Decision Document E96-01

Nicosulfuron

The active ingredient nicosulfuron and a formulated product Ultim®, for control of various annual grass weeds, quackgrass and redroot pigweed in field corn in Eastern Canada, were granted full registration in October, 1995.

This document provides a summary of data reviewed and the rationale for the registration decision concerning nicosulfuron and Ultim®.

This Decision Document has been prepared in keeping with the Pest Management Regulatory Agency's ongoing efforts to regulate pest control products in an open and transparent manner.

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1.0 Summary

The purpose of this document is to announce the regulatory decision on the active ingredient nicosulfuron and the end-use product Ultim® Herbicide. This document also provides a summary of the data submitted and reviewed to support the registration of these products.

Ultim® is a product containing two active ingredients, nicosulfuron and rimsulfuron. This document deals with the regulatory decision on nicosulfuron and Ultim® only. The decision concerning rimsulfuron will be addressed in a separate publication.

Agricultural specialists in the Pest Management Regulatory Agency (PMRA) have assessed the performance and value of the use of Ultim®. Officials of PMRA's Environmental and Health Evaluation Divisions assessed the risks associated with its use.

Health specialists indicated that, when Ultim® is used as proposed, residues of nicosulfuron in corn grain, corn oil, and livestock products will be below 0.1 parts per million (ppm) and are not considered to pose a hazard to consumers. The margin of safety (MOS) for occupational exposure is considered to be adequate when Ultim® is applied as specified on the product label.

Laboratory studies indicate that biotransformation would be the major route of nicosulfuron transformation in the environment. Laboratory results raised concerns regarding the potential for persistence of nicosulfuron residues in soil and natural aquatic systems.

Nicosulfuron is highly soluble in water and “intermediate” in terms of soil mobility according to soil thin layer chromatography. These results raised concerns regarding the potential for residues to leach through soil. However, concerns regarding soil persistence and mobility and the potential for groundwater contamination were alleviated by data from Canadian and American field dissipation studies.

Based on the low octanol/water partition coefficient of nicosulfuron, bioaccumulation/bioconcentration is not expected.

Nicosulfuron was practically nontoxic to birds, fish, and aquatic invertebrates. Application of Ultim® at the recommended rate is not expected to present a direct hazard to wild animals. Toxicity to bees, earthworms and soil microorganisms is not expected.

No significant effects on cell growth, biomass, cell counts or cell morphology were demonstrated on the algae *Selenastrum capricornutum* or *Anabaena flosaquae*. However, toxic effects to the growth of the diatom *Navicula pelliculosa* were

observed. Nicosulfuron is highly toxic to the growth of duckweed, *Lemna gibba*. The potential effects should be mitigated by the establishment of a 10-metre buffer zone around bodies of water or wetland.

In terrestrial environments, exposure of nontarget plants may adversely affect wildlife habitat. This potential risk is mitigated by observance of the Ultim® label statement establishing a five-metre buffer zone between the treatment area and terrestrial habitats.

Ultim® is an effective herbicide for the control of various annual grass weeds, quackgrass, and redroot pigweed in field corn. Application is made postemergence up to the six-leaf stage of corn. Broad spectrum weed control may be achieved by tank mixing with a broadleaf herbicide as indicated on the product label.

2.0 Pesticide Name and Properties

2.1 Pesticide Name

Common name: nicosulfuron

Chemical name: 2-[[(4,6-dimethoxypyrimidin-2-yl)amino-carbonyl]aminosulfonyl]-*N*, *N*-dimethyl-3-pyridinecarboxamide monohydrate

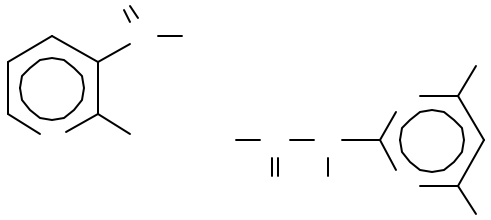
CAS Registry No: 111991-09-4

2.2 Physical and Chemical Properties:

2.2.1 Technical Product

Empirical Formula:	$C_{15}H_{18}N_6O_6S \cdot H_2O$
Molecular Weight:	428.4 (monohydrate)
Physical Form:	Solid
Colour:	White
Odour:	Paste-like
Melting Point:	141-144˚C
Vapour Pressure:	1.2×10^{-16} torr (25˚C)
Octanol/water partition coefficient (K_{OW}):	0.44 at pH 5 0.017 at pH 7 0.0069 at pH 9
Water Solubility at 25˚C:	359 mg/L at pH 5 12200 mg/L at pH 7 39000 mg/L at pH 9

