmentally relevant pHs 5-9.

Property	Result	Comment
Oxidizing properties	Stable at 25/C and 54/C for 14 days, under sunlight for 14 days, 24 h/day and with iron, zinc or aluminium at 25/C.	Sulfosulfuron is unlikely to produce any oxidative or reductive processes on plants which may result in a change of the nature and magnitude of residues.
Storage stability	Not applicable to the technical product.	Freezer storage stability studies indicated that total residues of sulfosulfuron were stable at -12/C for up to 533 days.

Table 2 End-use product: Sundance

Property	Result	Comment
Odour	No characteristic odour	N/A
Colour	Beige	N/A
Physical state	Granular powder	N/A
Formulation type	Wettable granules	N/A
Guarantee	75%	N/A
Container material and description	Paper	N/A
Tap density	0.62 g/mL	N/A
pH of 1% dispersion in water at 20/C	4.96	N/A
Oxidizing or reducing action	Oxidized by 1% $KMnO_4$. No reaction in contact with H_2O, Zn and $NH_4H_2PO_4$.	The formulated product is unlikely to trigger any oxidative or reductive processes on the plant surface that may affect the nature and magnitude of the residues.
Storage stability	Stable for 14 days at 54/C. Two year ambient temperature testing is underway.	The plant metabolism storage stability study appeared to indicate that storage of wet straw tissues versus forage extracts may allow for hydrolysis of bioincurred residues to occur.
Explodability	Not explosive under the test conditions.	N/A
Surfactants	3 EO alkyl (C_{12} - C_{15}) ether sulfate	Increased absorption expected.

1.3 Details of uses and further information

Sulfosulfuron is a sulfonylurea herbicide. Sulfosulfuron is classified as a Group 2 herbicide in which the mode of action is the inhibition of acetolactate synthase (ALS), which may also be called acetohydroxyacid synthase (AHAS). Sundance is a wettable granule formulation which has a guarantee of 75% sulfosulfuron and will be marketed in foil-lined bags.

Sundance may be used for post-emergent application on spring wheat and durum wheat in Western Canada for the control of specific grass and broadleaf weeds. Sundance is effective in controlling wild oats, redroot pigweed, common chickweed, wild mustard, stinkweed and volunteer Canola (excluding imazethapyr-tolerant Canola, i.e., Pursuit Smart Canola), and suppressing green foxtail, quackgrass and dandelion. Sundance may be applied at a rate of 27 g of product/hectare (ha) (20 g active ingredient [a.i.]/ha) with ground equipment only and must be applied with the surfactant Merge at 0.5% spray volume. Sundance is to be applied before the emergence of the fourth tiller of the crop with a preharvest interval of 67 days with a maximum of 1 application during the season.

Sundance can be tankmixed with 2,4-D ester at a rate of 420 g a.i./ha for control of the above weeds, in addition to the following annual broadleaf weeds: lambsquarters, wild buckwheat, and storksbill.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Three high-performance liquid chromatography (HPLC) methods and one gas chromatography (GC) method were used for the determination of the active substance and significant impurities (content $\geq$0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

An HPLC was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

2.3 Methods for residue analysis

2.3.1 Multiresidue methods for residue analysis

A multiresidue method (MRM) for testing sulfosulfuron and its sulfonamide metabolite (CP 147937) was conducted according to the Pesticide Analytical Manual Volume 1 (PAM 1), 3rd edition (1994), using Protocol A and C. This study was performed according to good laboratory practice (GLP) standards. Wheat straw and grain were chosen to represent the non-fatty and

fatty wheat matrices. Carbofuran, ethion and chlorpyrifos were the reference substances used for method calibration purposes.

Protocol A was terminated since the signal to noise ratio (2.0 and 2.2 observed at 1.00 ：g/mL) was considered unacceptable for quantitation purposes of sulfosulfuron and its sulfonamide metabolite, respectively in wheat straw and grain. Likewise, Protocol C was not completed since sulfosulfuron degraded under gas-liquid chromatography (GLC) conditions. Moreover, the sulfonamide metabolite could not be analyzed in wheat straw and grain by the GLC system due to inadequate sensitivity. Consequently, the MRM was not amenable to the determination of sulfosulfuron or its metabolites in plant and tissues.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) was defined from the wheat metabolism study as "the sum of sulfosulfuron and its ethyl sulfone metabolites, expressed as sulfosulfuron".

The HPLC common moiety method of analysis, proposed for wheat, determines residues of parent sulfosulfuron and its metabolites that can be hydrolyzed to the ethyl sulfone. This method was found to give satisfactory recoveries (73%-104%) for the analysis of grain, straw and forage. Representative chromatograms of control grain, straw and forage showed no known interferences from wheat components or from reagents, solvents and glassware. Spiked samples gave doublets and in some instances, the peak was not well defined. However, good linearity (r=0.9999) was observed in the range of 0.0025-0.1 ：g/mL for ethyl sulfone (external reference standard).

The interlaboratory validation validated the Monsanto method for sulfosulfuron-equivalent residues in wheat matrices measured as ethyl sulfone, indicating satisfactory reproducibility.

An endogenous method validation with the ^{14}C-sulfosulfuron pre- and post-emergence treated wheat forage, straw and grain (Imidazopyridine (Im) label containing bioincurred ^{14}C-residues) from the wheat metabolism study was conducted to verify the conversion of sulfosulfuron and its Im-containing metabolites (sulphonamide, desmethyl and guanidine) to the ethyl sulfone. Radiovalidation in wheat metabolism studies using sulfosulfuron labelled in the Im moiety demonstrated that identified Im-containing metabolites and sulfosulfuron represented 80% and 60% of the total residue in forage and straw, respectively. The residue levels present in grain were too low for accurate quantification. As the efficiency of the method was very good for the more complex straw and forage matrices, it is expected to be satisfactory for the grain matrix. The identity of the ethyl sulfone resulting from acid hydrolysis of sulfosulfuron residues are confirmed with mass spectral data.

Residues are calculated as mg/kg ethyl sulfone and are expressed in terms of sulfosulfuron parent equivalent. A limit of quantification (LOQ) of 0.008 mg/kg for ethyl sulfone, expressed as sulfosulfuron parent equivalent can be achieved; however, given the complexity of the method it is proposed that the LOQ be specified, for control purposes, as being 0.02 mg/kg. The standard

deviations measured with respect to recoveries following spiking at the LOQ appeared indicative of the method having satisfactory repeatability.

The radiovalidation indicated that total residues consisting of sulfosulfuron and its Im-moiety metabolites after conversion to ethyl sulfone were considered representative and adequate for use as an analytical procedure for the residue definition proposed. (Use of the method results in residue content of parent sulfosulfuron being over estimated by between 10% and 20%; unclear based on data.)

2.3.3 Methods for residue analysis of food of animal origin

The residue of concern (ROC) was defined from the livestock metabolism studies as "the sum of sulfosulfuron and its ethyl sulfone metabolites, expressed as sulfosulfuron" and was identical to that defined for wheat.

A HPLC common moiety method for the determination of residues of sulfosulfuron and its metabolites that can be hydrolyzed to the ethyl sulfone, in food of animal origin is proposed. This method was found to give satisfactory recoveries (80%-100%) for the analysis of milk, meat, fat, liver and kidney and has a LOQ of 0.004 mg/kg in the case of milk and tissues. The method was found to have satisfactory linearity, specificity and repeatability. Representative chromatograms of control milk and liver samples showed no background interferences. The spiked samples had a well resolved peak of the ethyl sulfone with no associated interferences. The detector response was linear in the range of 0.01 to 0.35 ppm ethyl sulfone.

An independent laboratory validation supported the reliability and reproducibility of the Monsanto Method Number RES-095-96, Version 0, for the determination of sulfosulfuron in milk, fat, kidney, liver and muscle samples. Whole milk and liver were selected to represent the range of residues expected in all livestock matrices.

2.3.4 Methods for residue analysis of soil

A method of analysis has been submitted for the determination of residues of sulfosulfuron and its major transformation product, i.e., sulfonamide, in soil. The method is based on a quantitative conversion of sulfosulfuron to the ethylsulfone metabolite by acid hydrolysis and analysis by HPLC. The LOQ for sulfosulfuron and sulfonamide were 0.001 and 0.005 mg/kg, respectively.

2.3.5 Methods for residue analysis of water

A method of analysis has been submitted for the determination of residues of sulfosulfuron and its major transformation product, i.e., sulfonamide, in water. The method is based on a quantitative conversion of sulfosulfuron to the ethylsulfone metabolite by acid hydrolysis and analysis by HPLC. The LOQ for sulfosulfuron and sulfonamide were 0.0001 and 0.0005 mg/L, respectively.

An endogenous radiovalidation study was conducted with milk and liver samples from the radiolabelled goat metabolism study. As well, an exogenous radiovalidation study was carried out with control milk and tissue samples spiked with Im-labelled ^{14}C-sulfosulfuron. The results of the endogenous and exogenous radiovalidation studies showed that Im-containing sulfosulfuron residues accounted for 80%-85% of the total reactive residues (TRR) in milk and liver samples, with good repeatability between replicates. Likewise, the recoveries obtained in the Monsanto method RES-095-96, Version 0 were >71% in milk and >85% in liver samples. The extraction efficiencies for endogenous Im-containing sulfosulfuron residues in milk and liver were 92% and 101% respectively, which were comparable to those obtained in the goat metabolism study (95% in milk; 104% in liver).

The results of the rat metabolism study confirmed that parent sulfosulfuron corresponded to >80% of the excreted dose.

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

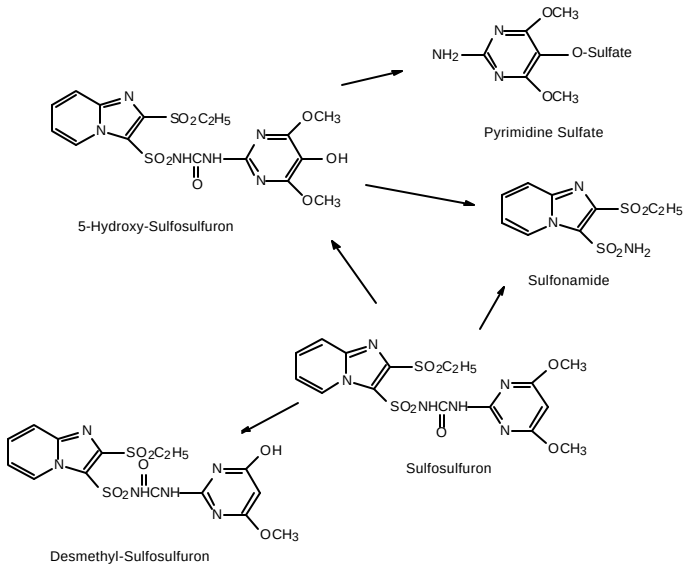
Male and female Sprague Dawley rats received either a single low intravenous dose (10.0 mg/kg body weight [bw]), single low oral dose (10.0 mg/kg bw), single high oral dose (1,000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of sulfosulfuron, purity 98%, 4 or 5 rats per sex per group. Radiolabelled sulfosulfuron consisted of a 1:1 ratio of sulfosulfuron labelled with ^{14}C at the C-3 position of the imidazopyridine ring; and sulfosulfuron labelled with ^{14}C at the C-5 position of the pyrimidine ring. The test material was well absorbed after single or multiple oral administration of the low dose, i.e., >90% of the administered dose (AD). However, only 35% to 40% of the AD was absorbed after a single oral high dose. The test material was rapidly excreted for all dose groups; >80% and >90% of the AD had been excreted within 24 hours (h) and 72-h post-dosing, respectively. For all low dose groups, the major portion of the radioactivity was excreted via the urine, i.e., between 77% to 87% of the administered dose, while between 5% and 13% was eliminated via the feces. For the high dose group, the major route of elimination was via the feces, i.e., 55% to 63% of the AD, while between 31% and 33% was excreted in the urine.

Elimination was found to be biexponential for all groups, with the mean half-life for the initial phase determined to be 2.2-5.8-h , and for the terminal phase was 21.4- to 56.7-h.

The expired air contained <0.04% of the AD (as determined in the pilot phase). The liver contained the highest traces of radioactivity, i.e., <0.13% of the AD, with all other individual tissues containing 0.01% or less of the AD, indicating that sulfosulfuron did not accumulate nor was retained in the various tissues.

Based on the metabolic profiles obtained in this study for all groups, the major fraction was identified as unchanged sulfosulfuron, accounting for ~88% to 96% of the TRR. Four other metabolites were identified (desmethyl sulfosulfuron, 5-hydroxy sulfuron, sulfonamide and pyrimidine sulfate), each accounting for less than 0.5% of the TRR. The metabolic pathways for sulfosulfuron were determined to be: (1) ring hydroxylation of the 5-position carbon of the pyrimidine ring, and (2) demethylation of the methoxy group at either the 4- or 6-position of the pyrimidine ring resulting in the formation of the desmethyl and 5-hydroxy-sulfosulfuron as the most abundant metabolites. The cleavage of the sulfonylurea bridge to form separate imidazopyridine and pyrimidine metabolites was a minor pathway. Please refer to Figure 1.

Figure 1 - Proposed pathway for metabolism of sulfosulfuron in rats



3.1.2 Acute toxicity - technical and formulation

Technical sulfosulfuron, purity 98.9%, was considered to be of low acute toxicity by the oral, dermal and inhalation routes in Sprague Dawley rats (oral and dermal LD_{50}s >5.0 g/kg bw; LC_{50} >3.0 mg/L). It was minimally irritating when applied to the skin, or instilled into the eyes, of New Zealand White rabbits. Results of skin sensitization testing using Hartley-derived albino guinea pigs, employing both the modified Buehler method and the maximization test, were negative.

Based on the results of acute toxicity testing, no signal words are required to be displayed on the primary display panel of the technical material.

Sundance, containing 73.7% technical sulfosulfuron, was considered to be of low acute toxicity by the oral, dermal and inhalation routes in Sprague Dawley rats (oral and dermal LD_{50}s >5.0 g/kg bw; LC_{50} >2.6 mg/L). It was slightly irritating when applied to the skin of New Zealand White rabbits, and was minimally irritating when instilled into the eyes of the same species. Results

of skin sensitization testing in Dunkin Hartley guinea pigs, employing the maximization test, were negative.

Based on the results of acute toxicity testing, no signal words are required to be displayed on the primary display panel of the formulation.

3.1.3 Genotoxicity

In a microbial reverse gene mutation study (in vitro), using both the standard plate incorporation assay and the preincubation modification to the standard assay, *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 were exposed to sulfosulfuron, purity >98.5%, dissolved in dimethyl sulfoxide (0.1 mL/plate). Dose levels chosen were 5, 15, 50, 150, 500, 1,500 and 5,000 ：g/plate, both in the presence and absence of metabolic activator (i.e., S9 fraction derived from Aroclor 1254-induced Sprague Dawley male rat livers). Cytotoxicity was seen for the majority of strains at doses $1,500 ：g/plate +/-S9 using both testing procedures. All strains responded in the expected manner to the appropriate positive control. There was, however, no evidence that sulfosulfuron induced a mutagenic effect in any strain at any non-cytotoxic dose, using either procedure.

Hence, under the conditions of this study, sulfosulfuron was considered non-mutagenic for point mutation.

In an in vitro mammalian cell gene mutation assay, cultures of normal ($HGPRT^+$) Chinese hamster ovary (CHO) cells were exposed for 3-h to doses of 624-5,000 ：g/mL of sulfosulfuron, purity >98.5%, in the absence and presence of 1%, 5% or 10% metabolic activator (initial trial). The confirmatory trial investigated 5 doses ranging from 312-5000 ：g/mL -/+5% metabolic activator. Metabolic activator was S9 homogenate from Aroclor 1254-induced rat livers and the test material was delivered to the test system in Ham's F12 medium (without serum).

Sulfosulfuron was insoluble at $2,500 ：g/mL. Marginal cytotoxicity (. 40% reduction in cell survival) was seen at 5,000 ：g/mL without S9. The S9-activated test material and lower non-activated concentrations (#2,500 ：g/mL) were not cytotoxic. The positive controls induced the expected mutagenic responses. There was, however, no evidence that sulfosulfuron was mutagenic at any dose under any assay condition.

Under the conditions of this assay, sulfosulfuron was considered non-mutagenic for point mutations, frame-shift mutations and deletions.

In an in vitro cytogenetic assay, cultured human lymphocytes, obtained from a single donor, were exposed to sulfosulfuron, purity 98.5%, in initial (3-h exposure in the presence and absence of metabolic activator to sulfosulfuron, followed by 17-h incubation and then 2-h exposure to colcemid) and confirmatory (in the absence of metabolic activator: 19.5- and 43.4-h exposures to sulfosulfuron, followed by colcemid; in the presence of metabolic activator: same as initial) assays.

The metabolic activator was S9 homogenate derived from Aroclor 1254-induced rat livers and the test material was delivered to the test system as a solution in DMSO. Dose levels evaluated, both in the presence and absence of metabolic activator, for all assays and harvest times, were 100, 250, 500, 750 and 1,000 ：g/mL. At 1,000 ：g/mL, both in the presence and absence of metabolic activator, a precipitate was observed, and reductions (from 14.9% to 66.7%) were seen in mitotic indices. However, there were no indications of any increased incidence of cells with chromosomal aberrations and/or numbers of polyploid cells. The positive controls induced the expected high yields of metaphase spreads with chromosomal aberrations. Based on these considerations, it is concluded that sulfosulfuron did not induce a clastogenic response in human lymphocytes either in the presence or absence of S9 at doses up to and including those associated with cytotoxicity and/or test material precipitation.

Under the conditions of this assay, it was concluded that sulfosulfuron was non-clastogenic.

In an in vitro chromosomal assay, Chinese hamster lung fibroblasts were exposed to sulfosulfuron, purity 98.9%, dissolved in 0.5% carboxymethylcellulose. Dose levels chosen were 0 (solvent control), 1,000, 1,250, 2,000, 2,500, 3,000 and 5,000 ：g/mL, both in the presence and absence of metabolic activator (rat liver S9 activation mixture). Precipitation of the test material occurred at all concentrations tested. An increase in the incidence of cells with chromosomal structural aberrations occurred at dose levels of 2,000 ：g/mL and higher, in the absence of metabolic activator only. There was no effect at any dose level tested in the presence of metabolic activator. Under the conditions of this assay, it was concluded that sulfosulfuron was clastogenic in the absence of metabolic activator at dose levels of 2,000 ：g/mL and higher.

Sulfosulfuron was not clastogenic in the presence of metabolic activator at any dose level tested.

In an in vivo mammalian cytogenetics (micronucleus) assay, groups of CD-1^{R} mice (5 males:5 females per dose per sacrifice time) were gavaged orally with single doses of solvent carrier (Tricaprylin, 10 mL/kg) or sulfosulfuron, purity >98.5% (1,250, 2,500 and 5,000 mg/kg bw), and sacrificed 24-, 48- and 72-h post-dosing. A positive control group of 5 males and 5 females received a single oral dose (40 mg/kg bw) of cyclophosphamide and the animals were sacrificed 24-h later. Slides were prepared from harvested bone marrow, and were evaluated for the presence of micronucleated polychromatic erythrocytes (MPCEs) as well as possible cytotoxicity (ratio of PCEs to total erythrocytes). No mortalities occurred during the micronucleus assay; hypoactivity was observed in one animal in the 2,500 mg/kg bw group and one at 5,000 mg/kg bw. There was no evidence of target cell cytotoxicity (a significant decrease in the PCE/total erythrocyte ratio). The positive control induced the expected high yield of MPCEs in mice sacrificed at 24-h. The mean incidence of MPCEs was statistically (p#0.01) elevated in 2,500 mg/kg bw females sacrificed at 24-h, however the value (2.7/1,000 PCEs; concurrent vehicle controls, 1.0/1,000 PCEs) was within historical corn oil vehicle range (0-7.4/1,000 PCEs), and the incidence in 5,000 mg/kg bw females sacrificed at 24-h was not significantly elevated (1.4/1,000 PCEs), indicating the statistically significant elevation at 2,500 mg/kg bw was a sporadic event. Sulfosulfuron did not induce a clastogenic effect in either sex at any sacrifice time.

Under the conditions of this assay, it was concluded that sulfosulfuron was non-clastogenic.

In a pharmokinetic study in mice, four CD-1 males were administered ^{14}C-labelled sulfosulfuron in corn oil (approximately 10 ：Ci/mouse) at 2,000 mg/kg bw. Two animals were sacrificed at 2-h post-dose, and 2 at 8-h post-dose. Two males received corn oil only; one was sacrificed 2-h later and the other 8-h later. Blood and femoral bone marrow were processed, and radioactivity was measured by liquid scintillation counting (LSC).

Significant amounts of radioactivity were detected in blood plasma and bone marrow at both sacrifice times from dosed animals (2-h: blood plasma, 1,292 ：g equivalents/g tissue; bone marrow, 415 ：g equivalents/g tissue; 8-h: blood plasma, 324 ：g equivalents/g of tissue; bone marrow, 29 ：g equivalents/g of tissue). These findings demonstrate transport of parent compound and/or its metabolites to bone marrow, and indicates that target cell exposure occurred in the mouse micronucleus assay.

This ancillary study, although it does not meet or satisfy any specific guideline requirement, was designed to demonstrate that sulfosulfuron and/or its metabolites reach mouse bone marrow following administration via oral gavage, as supporting data to the mouse micronucleus assay.

3.1.4 Sub-chronic and chronic toxicity

The sub-chronic and chronic toxicity of sulfosulfuron were investigated in mice, rats and dogs. A series of range-finding 28-d studies were conducted initially. These were used to establish appropriate dose levels to be used in the 90-d studies, which in turn were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Sub-chronic and chronic toxicity in the mouse

Male and female CD-1 mice were fed test diets containing sulfosulfuron, purity 99%, at dietary concentrations of 0, 10, 100, 1,000 and 4,000 ppm (equal to 0, 2, 17, 186 and 701 mg/kg bw/d for males, and 0, 2.7, 22, 274 and 987 mg/kg bw/d for females) for a period of 4 weeks, 5 mice per sex per group.

For males, the no observable adverse effect level (NOAEL) was determined to be 4,000 ppm (equal to 701 mg/kg bw/d) based on a slight, but statistically significant increase in palmitoyl CoA oxidase activity. In the absence of any other treatment-related findings, this was not considered to be an adverse effect. For females, the no observable effect level (NOEL) was set at 4,000 ppm (equal to 987 mg/kg bw/d) since there were no treatment-related effects for females at any dose level tested.

Male and female CD-1 mice were fed test diets containing sulfosulfuron, purity 99.1%, at dietary concentrations of 0, 100, 1,000, 3,000 and 7,000 ppm (equal to 0, 18, 163, 550 and

1,144 mg/kg bw/d for males, and 0, 32, 313, 887 and 2,123 mg/kg bw/d for females), for a period of 90-d, 10 mice per sex per group.

The NOEL was determined to be 7,000 ppm (equal to 1,144 mg/kg bw/d for males, and 2,123 mg/kg bw/d for females), since there were no treatment-related effects observed in male or female mice at any dose level tested.

Male and female CD-1 mice were fed test diets containing sulfosulfuron, purity 98.4%, at dietary concentrations of 0, 30, 700, 3,000 and 7,000 ppm (equal to 0, 4.0, 93, 394 and 944 mg/kg bw/d for males, and 0, 6.5, 153, 635 and 1,388 mg/kg bw/d for females), 60 mice per sex per group, for a period of 18 months.

For males, the NOEL for systemic toxicity was determined to be 700 ppm (equal to 93 mg/kg bw/d), based on treatment-related effects in the urinary system at dose levels of 3,000 and 7,000 ppm. Treatment-related clinical observations, noted in the 7,000 ppm group only, were an increased incidence of abdominal swelling, abnormal penile erection and urine-stained fur. At necropsy, treatment-related findings were observed in the kidneys (dilated pelvis) and ureters (calculi) in the 7,000 ppm group, and in the urinary bladder (calculi, thick walled, enlarged) in the 3,000 and 7,000 ppm groups. Histopathological examination supported these findings, i.e., in the kidneys, there was an increased incidence of pelvic dilatation and papillary necrosis noted in the 7,000 ppm group, and in the urinary bladder there was an increased incidence of calculi, dilatation, inflammation, ulceration, hyperplasia of the mucosal epithelium and squamous metaplasia of the transitional cell epithelium observed in the 3,000 and 7,000 ppm groups. An increase in blood urea nitrogen in the 7,000 ppm group was also considered to be treatment-related.

For females, the NOEL for systemic toxicity was determined to be 7,000 ppm (equal to 1,388 mg/kg bw/d), since there were no treatment-related effects observed at any dose level tested.

For males, the NOEL for tumorigenicity was set at 3,000 ppm (equal to 394 mg/kg bw/d) based on an increased incidence of mesenchymal tumours in the urinary bladder of 5 males in the 7,000 ppm group. All of the 5 affected males also had bladder calculi and hyperplasia of the transitional cell epithelium, and 2 of the 5 also exhibited squamous mucosal metaplasia.

For females, the NOEL for tumorigenicity was set at 7,000 ppm (equal to 1,388 mg/kg bw/d), since there was no evidence of oncogenic potential of sulfosulfuron at any dose level tested.

3.1.4.2 Sub-chronic and chronic toxicity in the rat

Sulfosulfuron, purity 98.8%, vehicle 0.5% carboxymethylcellulose, was administered by dermal application to male and female Sprague Dawley (CD) rats at dose levels of 0, 100, 300 and 1,000 mg/kg bw per application over a 28-d period. Frequency of application was 6-h/d, 5-d/week, 8 rats per sex per group.

The NOEL was determined to be 1,000 mg/kg bw per application, since there were no treatment-related effects observed in male or female rats at any dose level tested.

There were no signs of local dermal irritation observed in male or female rats to sulfosulfuron at any dose level tested.

Sulfosulfuron, purity 99%, was administered in the diet to Charles River Sprague Dawley rats at doses of 0, 20, 200, 2,000 or 10,000 ppm (equal to 0, 1.32, 13.71, 136.47 and 668.74 mg/kg bw/d for males, and 0, 1.52, 15.64, 154.13 and 767.86 mg/kg bw/d for females) for a period of 4 weeks, 5 rats per sex per group.

The NOEL for this study was determined to be 10,000 ppm (equal to 668.74 mg/kg bw/d for males, and 767.86 mg/kg bw/d), since there were no treatment-related effects observed in male or female rats at any dose level tested.

Sulfosulfuron, purity 98.9%, was administered in the diet to Charles River Sprague Dawley rats at dose levels of 0, 20, 200, 2,000, 6,000 or 20,000 ppm (equal to 0, 1.22, 12.1, 123.2, 370 and 1,278 mg/kg bw/d for males, and 0, 1.47, 14.6, 144.3, 448 and 1489 mg/kg bw/d for females), for a period of 92 days, 10 rats per sex per group. An additional 10 pregnant females were assigned to each dose level for the concurrent reproductive study.

The NOEL for this study was determined to be 6,000 ppm (equal to 370 mg/kg bw/d for males, and 448 mg/kg bw/d for females), based on lower mean body weights in the 20,000 ppm group. In addition, calculi noted in the kidneys and/or bladder of 1 male and 2 females in the 20,000 ppm group were considered possibly to be related to treatment, since urinary calculi are not normally seen in animals of the age used in this study. Based on the results of this study, the dose levels chosen for the long term rat study were 0, 50, 500, 5,000 and 20,000 ppm.

Male and female Sprague Dawley rats were continuously fed test diets containing sulfosulfuron, purity 98.4%, at dietary concentrations of 0, 50, 500, 5,000 and 20,000 ppm (equal to 0, 2.4, 24.4, 244.2 and 1,178.3 mg/kg bw/d for males, and 0, 3.1, 30.4, 314.1 and 1296.5 mg/kg bw/d for females), 60 rats per sex per group, for a period of up to 22 months. An interim sacrifice was conducted on 10 randomly chosen rats per sex per group after 12 months on study.

The NOEL for systemic toxicity was determined to be 500 ppm (equal to 24.4 mg/kg bw/d for males, and 30.4 mg/kg bw/d for females), based on treatment-related effects to the urinary system at dose levels of 5,000 and 20,000 ppm.

Treatment with sulfosulfuron resulted in significantly increased mortality for males in the 20,000 ppm group. By day 250, mortality rate had already attained 37%; (and so it was decided to sacrifice all remaining males in the 20,000 ppm group on day 259) the cause of all of these deaths was identified as resulting from urinary calculi and related abnormalities in the kidneys, urinary bladder and ureters. In addition, a slight increase in the mortality rate was noted for females in the

20,000 ppm group, which was also associated with an increased incidence of urinary calculi and related abnormalities. The effect was less pronounced than for males, and did not necessitate early sacrifice of the 20,000 ppm group females.

The only treatment-related clinical observation was an increased incidence of blood-like urine colour in the 20,000 ppm group, males only. Treatment with sulfosulfuron also resulted in slightly lower mean body weight gain in the 20,000 ppm group, both sexes.

At necropsy, treatment-related findings were observed in the kidneys (calculi, pelvic dilatation), urinary bladder (calculi, thickened mucosa) and ureters (calculi, dilatation) in the 20,000 ppm group, both sexes, and in the 5,000 ppm group, females only. In addition, an increased incidence of enlarged parathyroids and emaciation were observed in 20,000 ppm females.

Histopathological examination supported the findings noted at necropsy. In the kidneys, treatment-related findings were pelvic epithelial hyperplasia and pelvic dilatation (20,000 ppm group, both sexes, 5,000 ppm group, females only), calculi (5,000 and 20,000 ppm groups, both sexes), squamous metaplasia and pyelonephritis (20,000 ppm group, females only), mineralization in the cortex and medulla (20,000 ppm group, both sexes, 5,000 ppm group, males only) and papillary necrosis (20,000 ppm group, males only). In the urinary bladder, treatment-related findings were calculi (20,000 ppm group, males only); mucosal epithelial hyperplasia [(20,000 ppm group, both sexes), a slight increase noted at 5,000 ppm, males only], and hemorrhage (5,000 and 20,000 ppm groups, males only). Treatment-related findings observed in the ureters were noted in the 20,000 ppm group, both sexes, evident as dilatation, mucosal epithelial hyperplasia, erosion/ulceration, amorphous debris (males only) and squamous metaplasia (females only). Mineralization of various tissues, e.g., aorta, heart, lung, muscle was observed in the 20,000 ppm group, females only (these tissues were not examined in 20,000 ppm males) and in the 5,000 ppm group, males only. In addition, an increased incidence of parathyroid hyperplasia and fibrous osteodystrophy was noted for females in the 20,000 ppm group.

Urinalysis revealed an increased incidence of unidentifiable and/or abnormal crystal types in the 5,000 and 20,000 ppm groups, both sexes.

A slight increase in mean blood urea nitrogen, sodium and chloride values observed in the 5,000 and 20,000 ppm groups, females only, was considered to be treatment-related. Examination of the individual animal data revealed that the individual values that were increased fell well above the normal range of values, and were from those animals that also exhibited urinary calculi and associated abnormalities in the kidneys and/or urinary bladder.

A single papilloma and a single transitional cell carcinoma were observed in the urinary bladder of 2 different females in the 5,000 ppm group. Both affected females also had calculi in the urinary bladder. Although bladder tumours were not observed in any of the females in the 20,000 ppm group, it is known that calculi can elicit hyperplasia and neoplasia resulting from direct irritation to the bladder epithelium. Hence, the 2 tumours observed in the 5000 ppm group were considered

to possibly be related to treatment. Therefore, a conservative NOEL for tumorigenicity was set at 500 ppm (equal to 24.4 mg/kg bw/d for males and 30.4 mg/kg bw/d for females).

NOTE: There were no other tumours related to treatment with sulfosulfuron.

3.1.4.3 Sub-chronic toxicity in the dog

Male and female beagle dogs were dosed orally with gelatin capsules containing sulfosulfuron (purity unstated) at concentrations of 0 (empty capsule), 30, 100, 300 or 1,000 mg/kg bw/d for a period of 4 weeks, 5-d per week, 2 dogs per sex per group.

The NOEL was determined to be 1,000 mg/kg bw/d, since there were no findings which were considered to be related to treatment with sulfosulfuron in male or female dogs at any dose level tested.

Based on the results of this study, the dose levels chosen for the 3-month dog study were 0, 30, 100, 300 and 1,000 mg/kg bw/d.

Male and female beagle dogs were dosed orally with gelatin capsules containing sulfosulfuron, purity 98.4%, at concentrations of 0 (empty capsule), 30, 100, 300 and 1,000 mg/kg bw/d, for a period of 3 months, 5-d per week, 5 dogs per sex per group.

The NOAEL for males was determined to be 300 mg/kg bw/d based on unidentifiable crystals observed in the urine at dose levels of 300 and 1,000 mg/kg bw/d, and slightly higher plasma sodium (100 mg/kg bw/d and higher) and chloride (30 mg/kg bw/d and higher) levels. These findings were observed at the 45-d, but not at the 90-d sampling period. In the absence of any other findings at 100 and 300 mg/kg bw/d, these findings were not considered adverse. In the 1,000 mg/kg bw/d group, one male dog was sacrificed *in extremis* on study day 75, due to urolithiasis. Treatment-related findings observed in this male at necropsy were renal edema and wedge-shaped foci in the renal cortices; urethral calculi and associated necrosis; inflammation, ulceration and edema of the urinary bladder; calculi in the urinary bladder; dilated ureters; and inflammation, vasculitis/perivasculitis and hemorrhage of the prostate gland.

For females, the NOEL was determined to be 100 mg/kg bw/d based on treatment-related findings observed in the urinary bladder at higher dose levels, i.e., red/purple foci of discoloration, inflammation, ulceration, hemorrhage and unidentifiable crystals in the 300 and 1,000 mg/kg bw/d groups; and hyperplasia in the 1,000 mg/kg bw/d group. The only other finding considered to possibly be related to treatment was a slight increase in plasma sodium in the 1,000 mg/kg bw/d group, and in plasma chloride in the 300 and 1,000 mg/kg bw/d groups, observed at the day 45 sampling period only.

Male and female beagle dogs were dosed orally with gelatin capsules containing sulfosulfuron, purity 98.5%, at concentrations of 0 (empty capsule), 5, 20, 100 and 500 mg/kg bw/d, for a period of 1 year, 5-d per week, 5 dogs per sex per group.

The NOEL for males was determined to be 100 mg/kg bw/d based on treatment-related findings in the urinary bladder in the 500 mg/kg bw/d group, i.e., thickened mucosa with red foci, calculi, hemorrhage and edema. Clinically, a yellow precipitate was noted in the urine at this dose level, and unidentifiable crystals were observed in the urine at the 6-month sampling period.