Chemical Structure



Solubility in various solvents:

Solvent	**Solubility (mg/L)**
Methylene chloride	160,000
N,N-dimethlyformamide	64,000
Chloroform	64,000
Tetrahydrofuran	26,000
Acetonitrile	23,000
Acetone	18,000
Ethanol	4,500
Ethyl acetate	3,800
Benzene	1,700
2-Propanol	1,200
Methanol	440
Toluene	370
Xylenes	200
n-hexane	<19

2.2.2 Formulated Product

Product name:	Ultim® Herbicide
Guarantee:	12.5% nicosulfuron + 12.5% rimsulfuron
Flammability:	not applicable
Storage stability:	52 weeks at room temperature

3.0 Development and Use History

Nicosulfuron is manufactured by E.I. DuPont de Nemours & Co. in Belle, West Virginia. The Canadian registrations for both nicosulfuron technical and Ultim® Herbicide are held by DuPont Canada Inc.

Field testing with Ultim® began in 1990 and continued for a four-year period to 1993. Testing was conducted in Ontario and Quebec with the main focus in Ontario. The original request to register Ultim® was received at Agriculture and Agri-Food Canada in October 1990. Nicosulfuron is currently registered in Canada, the United States, and Mexico and in several other countries. The Ultim® formulation is registered only in Canada.

4.0 Biological Properties

Both nicosulfuron and rimsulfuron are members of the sulfonylurea family of herbicides. Ultim® is a preformulated mixture of nicosulfuron and rimsulfuron, applied postemergence. It is absorbed through the leaves and translocated throughout the plant, including the root system. The herbicidal activity of the active ingredients is due to the inhibition of the enzyme acetolactate synthase (ALS), resulting in the interruption of cell division and elongation in the plant. The ALS enzyme is found only in plants and does not occur in humans or animals. Crop tolerance of corn to Ultim® is due to metabolism of the active ingredients to nonphytotoxic metabolites. The ability of the corn crop to metabolize Ultim® decreases when the crop is stressed thereby increasing the possibility of phytotoxic effects.

5.0 Regulatory Position and Rationale

Based on results of acute, short-term, and long-term dosing in rats, mice, and dogs, nicosulfuron was found to be generally low in toxicity. Both technical nicosulfuron and Ultim® were not acutely toxic to laboratory animals by the oral, dermal, and inhalation routes. Formulated Ultim® is mildly irritating to rabbit eyes. There is no evidence of oncogenicity/carcinogenicity in rats or mice. Nicosulfuron was not teratogenic in rats or rabbits. Mutagenicity assays did not suggest that nicosulfuron has genotoxic potential. Although no exposure study was conducted on Ultim®, a study on tribenuron methyl (EXPRESS®), also a sulfonylurea, was used as a surrogate. Exposure for a worker of 70 kg wearing long pants, short-sleeved shirt and no gloves was estimated to be 0.018 mg/kg bw/day for both nicosulfuron and rimsulfuron. Based on this exposure value and a No Observed Effect Level (NOEL) of 9.6 mg/kg bw/day, (based on lowest definitive No Observed Effect Level from rimsulfuron toxicology package, combined results of 90-day and 1-year dog studies), the calculated MOS of 533 was considered adequate.

Nicosulfuron is practically nontoxic to birds, fish, and aquatic invertebrates. Ultim® should not pose a direct hazard to wild mammals and toxicity to bees, earthworms, or soil

microorganisms is not expected. The negative effect of nicosulfuron on diatoms may affect the food chain in freshwater aquatic ecosystems. In addition, the effect of nicosulfuron on duckweed could impact on the waterfowl food supply. Wildlife habitat may be adversely affected by exposure of nontarget plants to nicosulfuron through direct overspray or spray drift. These risks are mitigated by the label restriction of no aerial application and a buffer zone statement directing a 10-metre buffer zone around bodies of water or wetland and a five-metre zone around terrestrial habitats.

It was concluded that Ultim®, when used according to the label instructions, is efficacious in controlling the weed species indicated on the label, safe to the crop and does not present an unacceptable risk to the user or the environment.