The NOAEL for females was set at 500 mg/kg bw/d based on the observation of unidentifiable crystals in the urine at this dose level, at the 6-month sampling period only. In the absence of any other treatment-related findings, this was not considered to be an adverse effect.

NOTE: Since the NOELs for both the 3-month and 1-year dog studies were based on treatment-related effects noted in the urinary bladder, it was considered most appropriate to combine the results of these 2 studies to determine the overall definitive NOEL for dogs. Hence, the NOEL for male and female dogs was determined to be 100 mg/kg bw/d.

3.1.5 Reproductive and developmental toxicity

A two-generation reproduction study was conducted using Sprague Dawley rats, fed test diets containing sulfosulfuron, purity 98.4%, at dietary concentrations of 0, 50, 500, 5,000 and 20,000 ppm (equal to 0, 3.1, 31.1, 312.1 and 1,312.8 mg/kg bw/d for males, and 0, 3.6, 36.2, 363.2 and 1,454.1 mg/kg bw/d for females), 30 per sex per group, continuously throughout the study period. Each female in each generation was mated to produce one litter only.

The NOEL for systemic toxicity was determined to be 5,000 ppm (equal to 312.1 mg/kg bw/d for males and 363.2 mg/kg bw/d for females), based on treatment-related gross and histopathological effects to the urinary system in the 20,000 ppm group.

Treatment with sulfosulfuron resulted in early mortality in the 20,000 ppm group, males only (two F0 males and one F1 male); the cause of death was identified as resulting from urinary calculi. The only clinical observation considered to possibly be treatment-related was urine containing granular, sand-like material noted for one F0 male. A slight decrease in mean body weight gain was noted in the 20,000 ppm group, during the premating period in F0 males (~5% less than control) and F0 females (~12% less than control), and for F0 females during the first 2 weeks of gestation (~27% less than control). A similar effect was not noted in the F1 generation animals (lower body weights were attributed to lower initial body weights; however, there were no treatment-related effects on mean body weight gain for F1 males or females). At gross necropsy, findings considered possibly to be treatment-related were observed in the kidneys (calculi, pelvic dilatation); ureter (calculi, distended/dilated); and urinary bladder (calculi, enlarged/distended, thick-walled) of F0/F1 males and/or females in the 20,000 ppm group. Treatment-related histopathological findings in the 20,000 ppm group were bilateral hydronephrosis (F0 males and

F0 and F1 females); pelvic epithelial hyperplasia (F0 and F1 females); and possibly nephropathy (F0 females).

The NOEL for reproductive toxicity was set at 20,000 ppm (equal to 1,312.8 mg/kg bw/d for males, and 1,454.1 mg/kg bw/d for females), since there were no adverse, treatment-related effects on reproductive parameters at any dose level tested.

NOTE: There was a statistically significant reduction in the number of 20,000 ppm males with confirmed copulation at the F0 mating, but copulatory performance was normal in a second trial with virgin, untreated females and in the F1 mating.

In a range-finding teratology study, pregnant Crl:CD BR rats were dosed by oral intubation with sulfosulfuron, purity 99%, as a suspension in corn oil, at dose levels of 0, 25, 125, 250, 500 and 1,000 mg/kg bw/d, 8 mated females per group, from day 6 to 15 of gestation, inclusive.

The NOELs for maternal and fetotoxicity were determined to be 1,000 mg/kg bw/d, since there were no treatment-related maternal or fetal effects observed at any dose level tested.

Since there were no treatment-related effects observed at dose levels up to and including the highest dose level of 1,000 mg/kg bw/d (limit dose) tested in the dose range-finding teratology study, doses chosen for the main study were 0, 100, 300 and 1,000 mg/kg bw/d (limit dose).

Pregnant Sprague Dawley rats (Crl:CD BR) were dosed by gavage with sulfosulfuron, purity 99.1%, as a suspension in corn oil, at dose levels of 0 (vehicle control), 100, 300 and 1,000 mg/kg bw/d, 25 mated females per group, from day 6 to 15 of gestation, inclusive. The NOELs for maternal toxicity, fetotoxicity and teratogenicity were set at 1,000 mg/kg bw/d since there was no evidence of maternally toxic, fetotoxic or teratogenic effects related to treatment with sulfosulfuron at any dose level tested.

In a range-finding teratology study, pregnant New Zealand White rabbits were dosed by oral intubation with sulfosulfuron, purity 99.1%, as a suspension in 0.5% methylcellulose, at dose levels of 0, 50, 100, 250, 750 and 1,000 mg/kg bw/d, 7 inseminated females per group, from day 7 to 19 of gestation, inclusive.

The NOELs for maternal and fetotoxicity were determined to be 1,000 mg/kg bw/d, since there were no treatment-related maternal or fetal effects observed at any dose level tested.

Since there were no treatment-related effects observed at dose levels up to and including the highest dose level of 1,000 mg/kg bw/d (limit dose) tested in the dose range finding study, doses chosen for the main study were 0, 50, 250 and 1,000 mg/kg bw/d (limit dose).

Pregnant New Zealand White rabbits were dosed by gavage with sulfosulfuron, purity >98.5%, as a suspension in 0.5% carboxymethylcellulose, at dose levels of 0 (vehicle control), 50, 250 and 1,000 mg/kg bw/d, 20 pregnant females per group, from day 7 to 19 of gestation, inclusive.

The NOELs for maternal toxicity, fetotoxicity and teratogenicity were set at 1000 mg/kg bw/d since there was no evidence of maternal toxicity, fetotoxicity or teratogenic effects related to treatment with sulfosulfuron at any dose level tested.

3.1.6 Neurotoxicity (acute, delayed and sub-chronic)

Male and female Sprague Dawley rats were dosed once by oral gavage with sulfosulfuron, purity 98.5%, as a suspension in corn oil at dose levels of 0, 125, 500 and 2,000 mg/kg bw, 10 rats per sex per group. Special neurological examinations included a Functional Observational Battery (FOB) and motor activity testing; and a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 2,000 mg/kg bw, since there were no treatment-related effects observed in male or female rats at any dose level tested.

Male and female Sprague Dawley rats were fed test diets containing sulfosulfuron, purity 98.5%, at dietary concentrations of 0, 200, 2,000 and 20,000 ppm (equal to 0, 12, 122 and 1,211 mg/kg bw/d for males, and 0, 14, 141 and 1,467 mg/kg bw/d for females), 10 rats per sex per group, for a period of 14 weeks. Special neurological examinations included a FOB and motor activity testing (in-life); and a detailed histopathological examination of perfused central and peripheral nervous system tissues.

The NOEL was determined to be 20,000 ppm (equal to 1,211 mg/kg bw/d for males, and 1,467 mg/kg bw/d for females) since there were no treatment-related effects observed at any dose level tested.

3.1.7 Overall toxicological summary

A detailed review of the toxicology database available for the new herbicide sulfosulfuron has been completed. Data submitted were complete and comprehensive, and included the full battery of studies currently required for registration purposes. Studies were well conducted and in conformance with currently acceptable international testing protocols.

Metabolism studies in rats indicated that sulfosulfuron was well absorbed after single or multiple oral administration of low doses of 10.0 mg/kg bw (>90%), whereas only 35%-40% was absorbed after a single oral high dose of 1,000 mg/kg bw, and was rapidly excreted after low or high doses (>80% within 24-h post-dosing). For all low dose groups, the major portion of the radioactivity was excreted via the urine, i.e., between 77% to 87% of the AD, while between 5% and 13% was eliminated via the feces. For the high dose group, the major route of elimination

was via the feces, i.e., 55% to 63% of the AD, while between 31% and 33% was excreted in the urine.

The major fraction of TRR extracted from urine and feces was identified as unchanged sulfosulfuron (>88%), with limited metabolism via demethylation and pyrimidine ring hydroxylation prior to excretion in the urine and feces. Tissue retention of radioactivity from labelled sulfosulfuron was very low, and the expired air contained <0.04% of the AD. The renal excretion of sulfosulfuron and its metabolites has major toxicological implications, as the kidney, ureters and urinary bladder have proven to be target organs in sub-chronic and chronic studies in mice, dogs and rats. A consistent pattern of injury to the urinary tract has emerged in all three species, associated with the presence of crystals that may aggregate and form calculi.

Acute single dosing revealed that technical sulfosulfuron and the Sundance formulation were of low toxicity by the oral, inhalation and dermal routes to laboratory animals and were minimally irritating when instilled into the eyes of rabbits. Technical sulfosulfuron was minimally irritating when applied to rabbit skin, whereas the Sundance formulation induced slight skin irritation. Neither possessed skin-sensitizing properties when tested on guinea pigs according to the modified Buehler and/or maximization methods.

In dogs, histological urinary bladder lesions consisted principally of epithelial inflammation, ulceration and haemorrhage, which occurred at and above doses of 300 mg/kg bw/d. Chronically exposed male mice displayed inflammation, mucosal hyperplasia and squamous metaplasia of the urinary bladder epithelium at 3,000 and 7,000 ppm, together with mesenchymal tumours at 7,000 ppm, which may have arisen from prolonged epithelial tissue injury and repair. The chronic rat study was compromised by the choice of a highest dietary level of 20,000 ppm. This caused one third of the high dose males to die from urolithiasis by day 250 (the remaining high dose males were sacrificed on day 259). Survival of high dose females was also reduced, but the effect was less pronounced. Given the high incidence of bladder mucosal epithelial hyperplasia at 20,000 ppm, it is possible that tumour formation could have occurred in males if treatment had continued. Paradoxically, although there were no neoplasms in the female rat urinary bladder at this dose, single cases of papilloma and transitional cell carcinoma of the bladder were observed at 5,000 ppm, and may have been related to treatment.

The urinary tract lesions caused by sulfosulfuron are similar to those elicited in rats by another substituted urea herbicide, diuron. However, diuron's effects were seen at lower doses and in the absence of crystalluria. They comprised bladder epithelial hyperplasia, papilloma and/or carcinoma in females treated at 250 ppm and in both sexes at 2,500 ppm. Renal pelvic epithelial hyperplasia was also seen at these doses, together with renal carcinoma in 2,500 ppm males. By contrast, the current database has demonstrated lowest observable effect levels (LOELs) for urinary tract injury of 3,000 ppm in mice, 5,000 ppm in rats and 300 mg/kg bw/d in dogs. The NOELs in chronic studies with sulfosulfuron were 700 ppm (93 mg/kg bw/d) and 500 ppm (24 mg/kg bw/d) in mice and rats, respectively, based on urinary tract lesions, and 100 mg/kg bw/d in dogs, based on crystalluria and bladder injury. TCAB and TCAOB, the carcinogenic impurities

suspected of association with the carcinogenic effect of diuron, are not declared components of sulfosulfuron.

Sulfosulfuron did not cause haemolytic anaemia, as seen in rats and dogs treated with diuron and linuron, or the interstitial cell testicular adenomas caused by linuron in rats. Sulfosulfuron was also devoid of reproductive toxicity in rats at feeding levels of up to 20,000 ppm, did not give rise to developmental toxicity in rats or rabbits at oral doses of up to 1,000 mg/kg bw/d, and showed no evidence of neurotoxicity in rats by either acute or sub-chronic exposure.

Sulfosulfuron disclosed no mutagenicity in *Salmonella* or CHO cells and was not clastogenic at up to 1000 ：g/mL in human lymphocytes or at up to 5,000 mg/kg bw in a mouse bone marrow micronucleus test. However, a second in vitro clastogenicity study, performed in cultured Chinese hamster lung fibroblasts, revealed high incidences of chromosomal aberrations at and above 2,000 ：g/mL, in the absence of metabolic activation. However, the effective concentrations were sufficiently high to cause precipitation of the test compound. Based on the results of the mutagencity studies, the weight of evidence indicates that sulfosulfuron is non-genotoxic.

The mechanism of bladder injury and tumorigenesis, and its relevance to humans, has been discussed extensively in the "Report of the Rodent Bladder Carcinogenesis Working Group" (published as a series of papers in Fd. Chem. Toxic. 33, No. 9, pp. 699-801 [1995]). The working group pointed out that although urinary tract stones are common in humans and the cellular structure of the urothelium is similar in rodents and humans, bladder tumours in humans are rarely associated with stones. Anatomical differences between rodents and humans predispose the residence and accumulation of precipitates in the rodent bladder and injury to the bladder epithelium, whereas in humans, foreign bodies have a diminished potential for damage to the bladder epithelium and an increased likelihood of being passed during urination.

It is concluded that a non-genotoxic rodent bladder carcinogen, acting via formation of calculi, should not pose a carcinogenic hazard to humans provided that intake is below the threshold concentration required for generation of urinary precipitates. Even if sulfosulfuron were capable of initiating chromosomal injury to the renal or bladder epithelial cells, the effect has only been demonstrated in vitro at concentrations high enough to cause precipitation from solution. Given that the current database has established a clear association between crystal formation and injury to the urinary tract, and has demonstrated NOELs for the effect, application of a safety factor should provide assurance that sulfosulfuron will not pose a carcinogenic hazard at the levels anticipated in the human dietary intake.

Table 3 Summary of the toxicity studies with sulfosulfuron

METABOLISM
Male and female Sprague Dawley rats received either a single low intravenous dose (10.0 mg/kg bw), single low oral dose (10.0 mg/kg bw), single high oral dose (1,000 mg/kg bw) or 15 daily low oral doses (10.0 mg/kg bw) of sulfosulfuron, purity 98%, 4 or 5 rats per sex per group. Radiolabelled sulfosulfuron consisted of a 1:1 ratio of sulfosulfuron labelled with ^{14}C at the C-3 position of the imidazopyridine ring; and sulfosulfuron labelled with ^{14}C at the C-5 position of the pyrimidine ring. The test material was well absorbed after single or multiple oral administration of the low dose, i.e., >90% of the AD. However, only 35% to 40% of the AD was absorbed after a single oral high dose. The test material was rapidly excreted for all dose groups; >80% and >90% of the AD had been excreted within 24 h and 72 h post-dosing, respectively. For all low dose groups, the major portion of the radioactivity was excreted via the urine, i.e., between 77% to 87% of the administered dose, while between 5% and 13% was eliminated via the feces. For the high dose group, the major route of elimination was via the feces, i.e., 55% to 63% of the AD, while between 31% and 33% was excreted in the urine. Elimination was found to be biexponential for all groups, with the mean half-life for the initial phase determined to be 2.2- to 5.8-h, and for the terminal phase was 21.4- to 56.7-h. The expired air contained <0.04% of the AD (as determined in the pilot phase). The liver contained the highest traces of radioactivity i.e., <0.13% of the AD, with all other individual tissues containing 0.01% or less of the AD, indicating that sulfosulfuron did not accumulate nor was retained in the various tissues. Based on the metabolic profiles obtained in this study for all groups, the major fraction was identified as unchanged sulfosulfuron, accounting for ~88% to 96% of the TRR. Four other metabolites were identified (desmethyl sulfosulfuron, 5-hydroxy sulfuron, sulfonamide and pyridine sulfate), each accounting for less than 0.5% of the TRR. The metabolic pathways for sulfosulfuron were determined to be: (1) ring hydroxylation of the 5-position carbon of the pyrimidine ring, and (2) demethylation of the methoxy group at either the 4- or 6-position of the pyrimidine ring, resulting in the formation of the desmethyl and 5-hydroxy-sulfosulfuron as the most abundant metabolites. The cleavage of the sulfonylurea bridge to form separate imidazopyridine and pyrimidine metabolites was a minor pathway.

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES - TECHNICAL			
Oral	Rat - Sprague Dawley (SD), 5/sex, 5,000 mg/kg bw	LD_{50}> 5,000 mg/kg bw	Clinical observations consisted of mucoid/soft stools. **LOW TOXICITY**
Dermal	Rat - SD, 5/sex, 5,000 mg/kg bw	LD_{50}> 5,000 mg/kg bw	Slight focal erythema was noted in 1 male and 1 female rat, recovery by day 4, **LOW TOXICITY**
Inhalation	Rat - SD, 5/sex, 3.0 mg/L	LC_{50}>3.0 mg/L	MMAD[1]=7.1 : m, GSD[1]=2.6 65% < 10 : m; 20.8% < 3.3 : m Clinical signs consisted of red nasal and ocular discharge during exposure; enlarged liver in 2 males. **LOW TOXICITY**
Skin Irritation	Rabbit - New Zealand White (NZW), 2 males and 4 females, 0.5 g dose	PIS[1]=0.02	**MINIMALLY IRRITATING**
Eye Irritation	Rabbit - NZW, 5 males and 1 female, 0.1 mL dose	MAS[1]=11.7	**MINIMALLY IRRITATING**
Skin Sensitization (Modified Buehler method)	Guinea pig - Hartley, Test material administered undiluted, 0.4 mL induction and challenge Positive control reference data with DNCB	Test material non-irritating No evidence of sensitization Positive control was sensitizing, demonstrating responsiveness of assay	**NOT A SENSITIZER**
Skin Sensitization (Maximization Test)	Guinea pig - Hartley, Test Material 5% intradermal injection (induction) followed by a topical application of 100% (challenge) Positive control reference data with DNCB	Test material not sensitizing but positive control was sensitizing - demonstrating responsiveness of assay	**NOT A SENSITIZER**

[1] MMAD: Mass Median Aerodynamic Diameter
GSD: Geometric Standard Deviation
PIS: Primary Irritation Score
MAS: Maximum Average Score

ACUTE STUDIES - FORMULATION			
Oral	Rat - SD, 5/sex, 5,000 mg/kg bw	LD_{50}>5,000 mg/kg bw	Clinical observations consisted of excessive salivation in 1 male - recovery by day 1; and moist rales in 1 female - recovery by day 3. One male lost weight during week 1. **LOW TOXICITY**.
Dermal	Rat - SD, 5/sex, 5,000 mg/kg bw	LD_{50}>5,000 mg/kg bw	Foci of erythema were noted on 2 males and 5 females - recovery by day 6 - **LOW TOXICITY**
Inhalation	Rat - SD, 5/sex, 2.8 mg/L	LC_{50}>2.8 mg/L	MMAD=3.8 ：m, GSD = 2.3 87.5% <10：m; 43.0% <3.3：m Clinical signs consisted of laboured breathing - recovery by day 1 post-exposure. **LOW TOXICITY**
Skin Irritation	Rabbit - NZW, 2 males and 4 females, 0.5 g dose	PIS = 0.02	**MINIMALLY IRRITATING**
Eye Irritation	Rabbit - NZW, 0.1mL dose 5 males and 1 female	MAS = 11.7	**MINIMALLY IRRITATING**
Skin Sensitization (Modified Buehler method)	Guinea pig - Hartley, Test material administered undiluted, 0.4 mL induction and challenge Positive control reference data with DNCB	Test material non-irritating No evidence of sensitization Positive control was sensitizing - demonstrating responsiveness of assay	**NOT A SENSITIZER**
Skin Sensitization (Maximization Test)	Guinea pig - Hartley, Test Material 5% intradermal injection (induction) followed by a topical application of 100% (challenge) Positive control reference data with DNCB	Test material not sensitizing but positive control was sensitizing - demonstrating responsiveness of assay	**NOT A SENSITIZER**

SHORT TERM			
4-week dietary	Mouse - CD-1, 5/sex/group, 0, 10, 100, 1,000 and 4,000 ppm, (equal to 0, 2.0, 17, 186 and 701 mg/kg bw/d in males, and 0, 2.7, 22, 274 and 987 mg/kg bw/d in females)	Males, NOAEL=4,000 ppm (701 mg/kg bw/d) Females, NOEL=4,000 ppm (987 mg/kg bw /d)	The only treatment-related effect was slightly increased palmitoyl CoA oxidase activity for males only in the 4,000 ppm (considered a non-adverse effect)
90-day dietary	Mouse - CD-1, 10/sex/group, 0, 100, 1,000, 3,000 and 7,000 ppm (equal to 0, 18, 163, 550 and 1,144 mg/kg bw/d for males, and 0, 32, 313, 887 and 2,123 mg/kg bw/d for females)	NOEL=7,000 ppm (1,144 mg/kg bw/d for males, and 2,123 mg/kg bw/d for females)	No treatment-related effects at any dose level tested.
4-week dietary	Rat - SD, 5/sex/group, 0, 20, 200, 2,000 and 10,000 ppm (equal to 0, 1.32, 13.71, 136.47 and 668.74 mg/kg bw/d for males, and 0, 1.52, 15.64, 154.13 and 767.86 mg/kg bw/d for females)	NOEL=10,000 ppm (equal to 668.74 mg/kg bw/d for males, and 767.86 mg/kg bw/d for females).	No treatment-related effects at any dose level tested.
28-day dermal	Rat - SD, 8/sex/group, 0, 100, 300 and 1,000 mg/kg bw/d	NOEL = 1,000 mg/kg bw/d	No treatment-related effects at any dose level tested.
90-d dietary	Rat - SD, 20/sex/group 0, 20, 200, 2,000, 6,000 and 20,000 ppm (equal to 0, 1.22, 12.1, 123.2, 370 and 1,278 mg/kg bw/d for males and 0, 1.47, 14.6. 144.3, 448 and 1489 mg/kg bw/d for females)	NOEL=6,000 ppm (370 mg/kg bw/d for males and 448 mg/kg bw/d for females)	**20,000 ppm:** Lower mean body weight gain; calculi in the kidneys and/or bladder (1 male, 2 females) possibly treatment-related.
4-week; gelatin capsule	Dog - Beagle, 2/sex/group; 0, 30, 100, 300 and 1,000 mg/kg bw/d	NOEL=1,000 mg/kg bw/d	No treatment-related findings at any dose level tested.

90-d; gelatin capsules	Dog - Beagle; 5/sex/group; 0, 30, 100, 300 and 1,000 mg/kg bw/d	Males, NOAEL=300 mg/kg bw/d Females, NOEL=100 mg/kg bw/d	**For males, at 300 and 1,000 mg/kg bw/d**: Unidentifiable crystals in the urine; one male in the 1,000 mg/kg bw/d group died due to treatment-related urolithiasis. **For females, at 300 and 1,000 mg/kg bw/d:** Treatment-related findings in the urinary bladder.
1-year; gelatin capsule	Dog - Beagle; 5/sex/group; 0, 5, 20, 100 and 500 mg/kg bw/d	Males, NOEL=100 mg/kg bw/d Females, NOAEL=500 mg/kg bw/d	**For males, at 500 mg/kg bw/d:** Treatment-related findings in the urinary bladder. **For females, at 500 mg kg bw/d:** Unidentifiable crystals in the urine at 6 months only; not considered adverse in the absence of any other findings.
CHRONIC TOXICITY/ONCOGENICITY			
18-month feeding	Mouse - CD-1, 60/sex/group, 0, 30, 700, 3,000 and 7,000 ppm (equal to 0, 4.0, 93, 394 and 944 mg/kg bw/d for males and 0, 6.5, 153, 635 and 1,388 mg/kg bw/d for females)	**Chronic Effects** Males, NOEL=700 ppm (93 mg/kg bw/d) Females, NOEL=7,000 (1388 mg/kg bw/d) **Oncogenicity** Males, NOEL=3,000 ppm (394 mg/kg bw/d) Females, NOEL=7,000 ppm (1,388 mg/kg bw/d)	**For males, at 3,000 and 7,000 ppm:** Treatment-related findings in the urinary system (urinary calculi and associated changes). **For females:** No treatment-related findings at any dose level. **For males, at 7,000 ppm:** Mesenchymal tumours in the urinary bladder. **For females:** No oncogenic effects noted in females.

2-year feeding	Rat - SD, 60/sex/group, 0, 50, 500, 5,000 and 20,000 ppm (equal to 0, 2.4, 24.4, 244.2 and 1,178.3 mg/kg bw/d for males and 0, 3.1, 30.4, 314.1, 448 and 1,489 mg/kg bw/d for females)	**Chronic Effects** NOEL=500 ppm (24.4 mg/kg bw/d for males, and 30.4 mg/kg bw/d for females) **Oncogenicity** NOEL=500 ppm (24.4 mg/kg bw/d for males and 30.4 mg/kg bw/d for females)	**5,000 and 20,000 ppm:** Treatment-related findings in the urinary system (urinary calculi and associated changes). **20,000 ppm:** Increased mortality. **Females only, at 5,000 ppm:** In the urinary bladder, a single papilloma, and a single transitional cell carcinoma (2 separate females). Both affected females also had calculi in the urinary bladder; hence, the 2 tumours were considered to possibly be related to treatment, resulting from direct irritation to the bladder epithelium. No treatment-related oncogenic findings were observed for females in the 20,000 ppm group. No oncogenic effects were noted in males at any dose level.
REPRODUCTION / DEVELOPMENTAL TOXICITY			
Two-generation, one litter per female.	Rat - SD, 30/sex/ group, 0, 50, 500, 5,000 and 20,000 ppm (equal to 0, 3.1, 31.1, 312.1 and 1,312.8 mg/kg bw/d for males, and 0, 3.6, 36.2, 363.2 and 1,454.1 mg/kg bw/d for females)	**Systemic Effects** NOEL=5,000 ppm (312.1 mg/kg bw/d for males, and 363.2 mg/kg bw/d for females) **Reproductive Effects** NOEL=20,000 ppm (1,312.8 mg/kg bw/d for males, and 1,454.1 mg/kg bw/d for females)	**20,000 ppm:** Treatment-related findings in the urinary system (urinary calculi and associated changes). Early mortality, males only. No reproductive effects were noted at any dose level tested.
Teratogenicity	Rat - Crl:CD BR, 25/group, 0, 100, 300 and 1,000 mg/kg bw/d	Maternal, fetal and teratogenic NOEL=1,000 mg/kg bw/d	No maternally toxic, fetotoxic or teratogenic effects noted at any dose level tested.
Teratogenicity	Rabbit -NZW, 20/group, 0, 50, 250 and 1,000 mg/kg bw/d	Maternal, fetal and teratogenic NOEL=1,000 mg/kg bw/d	No maternally toxic, fetotoxic or teratogenic effects noted at any dose level tested.

MUTAGENICITY			
STUDY	**SPECIES/STRAIN or CELL TYPE**	**DOSES EMPLOYED**	**SIGNIFICANT EFFECTS/ COMMENTS**
Salmonella / Ames Assay, in vitro	*S. typhimurium* - TA 1535, TA 1537, TA 98, TA 100 and TA 102	0, 5, 15, 50, 150, 500, 1,500 and 5,000 ：g/plate, ± S9	Negative
Mammalian cell gene mutation assay, in vitro	Chinese hamster ovary cells (normal $HGPRT^+$)	312, 624, 1,250, 2,500 and 5,000 ：g/mL, ± S9	Negative
Cytogenetic assay, in vitro	Cultured human lymphocytes	100, 250, 500, 750 and 1,000 ：g/mL.	Negative
Chromosomal assay, in vitro	Chinese hamster lung fibroblasts	0, 1,000, 1,250, 2,000, 2,500, 3,000 and 5,000 ：g/mL, ± S9	Negative in the presence of metabolic activator Positive (clastogenic) in the absence of metabolic activator at dose levels of 2,000 ：g/mL and higher.
Mammalian cytogenetics (micronucleus) assay, in vivo	Mouse - CD-1	0, 1250, 2,500 and 5,000 mg/kg bw, with sacrifice at 24, 48 and 72 h after dosing	Negative
Ancillary in vivo pharmacokinetic study to the micronucleus assay	Mouse - CD-1	2,000 mg/kg bw, with sacrifice at 2 and 8 h after dosing	Significant amounts of radioactivity were detected in the blood plasma and bone marrow, indicating that target cell exposure occurred in the micronucleus assay.
NEUROTOXICITY			
Acute oral, gavage	Rat - SD, 10/sex/group, 0, 125, 500 and 2,000 mg/kg bw	NOEL=2,000 mg/kg bw	No treatment-related effects were noted at any dose level tested.
14-week feeding study	Rat - SD, 10/sex/group, 0, 200, 2,000 and 20,000 ppm (equal to 0, 12, 122 and 1,211 mg/kg bw/d for males, and 0, 14, 141 and 1,467 mg/kg bw/d for females)	NOEL=20,000 ppm (1,211 mg/kg bw/d for males, and 1,467 mg/kg bw/d for females)	No treatment-related effects were noted at any dose level tested.

3.2 Determination of acceptable daily intake (ADI)

The lowest NOEL was in the chronic rat study at a level of 24.4 mg/kg bw/d, based on urolithiasis and associated pathological and biochemical findings at higher doses. For the calculation of the ADI, a safety factor (SF) of 100 is proposed.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF}} = \frac{24.4 \text{ mg/kg bw/d}}{100} = 0.24 \text{ mg/kg/day of sulfosulfuron}$$

The maximum acceptable intake for a 60-kg person, calculated according to the formula ADI x 60 kg is 14.4 mg/day.

3.3 Acute reference dose (ArfD)

In the context of the low order of acute toxicity of sulfosulfuron, following exposure by oral, dermal and inhalation routes, it is not necessary or appropriate to propose an acute reference dose.

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

The formulation is of low acute toxicity by the dermal, inhalation and oral routes. It is a slight skin irritant and is minimally irritating to the eyes. Results of skin sensitization studies were negative.

Given the short term nature of the exposure for farmers (one to eight days per year), and the predominantly dermal exposure route, the 28-d dermal rat study was considered to be the most relevant to use in the risk assessment. This study was well conducted and did not demonstrate any local or systemic toxic effects at 1,000 mg/kg bw/d, the highest dose tested.

The 28-d dermal study was not considered relevant for the longer term custom applicators exposure (up to 40-d per year). The dietary NOEL of 100 mg/kg bw/d, determined both in the 3-month and 1-year dog dietary studies, was considered the most relevant to use in risk assessment. This NOEL was based on urinary bladder effects at higher dose levels.

Although there was evidence that sulfosulfuron is a non-genotoxic bladder carcinogen in rodents, it was concluded that it should pose no carcinogenic hazard to humans provided that the dose is below the threshold concentration required for generation of urinary precipitates. The lowest NOEL for tumorigenicity was set at 24 mg/kg bw/d, based on a 2-year rat study.

Reproductive, teratogenicity and mutagenicity testing showed negative findings. There were no signs of neurotoxicity.

3.5 Drinking water limit

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

A farmer applying Sundance by ground equipment could typically treat 100 ha/d and up to 800 ha during a growing season. A custom applicator could typically treat up to 300 ha/d and be exposed for up to 40-d per growing season.

Pesticide operator exposure was estimated using the Pesticide Handler Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader/applicator and flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates. The following PHED estimates meet North American Free Trade Agreement criteria for data quality, specificity and quantity.

To estimate total dermal and inhalation exposure for groundboom application, appropriate subsets of A and B grade data were created from the mixer/loader and from the applicator PHED database files. There were no relevant data available in the mixer/loader/applicator database file. The mixer/loader file was subset for open mixing, dry flowable formulations and to exclude replicates for packaging in water soluble packets. The applicator file was subset for application by groundboom tractor or truck with open cabs. The number of replicates for inhalation and dermal data were acceptable (range 16-40). In the PHED subsets, the mean and range of pesticide mixed and applied and the sampling time were of the same order of magnitude as the estimated 2 kg a.i./d handled by a farmer treating 100 ha with 20 g a.i./ha in an 8-h work day.

Protective clothing specified on proposed label for applicators and other handlers are long-sleeved shirts, long pants, shoes and socks. PHED does not contain sufficient data to estimate mixer/loader exposure without gloves, therefore exposure was estimated for mixer/loaders wearing long pants, long-sleeved shirts and gloves, and for applicators wearing long pants, long sleeved shirts and no gloves. PHED Version 1.1 uses actual data and does not assume clothing penetration factors.

All data were normalized for kg of a.i. handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part (arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution). Exposure estimates and margin of exposure calculations were based on: i) farmers mixing/loading and applying Sundance at 20 g a.i./ha to 100 ha/day, up to eight days per growing season, and ii) custom applicators mixing/loading or applying Sundance at 20 g a.i./ha to 300 ha/day, up to 40-d per growing season. Exposure was predominantly dermal. As no percutaneous absorption data were available, the default assumption was 100% absorption.

Although PHED does not include data from which to estimate exposure during clean-up/repair activities, PHED data provide an adequate basis for estimating occupational exposure for the

proposed use. The estimation of mixer/loader exposure wearing gloves is acceptable, if gloves are specified as additional personal protective equipment on the label.

Table 4 Estimated operator exposure and resulting margins of exposure

Operator Exposure Scenario		Daily exposure (dermal + inhalation) 70 kg operator (mg/kg bw/day)	Margin of Exposure
Application at 21 g a.i./ha. Mixer/loaders wearing long pants, long-sleeved shirts and gloves. Applicators wearing long pants, long-sleeved shirts and no gloves.	Farmer: Mixer/loader/applicator treating 100 ha	0.006	170,000[a]
	Custom applicator: Mixer/loader/applicator treating 300 ha	0.02	5,000[b]

a- Based on a NOEL of 1,000 mg/kg bw from a 28-d dermal rat study.
b- Based on a NOEL of 100 mg/kg bw from 3-month and 1-year dietary dog studies and a default assumption of 100% dermal absorption

The margins of exposure, calculated on the basis of typical North American use patterns, are acceptable for both farmers and custom applicators.

3.6.2 Bystanders

Given that application is by ground equipment only, and the proposed agricultural use scenario, exposure and risk to bystanders should be minimal.

3.6.3 Workers

Data are not available to make a quantitative estimate of re-entry exposure. The proposed use pattern, however, is such that re-entry exposure should be minimal. Application is at an early post-emergence weed stage (15-24 cm crop height). Workers may re-enter treated fields to monitor crops, although these tasks would involve little foliar contact and, therefore, minimal exposure and risk.

4.0 Residues

4.1 Definition of the residues relevant to maximum residue limits (MRLs)

4.1.1 Definition of the residues in wheat relevant to MRLs

Wheat metabolism study

In the metabolism study in wheat, the test material was applied at an exaggerated rate of application (3.5 times label rate, i.e., 70 g a.i./ha). Sulfosulfuron parent was found to be the major component of the residue in wheat foliage and in straw accounting for 61% and 37%, respectively. In wheat grain, the residue level was very low (<0.01 mg/kg) and was mostly either entrained in or incorporated into starch. Six metabolites were identified in foliage and straw. No single metabolite present accounted for 10% of the residue. Identified metabolites amounted to approximately 13% and 14% of the residue present in foliage and straw, respectively.