6.0 Use Summary and Benefits

6.1 Description of Product Use

Ultim® may be used for postemergent application on field corn in Eastern Canada. Ultim® is not for use on sweet corn or seed corn or on hybrids with 2500 Corn Heat Unit (CHU) or less. An application of Ultim® at a rate of 25 g a.i./ha with a nonionic surfactant, either Citowett Plus, Agral 90, or Agsurf at 2L/1000L spray solution (0.2% v/v), at the one- to six-leaf stage (4 visible collars or 30 cm in height, leaf extended) is effective in the control of various annual grasses including barnyard grass, fall panicum, green foxtail, yellow foxtail, proso millet and old witchgrass. In addition, Ultim® at the 25 g a.i./ha rate is also effective against quackgrass and redroot pigweed. For maximum effectiveness, application of Ultim® should be made at the one- to six-leaf stage for annual grasses (up to early tillering, 2-two leaf tillers), the three- to six-leaf stage for quackgrass (10-20 cm in height, leaf extended) and the two- to six-leaf stage of pigweed (10 cm tall or across). Application of Ultim® beyond the six-leaf stage of corn must be delayed until after the eight-leaf stage and before silking. Application at the later stage must be directed below the corn canopy to keep the spray out of the corn whorl or damage will result.

Ultim® can be applied in tank-mix combination with various broadleaf herbicides to enable broad spectrum weed control in a single pass. Ultim® can be tank mixed with cyanazine at 750 g a.i./ha for control of weeds listed on the Ultim® label in addition to common ragweed, lady's thumb, and lamb's quarters (triazine sensitive only). Ultim® tank mixed with bromoxynil or dicamba at 280 g a.i./ha will control weeds listed on the Ultim® label and those listed on the label of the tank mix partner (at the appropriate rate).

6.2 Crop Tolerance Assessment[1]

Tolerance of field corn to Ultim® Herbicide was evaluated in 243 trials conducted over a four-year period, 1990 to 1993. Ultim® was tested alone at rates ranging from the proposed label rate of 25 g a.i./ha up to 37.5 g a.i./ha, and in tank-mix combinations with bromoxynil (280 g a.i./ha), cyanazine (750 g a.i./ha), and dicamba (280 g a.i./ha). Fifty-four corn hybrids were tested over the four-year period. Data collected included visual evaluation of crop tolerance at 7-21 days after application (DAA) and 21 or more DAA. Yield data were collected from 19 trials, conducted over a three-year period, and were compared to the weed-free check treatment or a standard treatment. Standard treatments included: metolachlor+dicamba, EPTC, atrazine+dicamba, atrazine+metolachlor+linuron, metolachlor+atrazine, or atrazine+bromoxynil. The following is a summary of the results obtained.

6.2.1 Ultim® alone

The data submitted demonstrate acceptable crop safety for an application of Ultim® at 25 g a.i./ha. Both visual ratings of crop injury and the yield data collected for treatments of Ultim® at rates ranging from 1× to 1.5× indicate that Ultim® is safe for use on field corn when applied according to the label instructions (i.e., rate, timing of application, variety restrictions).

- Ultim® at 25 g a.i./ha

  Sixty-seven trials conducted over a four-year period reported an average of 6.6% (n=57) visual injury at 7-21 DAA and 1.6% (n=63) at 21 or more DAA. Yield data collected from seven trials, conducted over a three-year period, resulted in Ultim® yielding 100% compared to the standard treatment yield and 106% compared to the weed-free check.

- Ultim® at 31.25 g a.i./ha (1.25×)

  Twenty-one trials conducted over two years reported an average of 4.1% (n=12) visual injury at 7-21 DAA and 2.0% (n=17) at 21 or more DAA. In seven trials conducted over two years, Ultim® yielded 112% compared to the standard treatment and 101% compared to the weed-free check.

- Ultim® at 37.5 g a.i./ha (1.5×)

[1] *The number of field trials listed in this section may not represent the total number of research trials submitted by DuPont Canada Inc. in support of their application to register Ultim®; it represents the number of trials that were considered in the review.*

Twenty trials conducted over two years reported an average of 7.0% (n=25) visual injury at 7-21 DAA and 4.0% (n=17) at 21 or more DAA. In 12 trials conducted over three years, Ultim® yielded 99% compared to the standard treatment yield and 106% compared to the weed-free check.

- Yield data was also averaged over four trials (two years) for an application of Ultim® at 50 g a.i./ha (2×). The average yield from these trials was 107% compared to the weed-free check. In four trials (two years) Ultim® applied at 65-75 g a.i./ha (3×) yielded 109% compared to the weed-free check.

- Yield data was collected from five trials conducted over two years in which Ultim® was applied beyond the recommended leaf stage of corn. Ultim® was applied at rates of 25-75 g a.i./ha at corn leaf stages of six to eight leaf up to eight to nine leaf (an over the top application). These treatments resulted in yield reductions: 91% yield compared to the weed-free check and 86% compared to the standard check treatment.