Of the six metabolites identified in wheat foliage and straw, two (desmethyl sulfosulfuron and sulfonamide) were identified in the animal metabolism studies (rat, goat, hen). The remaining four metabolites identified in wheat foliage and straw were not observed in the animal metabolism studies. The metabolic pathway in animals differed from wheat. In wheat, cleavage of the sulfonyl urea bond appears to be of greater significance, whereas in animals the demethylation and pyrimidine (Pd) ring hydroxylation appear to be more important. As residues in treated wheat used for human and animal consumption are very low, and as each of the wheat metabolites not identified in animals (sulfamic acid, urea aminopyrimidine and N-hydroxy-urea) occurred individually at levels <10% and <0.05 mg/kg in foliage and straw following treatment at 3.5 times label rate (i.e., 70 g a.i./ha), they are not considered to be of toxicological significance.

Confined crop rotation study

The confined crop rotational study indicated that the application of Im and Pd ^{14}C-labelled sulfosulfuron to sandy loam soil at twice the proposed Canadian rate resulted in higher Im-labelled residues. Specifically, residues of sulfosulfuron and its metabolites (sulfonamide and sulfosulfuron sugar conjugate) in rotation crops (lettuce, radish, barley and rye) were #0.087 ppm, with the maximum being found in cereal straw and hay fractions at 60 DAT. The soil metabolism resulted in high concentrations of the Pd-labelled metabolite, aminopyrimidine. However, this metabolite was not bioavailable to plants and, therefore, was not included in the definition of the ROC.

Environmental chemistry and fate

Environmental chemistry and fate studies for sulfosulfuron indicated that microbial degradation and photolysis were the major degradation routes. Little or no volatilization or mineralization to CO_2 occurred, either in soil or aquatic environments. Therefore, the proposed application of the sulfosulfuron formulation (Sundance) would result in the fairly rapid degradation of sulfosulfuron (DT_{50} ~30 days) to sulfonamide, aminopyrimidine and desmethyl sulfosulfuron. Sulfosulfuron and its metabolite, sulfonamide, would be bioavailable for uptake from the soil by plants, and undergo further metabolism in the plants. The metabolite aminopyrimidine, however, would not be bioavailable, instead, remaining bound to the soil organic matter with slower degradation.

Storage stability

In the freezer storage stability studies, samples of ground wheat grain and forage were spiked with sulfosulfuron at a level of 0.2 mg/kg and stored at -12ºC (10ºF) for 531- to 533-d. Under these conditions, residues of the sulfone moiety decreased by 11% and 10% in grain and forage, respectively. The data presented appeared to indicate that residues of sulfosulfuron were stable at -12ºC (10ºF) in grain and forage. The studies presented could not demonstrate the freezer storage stability of sulfosulfuron or its metabolites in wheat grain and forage, since the common moiety method was used for analysis of residues. The use of the common moiety method in a storage stability study could not distinguish between the parent and potential degradation products. However, all tissue samples were frozen and subsequently analyzed within a period of 533-d (18 months) and the common moiety method determined the majority of the total terminal residues.

On the basis of all these considerations, it could be proposed that sulfosulfuron residues in wheat be regulated as sulfosulfuron parent compound. However, given the specificity of the method of analysis developed and submitted, the proposed residue definition is "the sum of sulfosulfuron and its ethyl sulfone metabolites, expressed as sulfosulfuron". This definition is proposed to reflect the extent of the residue determined by the method of analysis submitted. (It is considered that the method overestimates the residue of parent sulfosulfuron by between 10% and 20%; unclear based on data.)

4.1.2 Definition of the residues in food of animal origin relevant to MRLs

Animal metabolism

In the rat metabolism study, more than 90% of the administered dose of sulfosulfuron was excreted within 3 days of dosing and parent sulfosulfuron accounted for more than 80% of the excreted ^{14}C. Similarly, in the lactating goat metabolism study, >85% of the administered dose of sulfosulfuron was excreted within 3 days of dosing. Parent sulfosulfuron was the major terminal residue identified in kidney, liver, muscle and milk, accounting for 73% to 98%, 81% to 86%, 72% to 89% and 19% to 37%, respectively, of the extractable residues. The low levels of identified residues in muscle may be attributed to the higher level ($35% of the TRR) of non-extractable residues. In the laying hen metabolism study, >84% of the administered dose was excreta related. In the majority of the tissues and eggs, parent was the most abundant residue ranging from 8% to 33% of the extractable residues.

Storage stability

In the freezer storage stability study, samples of ground animal matrices (milk, muscle and liver) were spiked with sulfosulfuron at a level of 0.1 ppm and stored at -12ºC (10ºF) for 169 days. Under these conditions, residues of sulfosulfuron equivalents decreased by 5% to 8% (difference between t=0 and value at individual time points) in milk, muscle and liver. The results appeared to indicate that sulfosulfuron equivalent residues were stable at -12ºC (10ºF) in milk, muscle and liver for up to 169 days. The results could not elucidate the freezer storage stability of sulfosulfuron plus its metabolites in milk, muscle and liver, since the analytical method used measured for the sulfone moiety only. The use of the common moiety method in the storage stability study could not distinguish between the parent and its potential degradation products. All

tissue samples were frozen and subsequently analysed within a six-month period, however, and the common moiety method determined the majority of the total terminal residues.

On the basis of the data presented relating to metabolism of sulfosulfuron in livestock, it is evident that parent sulfosulfuron is the major component of the residue in meat, meat byproducts, milk and eggs and, accordingly, it is the moiety that should be used for the purposes of defining the ROC. Since the method of residue analysis proposed, however, determines parent sulfosulfuron and all metabolites that can be hydrolyzed to ethyl sulfone, it is not possible to restrict the residue definition to the parent molecule only. As a consequence of the specificity limitations imposed by the method of analysis available, it is proposed that the residue be defined as "the sum of sulfosulfuron and its ethyl sulfone metabolites, expressed as sulfosulfuron".

4.2 Residues relevant to consumer safety

The results of supervised field trials in wheat conducted across Canada, Europe and the United States have shown that the residues in grain and straw collected at harvest following the application of sulfosulfuron at the requested rate and twice the requested rate were below 0.01 mg/kg in the case of grain and were below 0.1 mg/kg in the case of straw.

The potential exposure of consumers to sulfosulfuron residues through dietary intake is very low. At the proposed recommended application rate of 20 g a.i./ha, residues of sulfosulfuron are not expected to occur in wheat grain at levels greater than the 0.02 mg/kg LOQ and residues greater than 0.01 mg/kg are not expected to occur in animal products such as milk, eggs and meat intended for human consumption. Using the "Apparent per Capita Domestic Consumption of Food in Canada, 1996" and considering direct wheat consumption, the potential daily intakes for adults, infants and children are all below 0.2% of the ADI (0.24 mg/kg bw/d calculated on the basis of the 24 mg/kg bw/d NOEL identified in the chronic exposure study in rats, using a 100-fold safety factor). Taking into account potential intake from consumption of food of animal origin, the potential daily intakes are below 0.4% of the ADI.

When allocating 10% of the ADI to drinking water and recalculating the dietary risk assessment, taking into account the potential intake from direct wheat consumption and consumption of food of animal origin, the potential daily intakes for all age groups are still below 0.4% of the ADI.

Accordingly, there is a large safety margin for all consumers, including infants and children.

4.3 Residues relevant to worker safety

Addressed in section 3.6.3.

4.4 Proposed MRLs and compliance with existing MRLs

4.4.1 Compliance with existing MRLs

Since the active substance is new, there are no existing MRLs. The question of compliance with existing MRLs therefore is not applicable.

4.4.2 Proposed MRLs

On the basis of the results of the extensive range of supervised trials carried out with respect to the single use proposed for sulfosulfuron, it is clear that residues in wheat grain will not exceed 0.02 mg/kg for sulfosulfuron residues in wheat and that residues in succeeding crops will not exceed 0.02 mg/kg. Accordingly, it is proposed that the MRL for wheat grain be set at 0.02 mg/kg.

As residues in wheat grain, treated at 1 to 2 times the Canadian use pattern, were not detectable (<0.01 mg/kg), there was no requirement to generate and submit processing studies.

Following use in accordance with the proposed label directions, sulfosulfuron residue levels in meat, fat, milk and egg are expected to be less than 0.01 mg/kg.

In light of these considerations, and the Good Agricultural Practice proposed for sulfosulfuron use on wheat at 20 g a.i./ha applied before emergence of the 4th tiller of the crop (PHI ~60-75 days), MRLs for sulfosulfuron are proposed as follows:

wheat grain	0.02 mg/kg
milk	0.006 mg/kg
meat and fat (cattle, goat, swine, horse, and sheep), meat and fat (poultry)	0.005 mg/kg
eggs	0.005 mg/kg
meat byproducts (cattle, goat, swine, horse and sheep), meat byproducts (poultry)	0.05 mg/kg

4.5 Proposed Import Tolerances

Since only a domestic use on wheat has been proposed, and since MRLs have been proposed for the commodities in which residues are likely to occur, the establishment of import MRLs is not applicable.

5.0 Fate and behaviour in the environment

5.1 Fate and behaviour in soil

The three modes of transformation of sulfosulfuron in soils, i.e., hydrolysis, phototransformation and biotransformation, were investigated in detail under laboratory conditions. Studies were performed using radiolabelled sulfosulfuron with ^{14}C in the imidazopyridine (Im-^{14}C),

radiolabelled sulfosulfuron with ^{14}C in the pyrimidine ring (Pd-^{14}C) and mixtures of both radiolabelled forms. It was demonstrated that chemical hydrolysis and microbial degradation were the principal mechanisms of transformation, although phototransformation may also contribute to the dissipation of sulfosulfuron in the terrestrial environment. The dissipation/accumulation of sulfosulfuron under field conditions in the wheat-growing areas in Canada, northern United States and Europe was also studied.

5.1.1 Phototransformation in soil

Sulfosulfuron transformed in soils exposed to natural sunlight over a 30-d period in Richmond, California, with dissipation half-life (DT_{50}) values of 46- and 51-d in Im-^{14}C and Pd-^{14}C labelled sulfosulfuron treatments, respectively. The corresponding values under dark controls were 55- and 117-d, respectively. The phototransformation profile of sulfosulfuron was similar for both light exposed and dark controls, indicating that the transformation was not directly the result of photolytic processes. However, the rate of transformation was faster in light exposed samples. While soil photodegradation may contribute to the dissipation of sulfosulfuron, it is not a significant route of transformation in soils. The major transformation products (>10% of applied radioactivity) detected were sulfonamide (~23% of applied radioactivity in the Im-^{14}C treatment) and aminopyrimidine (~25 % of applied radioactivity in the Pd-^{14}C treatment), both formed by hydrolytic cleavage.

5.1.2 Aerobic soil biotransformation

Sulfosulfuron transformed in U.S. silt loam and sandy loam soils under aerobic conditions with DT_{50} and DT_{90} values ranging from 30- to 37-d (74- to 88-d for combined extractable and non-extractable forms) and 206- to 262-d, respectively. These values indicated that sulfosulfuron was moderately persistent in soils under aerobic conditions. The maximum accumulation of residues of sulfosulfuron in 2 soils over a 360-d period was 21% of applied amount. Soil binding was a major route of dissipation of sulfosulfuron in soils. Mineralization to CO_2 or volatilization was not a major route of dissipation of sulfosulfuron in soil. Two major transformation products, i.e., sulfonamide and aminopyrimidine, and two minor transformation products, i.e., sulfosulfuron desmethyl and sulfosulfuron guanidine, were identified in both the readily extractable and bound residues in soils. The major route of transformation of sulfosulfuron was cleavage of sulphonyl-urea bond leading to the formation of aminopyrimidine and sulfonamide. A minor route of transformation involved the oxidative demethylation of sulfosulfuron to yield desmethyl, which is further degraded to guanidine.

Sulfosulfuron was moderately persistent to persistent in European soils (clay loam, silt clay loam and sandy loam) under aerobic conditions with DT_{50} values ranging from 92- to 226-d. At the end of the 100-d incubation period, the sulfosulfuron residues in soils ranged from 46.5% to 70% of applied radioactivity. The study indicated that the transformation was pH dependent, with faster transformation at low pH values. Two major transformation products, i.e., sulfonamide (maximum of 12.8% of applied radioactivity) and aminopyrimidine (maximum of 10.6% of applied radioactivity and formed by hydrolysis of sulfonylurea) were identified. In addition, two minor transformation products, i.e., desmethyl (maximum of 5.2% of applied radioactivity and formed by O-methylation) and sulfonic acid were identified. Small amounts of four unidentified

products were also detected. Increasing the moisture content from 40% to 70% in Evesham soil increased the hydrolysis products (sulphonamide and aminopyrimidine) in soil extracts and the DT_{50} of sulfosulfuron was reduced from 226- to 196-d. Hydrolysis was reported to be the main route of degradation of sulfosulfuron in the soils.

5.1.3 Anaerobic soil biotransformation

No data were submitted.

5.1.4 Field soil dissipation studies

The dissipation of sulfosulfuron and its transformation products was studied outdoors at the Regina Research Station in soil columns collected intact from five locations in Western Canada, i.e., Brandon (Manitoba), Regina and Saskatoon (Saskatchewan), and Lacombe and Lethbridge (Alberta). Sulfosulfuron was slightly persistent in Saskatoon and Lethbridge soils with DT_{50} values of 41- and 44-d, respectively, and moderately persistent in Lacombe, Regina and Brandon soils with 52-, 117- and 144-d, respectively. Two major transformation products, i.e., sulfonamide and aminopyrimidine (maximum of 21% and 14% of applied amount, respectively) and one minor transformation product, i.e., desmethyl (maximum of 7% of applied amount) were identified during the study. The leaching of sulfosulfuron and its transformation products was minimal with a maximum concentration of 0.28% of the applied amount in the leachates.

In soil dissipation studies conducted under field conditions at two sites in Canada, sulfosulfuron was moderately persistent and non-persistent in Alberta sandy loam and Saskatchewan loamy soils with DT_{50} values of 52- and 13-d, respectively (Table 5). The corresponding DT_{90} values were 1190- and 370-d, respectively, and the corresponding residue carry over were 3% and 15% of applied amount, respectively over a 192-d period. Sulfonamide was not detected in any samples at the Alberta site, whereas, at the Saskatchewan site, residues appeared in small amounts at 29 DAT in 0- to 15-cm soil layer and disappeared at 120 DAT. No sulfonamide residues were detected in the 15- to 30-cm layer at both the sites. The leaching of sulfosulfuron and sulfonamide residues was, therefore, minimal.

In U.S. soils, sulfosulfuron was moderately persistent in North Dakota sandy loam soil with DT_{50} and DT_{90} values of 75- and 250-d, respectively. The residues of the parent compound and the transformation product, sulfonamide, were primarily detected in the upper 15 cm of soil layer. Soil column studies conducted with radiolabelled sulfosulfuron (Im-^{14}C and Pd-^{14}C) in Washington state showed that sulfosulfuron was non-persistent to slightly persistent in soils under field conditions with DT_{50} values ranging from 13- to 41-d. The residue carry over at the end of 18-month period was 1% to 1.5% of the applied amount. The major transformation products identified in soils were sulfonamide, guanidine, aminopyrimidine and urea. The leaching of sulfosulfuron and its transformation products was minimal, with no residues detected below the 30- to 45-cm soil layer. The maximum cumulative amount of radioactivity in any of the leachates did not exceed 0.74 mg a.i./L (0.59% of applied amount). The sulfosulfuron, therefore, has a low potential to leach and contaminate the ground water.

Table 5 DT_{50} and DT_{90} values of sulfosulfuron in soil under field conditions

Country/Year	DT_{50} (days)	DT_{90} (days)
Canada 1996	52	1190
	13	370
U.S. 1995	75	250
	14	83
Belgium 1995/96	12	131
Germany 1995/96	47	247
Germany 1995/96	28	203
United Kingdom 1995/96	25	278
United Kingdom 1995/96	23	252
France 1995/96	25	276
France 1995/96	11	302
France 1995/96	32	358
Germany 1994/96	26	285
Germany 1994/96	22	243
Germany 1994/96	18	197

In field studies conducted at 11 European sites, the DT_{50} ranged from 11- to 47-d (mean 24-d) and DT_{90} ranged from 131- to 358-d (mean 261-d). Maximum residue levels of sulfosulfuron were detected in the 0- to 10-cm soil layer and sulfosulfuron did not significantly migrate down the soil profile. In other field studies conducted in the U.S., sulfosulfuron was non-persistent in Texas fine sandy loam soil with DT_{50} and DT_{90} values of 13.6 and 83.3, respectively. In California sandy loam, sulfosulfuron was non-persistent to slightly persistent with DT_{50} values of 13- to 25-d.

From the results of field dissipation studies, sulfosulfuron can be considered as moderately persistent under field conditions. Sulfosulfuron and its transformation products were primarily detected in the upper 0- to 15-cm soil layer and they have a low potential to leach to groundwater. The DT_{50} in field soils was much faster than in laboratory studies.

5.1.5 Mobility: Soil adsorption/desorption

Adsorption/desorption studies with two U.S. and three U.K. soils indicated that sulfosulfuron was highly to very highly mobile in soils with K_d and K_{oc} values of 0.076 to 0.710 and 5.3 to 89, respectively. The desorption K_d and K_{oc} values were 1.90 to 4.69 and 66 to 630. These values were higher than adsorption values, which indicate that sulfosulfuron, once adsorbed, is not readily desorbed. There was little correlation between the percent organic matter in the soil and the adsorption constants of sulfosulfuron. The results, however, suggested that a correlation may exist between the pH and the adsorption of sulfosulfuron.

Adsorption/desorption studies with sulfonamide, a major transformation product, indicated that it was highly mobile in two U.S. and two U.K. soils, with adsorption K_d values of 0.524 to 2.07 and K_{oc} values of 60.9 to 260.5. Studies conducted with another transformation product, desmethyl, in the same soils indicated that it was also very highly mobile in sandy loam soils with adsorption K_d values of 0.316 to 0.428 and K_{oc} values of 36.7 to 104.4, whereas in silt loam and clay loam soils, it was highly mobile with adsorption K_d values of 0.661 to 0.732 and K_{oc} values of 37.3 to 116.0. The adsorption pattern for desmethyl was similar to sulfonamide, but desmethyl, once adsorbed, appeared to be more tightly bound than sulfonamide.

In four U.S. soils, aminopyrimidine was moderately mobile in sandy loam and loamy sand (K_d 2.32-2.99 and K_{oc} 259.98-399.55), immobile in silt clay loam (K_d 165.20 and K_{oc} 8279.97) and had low mobility in silt loam soil (K_d 18.56 and K_{oc} 1042.43).

5.1.6 Mobility: Soil column leaching

In an aged soil column leaching study, parent compound, sulfosulfuron, was mobile in soils with 39% of the applied amount found in the leachates. Approximately 50% of applied radioactivity was retained in the top 0 to 5 cm soil column of which 23% was the parent compound. The transformation products, desmethyl and sulfonamide, were slightly mobile in soil (2.7% and 2.0% of applied radioactivity in the leachates), whereas aminopyrimidine showed limited mobility. These findings are generally in accordance with the results of the adsorption/ desorption studies. Since there was very limited degradation of sulfosulfuron in the test soil (DT_{50} >100 days), the study cannot be regarded as a good indicator of metabolite mobility.

On the basis of laboratory adsorption and soil column leaching studies, sulfosulfuron, sufonamide and desmethyl can be classified as having high potential for mobility in soils, and aminopyrimidine as having low to moderate mobility.

5.1.7 Mobility: soil thin layer chromatography

No data were submitted.

5.1.8 Mobility: field leaching data

Studies conducted with soil columns under field conditions in Canada and the U.S. indicated that the leaching of sulfosulfuron and its transformation products was minimal.

5.1.9 Expected environmental concentration in soil

According to the proposed label, the maximum application rate is 27 g/ha of Sundance (75% a.i.), which would amount to 20 g a.i./ha. Assuming a soil bulk density of 1.5 g/cm^3 and a soil depth of 15 cm, an application at the maximum label rate would result in an expected environmental concentration (EEC) of 0.009 mg a.i./kg soil.

5.2 Fate and behaviour in aquatic systems

5.2.1 Hydrolysis

Sulfosulfuron was stable to hydrolysis under neutral and alkaline conditions ($t_{1/2}$ of 168- and 156-d, respectively), but was more readily hydrolyzed under acidic conditions ($t_{1/2}$ of 48-d at pH 5- and 7-d at pH 4). Sulfonamide and aminopyrimidine were the major hydrolysis products in the Im-^{14}C and Pd-^{14}C treatments, respectively. The rate of hydrolysis was faster at 40°C than at 25°C.

5.2.2 Phototransformation in water

In aquatic systems, sulfosulfuron phototransformed rapidly with a DT_{50} value of 33- to 36-h equivalent to 3 days times 12-h sunshine days. In contrast, the parent compound was stable in the dark control solutions. Phototransformation was, therefore, a major route of transformation of sulfosulfuron in aquatic systems. Six major phototransformation products were identified (aminopyrimidine, sulfamic acid, N-hydroxyl urea, oxamic acid, sulfonic acid and sulfone), three from each label during irradiation. A further seven minor unidentified phototransformation products (maximum 8.74% at 144-h) were detected, three following irradiation of imidazopyridine ring-labelled ^{14}C-sulfosulfuron, and four following irradiation of pyrimidine ring-labelled ^{14}C-sulfosulfuron.

5.2.3 Aquatic aerobic biotransformation

Sulfosulfuron dissipated rapidly from water and sediment/water systems under aerobic conditions. The DT_{50} values of 16.1- to 19.5-d in water and 19.8- to 32.2-d in sediment/water systems at 20°C indicated that sulfosulfuron was slightly persistent in aquatic systems under aerobic conditions. The DT_{90} values ranged from 83.9- to 107-d. At a low temperature of 5.7°C, sulfosulfuron was moderately persistent with DT_{50} values of 58.3- and 104-d in water and sediment/water systems, respectively. In sediment/water systems, more of the radioactivity was associated with the sediments in extractable and non-extractable forms with time. Over 50% of this applied radioactivity was found in non-extractable form in the sediments, most of which was associated with the humin, fulvic acid and humic acid fractions. The major transformation product was desmethyl-sulfosulfuron (13% of applied radioactivity), which was formed by demethylation of the methoxy group to a hydroxy group. There were other minor transformation products, sulfonamide and aminopyrimidine, which were either formed by the microbial transformation, or by hydrolysis of the sulfonylurea bridge, splitting the parent molecule into two. In the same way, sulfonamide may also have formed from the transformation product of desmethyl.

5.2.4 Aquatic anaerobic biotransformation

Under anaerobic conditions in aquatic systems, sulfosulfuron was moderately persistent with DT_{50} values ranging from 136- to 154-d. In the absence of elevated levels of ammonia under natural conditions, the major transformation products under anaerobic aquatic conditions were sulfonamide, aminopyrimidine and desmethyl. No significant difference in the rate of transformation was observed between viable treatments and sterile controls. Hydrolysis is,

therefore, the major route of dissipation with the formation of sulfonamide and aminopyrimidine under anaerobic aquatic conditions.

5.2.5 Expected environmental concentration in water

Under the proposed use pattern, the potential exposure of surface water is through surface runoff, spray drift and accidental overspray on neighbouring water bodies. Assuming a scenario of 100% deposition, a direct overspray of Sundance at the maximum recommended label rate of 20 g a.i./ha would result in an EEC of 0.00675 mg a.i./L in a 30 cm depth of water. Assuming a 0.5% runoff for water soluble pesticides, 30 cm depth of pond water and a ratio of 100:1 of watershed area to pond area in the Prairies, the EEC in water would be 0.0034 mg a.i./L. In the case of deeper water bodies in the Prairies, the EEC for human drinking water, based on a 4000- m^3 dugout, a 100- to 2000-ha water shed and 0.5% runoff, would be 0.05 mg a.i./L

5.3 Fate and behaviour in air

The vapour pressure of sulfosulfuron was 3.05 times 10^{-8} Pa at 20°C and the calculated Henry's Law Constant at pH 5, 7 and 9 were 8.15 times 10^{-7}, 8.83 times 10^{-9} and 2.97 times 10^{-8} Pa/m3/mol respectively, at 20°C. These values indicate that sulfosulfuron is essentially non-volatile and the contamination of the atmosphere by sulfosulfuron is likely to be extremely low under the proposed use pattern and the low rate of application (20 g a.i./ha). Atmospheric contamination is, therefore, not considered to be a significant route of exposure under the proposed use pattern.

6.0 Effects on non-target species

6.1 Effects on terrestrial non-target species

6.1.1 Wild birds

Sulfosulfuron was practically non-toxic to the bobwhite quail and the mallard duck on an acute oral basis with LD_{50} values of >2,250 mg a.i./kg bw, the highest dose tested (Table 6). The no observable effect of concentration (NOEC) values were 810 and 2,250 mg a.i./kg bw for the bobwhite quail and the mallard duck, respectively.

On a dietary basis also, Sulfosulfuron was practically non-toxic to the bobwhite quail and the mallard duck with LC_{50} value of >5,620 mg a.i./kg diet dw*. Sulfosulfuron did not affect the reproductive performance of the mallard duck up to 250 mg a.i./kg diet dw. The NOEC and lowest observable effect of contamination (LOEC) values were 250 and 1,250 mg a.i./kg diet dw, respectively, based on reduction in 14-d survivor weight.

*The corresponding NOEC values were 5,620 and 3,160 mg a.i./kg diet dw, respectively.

6.1.2 Wild mammals

The effects on wild mammals were extrapolated from the following laboratory mammalian studies. On an acute basis, sulfosulfuron was considered to be of low toxicity to rats by oral, dermal and inhalation routes with oral and dermal LD_{50} of >5000 mg a.i./kg bw (Table 6). It was minimally irritating when applied to the skin or instilled into the eyes of New Zealand White rabbits.

In a short term 90-d study with rats, the NOEL based on reduced body weights and calculi in the kidney/bladder was 6,000 mg a.i./kg diet. In a four-week dietary toxicity study with mice, the NOEL based on increased palmitoyl CoA oxidase activity, was 4,000 mg a.i./kg diet. In three-month and one-year dog studies, a NOEL of 100 mg a.i./kg bw/d (fed by intubation of capsules) was proposed for the male and female dogs based on treatment-related effects on the urinary bladder.

In long-term studies with rats (22 months), a NOEL of 500 mg a.i./kg diet was proposed, based on effects of tumorigenicity. In a two-generation reproductive study with rats, no adverse effects on reproductive parameters were observed up to 20,000 mg a.i./kg diet. However, the NOEL for the systemic toxicity was 5,000 mg a.i./kg diet.

In teratogenicity studies with rat and rabbit, no adverse effects on maternal toxicity, fetotoxicity and teratogenic effects were reported up to 1,000 mg a.i./kg bw/d (NOEL), the highest dose tested. The active ingredient in capsules was introduced by intubation. No treatment-related adverse neurotoxic effects were reported in male and female rats up to 1,211 and 1,467 mg a.i./kg bw/d, respectively.

Table 6 Summary of toxicity of Sulfosulfuron to non-target terrestrial organisms

Group	Organism	Effect	NOEC (mg a.i./kg)	LC_{50}/LD_{50} (mg a.i./kg)	Classification
Wild birds	bobwhite quail (*Colinus virginanus*)	acute oral	810	>2,250	non-toxic
	mallard duck (*Anas platyrhynchos*)	acute oral	2,250	>2,250	non-toxic
	bobwhite quail (*Colinus virginanus*)	dietary	5,620	>5,620	non-toxic
	mallard duck (*Anas platyrhynchos*)	dietary	3,160	>5,620	non-toxic
	bobwhite quail (*Colinus virginanus*)	chronic (reproduction)	1,250	--	no-effect
	mallard duck (*Anas platyrhynchos*)	chronic (reproduction)	250	1,250 (LOEC)	no-effect

Group	Organism	Effect	NOEC (mg a.i./kg)	LC_{50}/LD_{50} (mg a.i./kg)	Classification
Wild mammals	rat - oral and dermal	acute	--	>5,000	non-toxic
	rat - 90-d dietary	short term	6,000	--	no-effect
	mice - 4-week dietary	short term	4,000	--	no-effect
	rat - 22 m	chronic	500	--	no-effect
	rat - 2-generation reproduction	chronic	5,000	--	no-effect
			20,000	--	no-effect
Invertebrates	honeybee	acute contact	25	>25	non-toxic
		acute oral	30	>30	non-toxic
	earthworm	acute	848	>848	no-effect
Plants	pre-emergence application	onion*, dry weight**	1.1 g a.i./ha	1.2 (EC_{25})	toxic
	post-emergence application	radish*, dry weight**	0.035	0.11 (EC_{25})	toxic

* most sensitive species

** parameter

6.1.3 Bees

Sulfosulfuron was relatively non-toxic to honeybees on acute oral and contact basis. The 48-h acute contact and oral LD_{50} values were >25 and >30 ：g a.i./bee, respectively, the highest doses tested (Table 6). The corresponding NOECs were 25 and 30 ：g a.i./bee, respectively.

6.1.4 Arthropod predators and parasites

No data were submitted.

6.1.5 Earthworm

Sulfosulfuron was non-toxic to earthworm (*Eisenia foetida*) up to 848 mg a.i/ha, and no adverse effects were observed up to this level. The NOEC and LC_{50} values for earthworm treated with a single concentration of sulfosulfuron were 848 and >848 mg a.i./kg^{-1} soil, respectively (Table 6).

6.1.6 Effects on soil micro-organisms

No data are required.

6.1.7 Terrestrial non-target plants

Pre-emergence application of sulfosulfuron up to 36 g a.i./ha did not affect the seed germination, seedling emergence and percent survival of ryegrass, corn, onions, oats, lettuce, radish, soya, tomato, cucumber and cabbage. However, the plant height and dry weight were significantly affected. Onion was the most sensitive species, and the most sensitive parameter was the dry weight with NOEC and EC_{25} values of 1.1 and 1.2 g a.i./ha, respectively (Table 6). Post-emergence application of sulfosulfuron resulted in phytotoxic effects (severe stunting and chlorosis) on all crops except tomato. The percent survival of radish was affected by the sulfosulfuron application with a NOEC of 4.4 g a.i./ha. The plant height and dry weight were the most sensitive parameters affected by the post-emergence application of sulfosulfuron. All the crops tested were affected except tomato plant height. Radish was the most sensitive species with a NOEC and an EC_{25} for plant dry weight of 0.035 and 0.11 g a.i./ha, respectively.

6.2 Effects on aquatic non-target species

6.2.1 Bioconcentration in fish

The octanol/water partition coefficient (log K_{ow}) for sulfosulfuron was <1 at 25°C. This value indicated that sulfosulfuron has a low potential to bioaccumulate in organisms. As this value is less than the threshold of 3 at which a fish bioconcentration study is required, no data on bioaccumulation in fish were required.

6.2.2 Fish

Sulfosulfuron was practically non-toxic to rainbow trout, bluegill sunfish and sheepshead minnow on an acute basis with LC_{50} values of >95, >96 and 101 mg a.i./L, respectively, the highest concentrations tested (Table 7). The corresponding NOEC values were 95, 96 and greater than 101 mg a.i./L, respectively. In chronic studies (reproduction), sulfosulfuron did not affect the time to hatch, hatching success, time to reach the swim up stage of development, larvae survival, fry survival and growth of rainbow trout up to 100 mg a.i./L.

6.2.3 Aquatic invertebrates

Sulfosulfuron was practically non-toxic to daphnids on an acute basis with LC_{50} and NOEC values of >96 and 96 mg a.i./L, respectively (Table 7). Sulfosulfuron did not significantly affect the reproductive performance, survival and growth of daphnids up to 102 mg a.i./L (NOEC). Sulfosulfuron was practically non-toxic to mysid shrimps on an acute basis with 96-h NOEC and LC_{50} values of 106 and >106 mg a.i./L, respectively. Sulfosulfuron had no significant effect on shell growth of Eastern Oyster up to 116 mg a.i./L, the single concentration tested. The 96-h NOEC and LC_{50} values were 116 and >116 mg a.i./L, respectively.

6.2.4 Algae

Sulfosulfuron was toxic to algae. Of the four algal species tested, *Selenastrum capricornutum* was the most susceptible species with 72 h NOEC and IC_{50} values of less than 0.047 and 0.193 mg a.i./L, respectively (Table 7). Sulfosulfuron was less toxic to freshwater and marine diatoms with a NOEC value of greater than or equal to 87 mg a.i./L.

6.2.5 Aquatic plants

Aquatic plant, duckweed (*Lemna gibba*), was very sensitive to sulfosulfuron with NOEC and EC_{50} values of 0.0005 and 0.001 mg a.i./L, respectively (Table 7). Sulfosulfuron significantly reduced the frond production and increased the percentages of dead and chlorotic fronds when compared to the negative controls.

6.3 Effects on biological methods of sewage treatment

No data are required.

Table 7 Summary of toxicity of Sulfosulfuron to non-target aquatic organisms

Group	Organism	Effect	NOEC (mg a.i./L)	LC_{50} (mg a.i./L)	Classification
Invertebrates	Daphnids *(Daphnia magna*)	acute	96	>96	non-toxic
		chronic (reproduction)	102	--	no effect
	water mysid (*Mysidopsis bahia*)	acute	106	>106	non-toxic
	Eastern Oyster (*Crassostrea virginica*)	shell growth	116	>116	no effect
Fish	rainbow trout (*Oncorhynchus mykiss*)	acute	95	>95	non-toxic
	bluegill sunfish (*Lepomis macrochirus*)	acute	96	>96	non-toxic
	sheepshead minnow (*Cyprinodon variegatus*)	acute	101	>101	non-toxic
	rainbow trout (*Oncorhynchus mykiss*)	chronic (early life cycle)	100	--	no effect
Algae	*Selenastrum capricornutum*	biomass 72 h	less than 0.047	0.193	
		growth rate 72 h	0.094	0.669	
	Scenedesmus subspicatus	growth rate 72 h	0.24	3.1	
	Anabaena flos-aquae	biomass 5 day	0.31	0.77	
	diatom (Navicula pellicilosa)	biomass 5 day	87	>87	
	Skeletonema costatum	biomass 5 day	103	>103	
Plants	*duckweed (Lemna gibba)*	frond inhibition	0.0005	0.001	toxic

6.4 Environmental risk assessment

6.4.1 Terrestrial organisms

Wild Birds

Concentrations of sulfosulfuron residues in plants and other food sources were estimated using linear conversions of application rates based on Hoerger and Kenaga (1972) and Kenega (1973). The maximum label application rate of 20 g a.i./ha was used to calculate the concentrations in different food sources to which wildlife may be exposed (Table 8).

Risk assessment for birds was done using NOELs for two bird species, i.e., bobwhite quail and mallard duck (Table 9). The proposed use pattern of the end-use product suggests that exposure of sulfosulfuron to birds is likely to be mainly from consumption of treated foliage and associated avian food sources, with the greatest risk arising from oral ingestion of treated foliage. The dietary intake (DI) of sulfosulfuron was estimated from information on the food consumption (FC) and EEC of sulfosulfuron in various foodstuffs (DI=FC×EEC). The most susceptible species to acute effects were bobwhite quail. The most susceptible species for dietary and reproduction effects was mallard duck.

Acute risk assessment: Assuming bobwhite quail will consume 30% small insects and 70% grain (EPA 1993), the EEC in the diet would amount to 1.68 mg a.i./kg dry weight (dw) and the daily intake would be 0.054 mg a.i./individual/d. The maximum number of days of intake of sulfosulfuron required that would have observable effects (NOEC ind/EEC) would be 3,820 (Table 9). As the number of days of intake of sulfosulfuron required to reach NOEL is 3,820-d, the birds are not at potential risk on an acute basis.

Table 8 EEC of Sulfosulfuron on vegetation and other food sources following a single application at the maximum rate of 20 g a.i./ha

Environmental Compartment	Concentration		Wet/dry weight ratios
	mg a.i./kg fw*	mg a.i./kg dw**	
Short range grass	4.3336	14.3008	3.3
Leaves and leafy crops	2.268	43.0919	19
Long grass	1.9845	8.7318	4.4
Forage crops	1.053	5.6862	5.4
Pods with seeds	0.2167	0.845	3.9
Grain and seeds	0.1802	0.6849	3.8
Fruit	0.1256	0.9542	7.6
Small insects	1.053	4.0014	3.8
Large insects	0.1802	0.6849	3.8

* fresh weight;

** dry weight

Dietary risk assessment: The NOEC for the mallard duck was 3,160 mg a.i./kg diet and the EEC in the diet was 0.68 mg a.i./kg dw. The values of risk factor (0.0002) and margin of safety (4,647) for the dietary risk indicated that the environmental concentration is much lower than the NOEC and that ingestion of this compound at the indicated levels would not pose a dietary risk to birds.

Risk assessment based on dietary reproduction study: The NOEC in the mallard reproduction study was 250 mg a.i./kg diet and the EEC in the mallard diet was 0.68 mg a.i./kg diet. The values of risk factor (0.003) and margin of safety (368) indicated that ingestion of this compound at the indicated levels would not pose a risk to mallard reproductive performance.

Wild mammals

The risk assessment for mammals (Table 9) was done using NOELs for rat and mouse. The likely major route of exposure of sulfosulfuron to wild mammals is through dietary sources, i.e., oral ingestion of treated foliage.

Acute risk assessment: The LD_{50} value for the acute effect was 5,000 mg a.i./kg bw. As no acute NOEL was available, one tenth of LD_{50}, i.e., 500 mg a.i./kg bw, was considered for the acute risk assessment. The standard body weight of 0.35 kg and food consumption of 0.06 kg dw/individual/d for rat (EPA, 1988) were used for the calculations. The EEC in typical rat food items, based on Hoerger and Kenaga (1976), was 10.22 mg a.i./kg diet. The DI of sulfosulfuron at the maximum application rate would be 0.6 mg a.i./individual/d.

The maximum number of days of intake of sulfosulfuron ($NOEL_{(ind)}$ / DI) that would have observable effects on rats would be 285 days. An assessment of these values indicated that the number of days of intake of sulfosulfuron required to reach NOEL is >285 days, and the rats are, therefore, not at potential risk on an acute basis.

Short-term dietary risk assessment: The most susceptible species to sulfosulfuron in short-term dietary toxicity studies was mice with 4,000 mg a.i./kg diet. The EEC in mouse diet, based on Hoerger and Kenaga (1976), was 14.69 mg a.i./kg diet. The values of risk factor (3.67×10^{-3}) and margin of safety (2.72×10^{2}) indicated that ingestion of this compound at the indicated levels would not pose a dietary risk to mice.

Chronic toxicity risk assessment: In a 2-generation 22-month reproduction study with rats, the NOEL based on systemic toxicity to reproduction parameters was 5,000 mg a.i./kg diet. The values of risk factor (0.002) and margin of safety (489) indicated that ingestion of this compound at the indicated levels would not pose a risk to reproductive performance of rats.

Honeybee

The 48-h acute oral and contact NOEC values were 30 and 25 ：g a.i./bee, respectively. Under the proposed maximum application rate of sulfosulfuron, the EEC in large insects was 0.6849 mg a.i./kg dw. Assuming an average bee weight of one gram, the EEC would be 0.6849 ：g a.i./bee. The risk factor and the safety factor for the acute contact toxicity were 0.0274 and 36.5, respectively (Table 9). The corresponding factors for the acute oral toxicity were 0.0228 and

43.8, respectively. An assessment of these values indicated that the bees were not at risk on an acute basis under the proposed maximum application rates.

Earthworm

The acute 14-d NOEC for earthworm was 848 mg a.i./ha. The EEC in soil at the proposed maximum application rate was 0.009 mg a.i./ha. The values of risk factor ($1.06x10^{-5}$) and safety factor ($9.42x10^{4}$) indicated that the effect on earthworms of application of sulfosulfuron at the proposed maximum application rate would be insignificant (Table 9).

Table 9 Summary of risk assessment to terrestrial organisms

Organism	Effect	NOEC or NOEL (mg a.i/kg or L)	EEC (mg a.i./L or kg)	Risk factor	Safety factor	Risk	Mitigatory measures
Bobwhite quail	acute oral	810	0.0454 (mg DI/ind/d)	3,820-d to reach NOEL		no acute risk	not required
	dietary	5,620	1.68	0.0003	3,350	no risk	not required
	reproduction	1,250	1.68	0.001	744	no risk	not required
Mallard duck	acute oral	2,250	0.087 (mg DI/ind)	26,000-d to reach NOEC		no acute risk	not required
	dietary	3,160	0.68	0.0002	4,647	no risk	not required
	reproduction	250	0.68	0.003	368	no risk	not required
Mammals	acute (rat)	500	0.613 mg DI/id/d	285-d to reach NOEL	--	--	not required
	mouse, short term	4,000	14.69	$3.67x10^{-3}$	$2.72x10^{2}$	no risk	not required
	chronic (rat)	500	10.22	0.02	48.9	no risk	not required
	reproduction, systemic (rat)	5,000	10.22	0.002	489	no risk	not required
Earthworm	acute	848	0.009	0.00001	94,200	no risk	not required
Honeybees	acute contact	25 ：g/bee	0.68 ：g/bee	0.0274	36.5	no risk	not required
	acute oral	30 ：g/bee	0.68 ：g/bee	0.0228	43.8	no risk	not required

6.4.2 Aquatic organisms

Risk assessment to aquatic organisms was done using the most sensitive invertebrate and fish species (Table 10). The EEC in a scenario of direct over spray (100% deposition) of sulfosulfuron at the maximum application rate would be 0.00675 mg a.i./L. The EEC in water due to surface runoff in the Prairies would be 0.0034 mg a.i./L.

The most sensitive aquatic invertebrate to sulfosulfuron was *Daphnia* with acute and chronic NOEC values of 96 and 102 mg a.i./L, respectively. The risk and safety factors for acute effects (0.00007 and 14,200, respectively) and chronic effects (0.00007 and 15,100, respectively) indicated that sulfosulfuron would not pose a risk to *Daphnia* on acute and chronic basis under the proposed maximum application rates (Table 10).

Table 10 Summary of risk assessment to aquatic organisms

Organism	Effect	NOEC or NOEL (mg a.i/L)	EEC (mg a.i./L)	Risk factor	Safety factor	Risk	Mitigatory measures
Daphnia magna	acute	96	0.00675	0.0001	14,200	no risk	not required
	chronic	102	0.00675	0.0001	15,100	no risk	not required
Fish: Rainbow trout*	acute	95	0.00675	0.0001	14,100	no risk	not required
	chronic	100	0.00675	0.0001	14,800	no risk	not required

* most susceptible species in the fish group

The most sensitive fish species to sulfosulfuron was rainbow trout with acute and chronic NOEC values of 95 and 100 mg a.i./L, respectively. The risk and safety factors for acute effects (0.00007 and 14,100, respectively) and chronic effects (0.00007 and 14,800, respectively) indicated that sulfosulfuron would not pose a risk to fish on acute and chronic bases under the proposed post-emergent application (Table 10). Further, the n-octanol/water partition coefficient value (log K_{ow} <1) indicated that the bioaccumulation of sulfosulfuron in organisms would be unlikely.

The EEC in water due to surface runoff (0.0034 mg a.i./L) is lower than the lowest NOEC to aquatic organisms (>95 mg a.i./L); therefore, sulfosulfuron would not pose a risk to aquatic organisms due to runoff under the proposed maximum application rates.

Non-target plants

The most sensitive algal species to sulfosulfuron was *S.capricornutum* with NOEC and LD_{50} values of less than 0.047 and 0.193 mg a.i./L, respectively. The EEC in water under direct over spray of maximum application rate (0.00675 mg a.i./L) is lower that the NOEC value. The risk factor (0.144) and safety factor (6.96) indicated that post-emergent application of sulfosulfuron would not adversely affect algae at the proposed maximum label rate (Table 11).

The aquatic plant, duckweed (*L. gibba)*, was very susceptible to sulfosulfuron with NOEC and EC_{50} values of 0.0005 and 0.001 mg a.i./L water, respectively. The values of risk factor and safety factor were 13.5 and 0.074, respectively (Table 11). An assessment of these values indicated that the environmental concentrations of sulfosulfuron are higher than NOEC values and would, therefore, adversely affect the non-target aquatic plants if there is a direct over spray on water bodies at the proposed maximum application rate. As the EEC in water (0.0034 mg a.i./L) due to surface runoff is greater than the NOEC, the surface runoff under the proposed use pattern in the Prairies would adversely affect the duckweed.

Sulfosulfuron was very toxic to crop plants and adversely affected the plant growth. The most susceptible terrestrial plant species to sulfosulfuron was radish with EC_{25} of 0.11 g a.i./ha. The proposed maximum application rate is 20 g a.i./ha. The values of risk factor and safety factor were 184 and 0.005, respectively. An assessment of these values indicated that the application rate of Sulfosulfuron is higher than EC_{25} value and would, therefore, adversely affect the non-target terrestrial plants if there is a direct overspray at the proposed maximum application rate.

Table 11 Summary of risk assessment to non-target plants

Organism	Effect	NOEC (mg a.i/L)	EEC (mg a.i./L)	Risk factor	Safety factor	Risk	Mitigatory measures
Algae* *S.capricornutum*	acute	0.047	0.0068	0.144	6.96	no risk	not required
Duckweed *L. gibba*	acute	0.0005	0.0068	13.5	0.074	risk	buffer zone: 6 m
Radish*	dry weight	0.11 g a.i./ha (EC_{25})	20.25 mg a.i./ha	184	0.005	risk	buffer zone: 30 m

* most susceptible species in the group

6.5 Environmental risk mitigation

An assessment of environmental safety with the use of Sundance has identified the following concerns:

- Sulfosulfuron is toxic to non-target terrestrial plants. Under the proposed use pattern, and, if there is an exposure to >0.5% of label application rate, sulfosulfuron would adversely affect the terrestrial wildlife habitat.

- Sulfosulfuron is toxic to aquatic plants. Under the proposed use pattern, and, if there is an exposure to >7% of label application rate, sulfosulfuron would adversely affect the aquatic wildlife habitat.

In order to protect the sensitive non-target terrestrial and aquatic plants, buffer zones between last spray swath and the edge of the sensitive areas are required. These buffer zones were calculated using Nordby and Skuterud (1975).

To protect the terrestrial non-target plant species from sulfosulfuron injury, a buffer zone of 30 m would be required between the last spray swath and the edge of sensitive terrestrial areas such as shelter belts and woodlots. To protect the non-target aquatic plant species from sulfosulfuron injury, a buffer zone of 6 m should be observed between the last spray swath and the edge of sensitive aquatic areas such as wetlands and ponds.

To protect the non-target aquatic plant species from sulfosulfuron in runoff, the following label statement is required:

"Do not spray if there is a forecast rain during or soon after application"

7.0 Efficacy data and information

7.1 Effectiveness

7.1.1 Intended uses

Sundance may be used for post-emergent application on spring wheat and durum wheat in Western Canada for the control of specific grass and broadleaf weeds. Sundance is effective in controlling wild oats, redroot pigweed, common chickweed, wild mustard, stinkweed and volunteer canola (excluding imazethapyr-tolerant canola, i.e., Pursuit Smart Canola), and suppressing green foxtail, quackgrass and dandelion. Sundance must be applied with the surfactant Merge at 0.5% v/v spray volume.

Sundance can be tankmixed with 2,4-D ester at a rate of 420 g a.i./ha for control of the above weeds, in addition to the following annual broadleaf weeds: lambsquarters, wild buckwheat, and storksbill.

Due to the residual nature of sulfosulfuron, care must be exercised in determining the crop to be planted the year after application. Fields with soil organic matter of 4% or greater may be rotated to all wheat varieties, including durum, canola, barley, peas and flax. Fields with soil organic matter of less than 4% may be rotated to all wheat varieties, including durum and imazethapyr-tolerant canola.

7.1.2 Mode of action

Sulfosulfuron is a sulphonyl urea with a mode of action that is almost certainly inhibition of acetolactate synthase (ALS), which may also be called acetohydroxyacid synthase (AHAS), a key enzyme in the aliphatic amino acid synthesis. The ALS enzyme is found only in plants and does not occur in humans or animals. Following foliar application, the herbicide almost immediately inhibits meristematic growth. Affected plants appear dark green and stunting occurs.

A reddening of the stem base develops, followed by slow necrosis and eventual death. The speed of plant death is related to the amount of active plant metabolism at the time of application.

The mechanism of selectivity is expected to be based on differential rates of metabolism among species, and is the basis of lack of injury to wheat cultivars.

7.1.3 Crops

Spring wheat and durum wheat are the crops on which data is presented and for which a label claim is made.

7.1.4 Effectiveness against wild oats (*Avena fatua*)

Control of wild oats was reported in 68 trials conducted over four years in 17 locations across the Prairie provinces. The average control for Sundance alone was 84% (n=53) at 14- to 40-d after application (DAA) and 86% (n=49) at 41 or more DAA.

In 29 side-by-side trials conducted over three years in 13 locations, the average control for Sundance alone was 82% (n=23) at 14- to 40-DAA and 86% (n=22) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 79% (n=23) at 14- to 40-DAA and 78% (n=22) at 41 or more DAA.

The data indicates a slight reduction in the level of control of wild oats when Sundance is tankmixed with 2,4-D ester. A statement will appear on the label indicating there may be a slight reduction in control of wild oats when Sundance is tankmixed with 2,4-D ester.

These data support the claim for control of wild oats.

7.1.5 Effectiveness against wild mustard (*Sinapsis arvensis*)

Control of wild mustard was reported in 14 trials conducted over four years in six locations across the Prairie provinces. The average control for Sundance alone was 93% (n=11) at 14- to 40-DAA and 98% (n=5) at 41 or more DAA.

In nine side-by-side trials conducted over three years in six locations, the average control for Sundance alone was 93% (n=8) at 14- to 40-DAA and 97% (n=3) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 93% (n=8) at 14- to 40-DAA and 97% (n=3) at 41 or more DAA.

These data support the claim for control of wild mustard.

7.1.6 Effectiveness against redroot pigweed (*Amaranthus retroflexus*)

Control of redroot pigweed was reported in 14 trials conducted over three years in nine locations across the Prairie provinces. The average control for Sundance alone was 85% (n=13) at 14- to 40-DAA and 80% (n=3) at 41 or more DAA.

In 11 side-by-side trials conducted over three years in eight locations, the average control for Sundance alone was 85% (n=10) at 14- to 40-DAA and 80% (n=3) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 94% (n=10) at 14- to 40-DAA and 84% (n=3) at 41 or more DAA.

These data support the claim for control of redroot pigweed.

7.1.7 Effectiveness against stinkweed (*Thlaspi arvense*)

Control of stinkweed was reported in 14 trials conducted over four years in six locations across the Prairie provinces. The average control for Sundance alone was 94% (n=15) at 14- to 40-DAA and 94% (n=2) at 41 or more DAA.

In seven side-by-side trials conducted over three years in three locations, the average control for Sundance alone was 91% (n=7) at 14- to 40-DAA and 97% (n=1) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 92% (n=7) at 14- to 40-DAA and 95% (n=1) at 41 or more DAA.

These data support the claim for control of stinkweed.

7.1.8 Effectiveness against common chickweed (*Stellaria media*)

Control of common chickweed was reported in 12 trials conducted over three years in five locations across the Prairie provinces. The average control for Sundance alone was 84% (n=9) at 14- to 40-DAA and 93% (n=8) at 41 or more DAA.

In side-by-side trials, the average control for Sundance alone was 91% (n=7) at 14- to 40-DAA and 97% (n=1) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 92% (n=7) at 14- to 40-DAA and 95% (n=1) at 41 or more DAA.

These data support the claim for control of common chickweed.

7.1.9 Effectiveness against volunteer canola (*Brassica napus and B. rapa*) (excluding imazethapyr-tolerant canola, i.e., Pursuit Smart Canola)

Control of volunteer canola was reported in 15 trials conducted over four years in eight locations across the Prairie provinces. The average control for Sundance alone was 94% (n=15) at 14- to 40-DAA. There were no trials that assessed efficacy at 41 or more DAA.

In side-by-side trials, the average control for Sundance alone was 96% (n=9) at 14- to 40-DAA with no trials recording data at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 98% (n=9) at 14- to 40-DAA. There were no trials which assessed efficacy at 41 or more DAA.

These data support the claim for control of volunteer canola (except imazethapyr-tolerant canola, i.e., Pursuit Smart Canola).

7.1.10 Effectiveness against green foxtail (*Setaria viridis*)

Control of green foxtail was reported in 46 trials conducted over four years in 12 locations across the Prairie provinces. The average control for Sundance alone was 72% (n=44) at 14- to 40-DAA and 74% (n=49) at 41 or more DAA.

In side-by-side trials, the average control for Sundance alone was 79% (n=10) at 14- to 40-DAA and 76% (n=5) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 78% (n=10) at 14- to 40-DAA and 65% (n=5) at 41 or more DAA.

These data support the claim for suppression of green foxtail.

7.1.11 Effectiveness against quackgrass (*Agropyron repens*)

Control of quackgrass was reported in 13 trials conducted over three years in eight locations across the Prairie provinces. The average control for Sundance alone was 72% (n=12) at 14- to 40-DAA and 76% (n=6) at 41 or more DAA.

In side-by-side trials, the average control for Sundance alone was 68% (n=5) at 14- to 40-DAA and 78% (n=2) at 41 or more DAA. The average control for the tankmix with 2,4-D was 68% (n=5) at 14- to 40-DAA and 72% (n=2) at 41 or more DAA.

These data support the claim for suppression of quackgrass.

7.1.12 Effectiveness against dandelion (*Taraxacum officinal*)

Control of dandelion was reported in 10 trials conducted over two years in seven locations across the prairie provinces. The average control for Sundance alone was 78% (n=10) at 14- to 40-DAA and 62% at 41 or more DAA.

In side-by-side trials, the average control for Sundance alone was 84% (n=6) at 14- to 40-DAA and 62% (n=2) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 88% (n=6) at 14- to 40-DAA and 74% (n=2) at 41 or more DAA.

These data support the claim for suppression for dandelion.

7.1.13 Effectiveness against wild buckwheat (*Polygonum convolvulus*)

Control of wild buckwheat was reported in 20 trials conducted over three years in 12 locations across the Prairie provinces. In side-by-side trials, the average control for Sundance alone was 73% (n=19) at 14- to 40-DAA and 79% (n=5) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 85% (n=19) 14- to 40-DAA and 90% (n=5) at 41 or more DAA.

These data support the claim for control of wild buckwheat with the Sundance + 2,4-D ester tankmix.

7.1.14 Effectiveness against lambsquarters (*Chenpodium album*)

Control of lambsquarters was reported in 11 trials conducted over three years in five locations across the Prairie provinces. In side-by-side trials, the average control for Sundance alone was 71% (n=11) at 14- to 40-DAA and 90% (n=1) at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 94% (n=11) at 14- to 40-DAA and 88% (n=1) at 41 or more DAA.

These data support the claim for control of lambsquarters with the Sundance + 2,4-D ester tankmix.

7.1.15 Effectiveness against storksbill (*Erodium cicutarium*)

Control of storksbill was reported in nine trials conducted over one year in five locations across the Prairie provinces. In side-by-side trials, the average control for Sundance alone was 59% (n=9) at 14- to 40-DAA. There were no trials which assessed efficacy at 41 or more DAA. The average control for the tankmix with 2,4-D ester was 90% (n=9) at 14- to 40-DAA. There were no trials which assessed efficacy at 41 or more DAA.

These data support the claim for control of storksbill with the Sundance + 2,4-D ester tankmix.

7.1.16 Effectiveness against volunteer imazethapyr-tolerant canola, i.e., Pursuit Smart Canola (*Brassica napus and B. rapa*)

The following rationale has been submitted in support of the claim of control for volunteer imazethapyr-tolerant canola, i.e., Pursuit Smart Canola with the Sundance + 2,4-D ester tankmix.

The submitted data indicates there is no antagonism with the Sundance + 2,4-D ester tankmix in terms of control of broadleaf weeds. 2,4-D ester is currently registered for the control of volunteer imazethapyr-tolerant canola. Based on these facts, the application of Sundance at 27 g/ha + 2,4-D ester should provide acceptable control of Volunteer Canola imazethapyr-tolerant canola, i.e., Pursuit Smart Canola. This rationale supports the claim for control of imazethapyr-tolerant canola with the Sundance + 2,4-D ester tankmix.

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 presented on the Sundance label:

Sundance is a Group 2 herbicide. Any weed population may contain plants naturally resistant to Sundance 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 Sundance or other Group 2 herbicides.

To delay herbicide resistance:

- Avoid the exclusive, repeated use of Sundance or other herbicides in the same herbicide group.

- Rotate with herbicides from a different herbicide group that control the same weeds as Sundance.

- Use tankmixes with herbicides from a different group when such a use is permitted.

- Integrate tillage or other mechanical cultural control methods into weed control programs whenever practical.

- Prevent movement of resistant weed seeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.

- Keep accurate records of crop rotation and herbicides used for each of your fields.

For further information contact your local Monsanto representative.

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

Spring wheat
A total of 26 trials were taken to yield and assessed for any yield effects on spring wheat of Sundance at the requested rate in the presence of weeds. The plots treated with Sundance overall yielded 110% compared to the check. In addition, 10 trials testing Sundance at twice the requested rate yielded 107% compared to the check.

A total of six trials were taken to yield and assessed for any yield effects on spring wheat of the Sundance + 2,4-D ester tankmix in the presence of weeds. The plots treated with the Sundance + 2,4-D ester tankmix overall yielded 120% compared to the check.

Durum wheat
A total of 13 trials were taken to yield and assessed for any yield effects on durum wheat of Sundance at the requested rate and at twice the requested rate in the presence of weeds. The plots treated with Sundance overall yielded 102% compared to the check and plots treated with Sundance at twice the requested rate yielded 100% compared to the check.

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

Spring wheat
Tolerance of spring wheat was evaluated in 84 trials conducted over a four-year period across the Prairie provinces. Eighteen spring wheat varieties were tested. Sundance was tested at rates ranging from the proposed label rate of 27 g/ha up to 54 g/ha. Data collected included visual evaluation of crop tolerance at 7- to 21-DAA and 21 or more DAA.

Sundance at 27 g/ha
Eighty-four trials conducted over a four-year period reported an average of 5% visual injury at 7- to 21-DAA and 5% at 21 or more DAA.

Sundance at 54 g/ha
Seventeen trials conducted over a three-year period reported an average of 6% visual injury at 7- to 21-DAA and 4% at 21 or more DAA.

The data submitted demonstrated acceptable crop safety for an application of Sundance at 27 g/ha. Visual ratings of crop injury for treatments of Sundance ranging from the requested rate to twice the requested rate indicate that Sundance provides commercially acceptable tolerance on spring wheat when applied according to label instructions, i.e., rate, timing of application.

Sundance at 27 g/ha + 2,4-D ester
Tolerance of spring wheat was evaluated in 21 trials conducted over a three-year period across the Prairie provinces. Six spring wheat varieties were tested. The tankmix with 2,4-D ester was compared to Sundance alone in all trials. Data collected included visual evaluation of crop tolerance at 7- to 21-DAA and 21 or more DAA.

Twenty-one trials testing the tankmix were conducted over a three-year period that reported an average of 5% (n=15) visual injury at 7- to 21-DAA and 6% (n=16) at 21 or more DAA. In the same 21 trials, Sundance alone reported an average of 6% (n=15) visual injury at 7- to 21-DAA and 8% (n=16) at 21 or more DAA.

The data submitted demonstrated acceptable crop tolerance for an application of Sundance at 27 g/ha + 2, 4-D ester. Visual ratings of crop injury for treatments of Sundance + 2,4-D ester indicate the tankmix provides commercially acceptable tolerance on spring wheat when applied according to label instructions, i.e., rate, timing of application.

Durum
Tolerance of durum wheat was evaluated in 16 trials conducted over a three-year period across the Prairie provinces. Five durum wheat varieties were tested. Sundance was tested at rates ranging from the proposed label rate of 27 g/ha up to 54 g/ha. Data collected included visual evaluation of crop tolerance at 7- to 21-d after application (DAA) and 21 or more DAA.

Sundance at 27 g/ha
Sixteen trials conducted over a three-year period reported an average of 7% visual injury at 7- to 21-DAA and 3% at 21 or more DAA.

Sundance at 54 g/ha
Sixteen trials conducted over a three-year period reported an average of 9% visual injury at 7- to 21-DAA and 4% at 21 or more DAA.

The data submitted demonstrated acceptable crop tolerance for an application of sulfosulfuron at 27 g/ha. Visual ratings of crop injury for treatments of Sundance ranging from the requested rate

to twice the requested rate indicate that Sundance provides commercially acceptable tolerance on durum wheat when applied according to label instructions, i.e., rate, timing of application.

Sundance at 27 g/ha + 2,4-D ester
The following rationale has been submitted in support of the claim of crop tolerance for Durum Wheat to the Sundance + 2,4-D ester tankmix.

The submitted crop tolerance data has proven durum wheat is tolerant to sulfosulfuron up to the 2 times the rate of application. 2, 4-D ester is currently registered for application on durum wheat. The submitted data has proven the tankmix with 2,4-D ester does not increase crop injury in spring wheat. Based on these facts, the application of Sundance at 27 g/ha + 2,4-D ester should not cause unacceptable crop injury to durum wheat. This rationale supports the claim of crop tolerance for durum wheat to the Sundance + 2,4-D ester tankmix.

7.5 Observation on undesirable or unintended side effects

7.5.1 Impact on succeeding crops

A total of 11 trials were conducted from 1992 to 1997 to examine the potential phytotoxic effects of Sundance on rotational crops in soils with greater than 4% organic matter. The test sites were located across the three Prairie provinces. The soil types at these sites included clay loam, silty clay loam and sandy loam. Organic matter values were all above 4% with a range of 4.5 to 7.8 and pH values ranged from 6.5 to 7.8.

The data supports the following recropping directions:

Fields with 4% or greater organic matter can be planted the following year with wheat, canola, barley, peas and flax.

A total of 12 trials were conducted from 1992 to 1997 to examine the potential phytotoxic effects of Sundance on rotational crops in soils with 4% or less organic matter. The test sites were located across the three Prairie provinces. The soil types at these sites included clay, sandy clay loam and clay loam. Organic matter values were all at or below 4% with a range of 2-4 and pH values ranged from 7.1 to 8.0.

The data submitted supports the following recropping directions:

Fields with 4% or less organic matter can be planted the following year with wheat and imazethapyr-tolerant canola.

7.6 Conclusion

The data provided indicates that, when used according to label directions, Sundance can be applied to spring wheat and durum wheat for the control and suppression of specific grass and broadleaf weeds. Sundance may be tankmixed with 2,4-D ester to provide additional broadleaf weed control. Care must be exercised when deciding which crop to plant the year following the

application of Sundance. The data submitted indicates that in soils with organic matter greater than 4%, the following crops may be sown the year after application of Sundance: spring wheat, durum wheat, canola, barley, peas and flax. In fields with soil organic matter of 4% or less the following crops may be sown the year after application of Sundance: spring wheat, durum wheat and imazethapyr-tolerant canola.

7.6.1 Summary

Crop:	spring wheat and durum wheat
Varieties:	All
Application timing:	Apply post-emerge to the crop before emergence of fourth tiller.
Product:	Sundance
Rate of application:	27 g/ha
PLUS Additional surfactant:	Merge at 0.5% v/v spray volume
Weed species controlled:	Grass weeds: Wild oats Broadleaf weeds: redroot pigweed, common chickweed, wild mustard, stinkweed and volunteer canola (excluding imazethapyr-tolerant canola, i.e., Pursuit Smart Canola)
Weed species suppressed:	Green foxtail, quackgrass, dandelion
Tankmix option:	2,4-D ester

8.0 Overall Conclusions

Sulfosulfuron provides commercially acceptable crop tolerance to spring wheat and durum wheat when applied at 27 g/ha. Sundance will control wild oats, redroot pigweed, common chickweed, wild mustard, stinkweed and volunteer canola (excluding imazethapyr-tolerant canola, i.e., Pursuit Smart Canola). Sundance may be tankmixed with 2,4-D ester for control of additional broadleaf weeds.

Sulfosulfuron was of low acute toxicity by the oral, dermal and inhalation routes in rats, was minimally irritating to the skin and eyes of rabbits, and did not cause dermal sensitization in guinea pigs.

Treatment-related effects of toxicological concern were observed in the urinary system. In mice, rats and dogs, the kidneys, ureters and urinary bladder were the target organs after sub-chronic and chronic exposure to sulfosulfuron. Findings were associated with the presence of crystals in all three species, which often aggregated to form calculi, resulting in irritation and damage to the

renal and/or urinary bladder epithelial cells. Tumours were noted in the urinary bladder of mice and rats after long-term exposure, at dose levels which induced calculi formation. However, sulfosulfuron was non-genotoxic, and is not considered to pose a carcinogenic hazard to humans as long as the intake is below the threshold concentration required for formation of urinary precipitates and calculi (and subsequently, epithelial damage). There were no other treatment-related effects of toxicological concern.

The recommended ADI was calculated to be 0.24 mg/kg bw, based on the lowest NOEL of 24.4 mg/kg bw/d, established in the two-year rat dietary study (on the basis of urolithiasis and associated pathological and biochemical findings at higher doses), and using a safety factor of 100.

The plant and animal metabolism studies demonstrated that sulfosulfuron represented the major terminal residue in extractable fractions of straw, forage, meat, liver, kidney, milk and eggs. The majority of the identified minor metabolites contained the imidazopyridine (Im) moiety. Consequently, the ROC was defined as the sum of sulfosulfuron and its ethyl sulfone metabolites, expressed as sulfosulfuron equivalents.

The proposed method of analysis for sulfosulfuron residues involves the quantitative conversion of sulfosulfuron to the ethyl sulfone metabolite by means of acid hydrolysis and the conversion of the metabolites containing the imidazopyridine (Im) moiety that can be hydrolyzed to the ethyl sulfone metabolite upon hydrolysis with acid. The sulfone is quantified by means of HPLC analysis with fluorescence detection. Residues unaccounted for by the method are not considered to be of toxicological significance. The LOQ for the method were set at 0.002 mg/kg for plant matrices and 0.004 mg/kg for milk and tissues.

The program of supervised field trials conducted (Belgium, Canada, France, Germany, U.K. and U.S.), which involved post-emergence application of sulfosulfuron to wheat, demonstrated that residues in grain and straw collected at normal harvest were below 0.01 mg/kg and 0.1 mg/kg respectively. Considering these results, the proposed MRL for sulfosulfuron in wheat grain is 0.02 mg/kg with a minimum preharvest interval of 67 days, expressed in terms of the latest growth stage proposed for application - before the emergence of the 4th tiller of the crop. MRLs for sulfosulfuron in animal products, as a result of feeding treated feed, are proposed as follows:

milk	0.006 mg/kg
meat and fat (cattle, goat, swine, horse, and sheep),	
meat and fat (poultry)	0.005 mg/kg
eggs	0.005 mg/kg
meat byproducts (cattle, goat, swine, horse and sheep),	
meat byproducts (poultry)	0.05 mg/kg

It is considered unlikely that residue levels greater than 0.02 mg/kg will occur in succeeding crops following use of sulfosulfuron as proposed (20 g a.i./ha).

Potential exposure to sulfosulfuron in the diet is very low. On the basis of the Canadian diet, it was estimated that potential daily intakes are no more than 0.4% of the proposed ADI (0.24 mg/kg/d), providing a large safety margin for all consumers, including infants and children.

Short term dermal and dietary toxicology studies were deemed most appropriate to use in occupational risk assessment. The calculated margins of exposure were acceptable for both farmers and custom applicators, provided chemical-resistant gloves are added to the proposed label as additional personal protective equipment for mixer/loaders.

Sulfosulfuron is moderately persistent in soils under field conditions. Although the laboratory studies indicate that sulfosulfuron and its transformation product, sulfonamide, are very mobile in soils, they have a low potential to contaminate the groundwater under field conditions.

Sulfosulfuron is very toxic to non-target terrestrial and aquatic plants. The proposed post-emergence application of sulfosulfuron has the potential to significantly affect the terrestrial and aquatic plant habitat because of spray drift and runoff. In order to protect the terrestrial habitats, a buffer zone of 30 m is required between the last spray swath and the edge of sensitive areas such as shelter belts and woodlots. To protect aquatic habitats, a buffer zone of 6 m should be observed between the last spray swath and the edge of sensitive areas such as wetlands and ponds. The following label statement is required to protect the non-target aquatic plant species from sulfosulfuron in runoff: “Do not spray if there is a forecast for rain during or soon after application”

Label Amendments:

“Wear a long-sleeved shirt, long pants, shoes and socks while mixing/loading or applying this product. In addition, wear chemical-resistant gloves while mixing/loading.”

“Maintain a buffer zone of 30 m between the last spray swath and the edge of sensitive areas such as shelter belts and woodlots. To protect aquatic habitats, a buffer zone of 6 m should be observed between the last spray swath and the edge of sensitive areas such as wetlands and ponds.”

“Do not spray if there is a forecast for rain during or soon after application”

Proposed Decision

It is proposed that Sundance of the specification submitted be registered for use as a plant protection product for the control of certain weeds in spring and durum wheat.