6.2.2 Ultim®+Bromoxynil

Phytotoxicity ratings from trials examining the Ultim® and bromoxynil tank mix indicate that initial damage can occur from the use of this tank mix; however, the damage is quickly outgrown as indicated by the follow-up evaluation. The injury described at the early evaluation date is consistent with a postemergent herbicide application on corn. In examining the tank mix of Ultim® at the 1× (25 g a.i.) to 1.5× (37.5 g a.i.) rates, the treatment appears acceptable when applied according to the label directions.

- Ultim® (25 g a.i.)+Bromoxynil (280 g a.i.)

  Sixty-one trials conducted over four years reported an average of 14.4% phytotoxicity (n=50) at 21DAA and 3.5% (n=49) at 21 or more DAA. Yield data were collected from six trials conducted over three years. The trials reporting yield values indicated acceptable phytotoxicity ratings early in the season. Based on five of the trials, conducted according to label directions, the tank mix yielded 101% compared to the standard treatments and 102% compared to the weed free check. The sixth trial reported was planted to a corn hybrid with a CHU rating of approximately 2500, which is not recommended on the Ultim® label. However, for the purpose of comparison the average yield for all 6 trials,

including the 2500 CHU hybrid, was 96% compared to the standard treatments and 95% compared to the weed free check. These values support the off labelling of corn hybrids of 2500 CHU or less.

- Ultim® (31.25 g a.i.)+Bromoxynil (280 g a.i.)

  Seven trials conducted in one year averaged 20.5% (n=4) phytotoxicity at 7-21 DAA and 4.3% (n=6) at 21 or more DAA. The yield taken from one trial conducted with these rates was 115% compared to a standard treatment.

- Ultim® (37.5 g a.i.)+Bromoxynil (280 g a.i.)

  Five trials conducted in one year averaged 12.9% (n=13) phytotoxicity at 7-21 DAA and 7.5% (n=2) at 21 or more DAA. The average yield from five trials (one year) was 97% compared to the standard treatments.

6.2.3 Ultim®+Cyanazine

Yield and visual ratings of crop phytotoxicity indicate that the tank mix of Ultim® 25 g a.i./ha with cyanazine at 750 g a.i./ha is acceptable for use on corn.

- Ultim® (25 g a.i.)+Cyanazine (750 g a.i.)

  Phytotoxicity values from 53 trials conducted over a three-year period averaged 9.3% (n=43) at 7-21 DAA and 2.0% (n=43) at 21 or more DAA. The average yield from two trials (two years) was 102% compared to standard treatments.

- Ultim® (31.25 g a.i.)+Cyanazine (750 g a.i.)

  The average phytotoxicity value from five trials conducted in a single year was 11% (n=3) at 7-21 DAA and 4% (n=4) at 21 or more DAA. The yield obtained from a single trial conducted with these rates was 111% compared to a standard treatment.

6.2.4 Ultim®+Dicamba

Based on data submitted, field corn appears tolerant to a tank mix treatment of Ultim® at 25 g a.i./ha with dicamba at 280 g a.i./ha.

- Ultim® (25 g a.i.)+Dicamba (280 g a.i.)

  Fifty-three trials conducted over four years indicated an average phytotoxicity value of 6.3% (n=45) at 7-21 DAA and 2.5% (n=41) at 21 or more DAA. Based on the average yield from two trials conducted over two years, this tank mix yielded 99% compared to the standard treatment.

- Ultim® (37.5 g a.i.)+Dicamba (280 g a.i.)

  The average yield value from three trials conducted in a single year was 99% compared to standard treatments.

6.2.5 Expert Committee on Weeds

A treatment of Ultim® alone at 25 g a.i./ha, or in combination with cyanazine (750 g a.i./ha), dicamba (280 g a.i./ha), or bromoxynil (280 g a.i./ha) applied with a nonionic surfactant at 0.2% v/v postemergence in corn appears in the accepted category of the Report of the Research Appraisal and Planning Committee, Expert Committee on Weeds, Eastern Canada, 1992 and 1993.

6.3 Efficacy Assessment[2]

Efficacy of Ultim® applied alone and in the various tank-mix combinations was studied over four growing seasons, from 1990 to 1993. All of the tank-mix treatments were evaluated for the annual grass weeds listed on the Ultim® label to ensure that control was maintained when Ultim® is applied in tank mixtures. The Ultim®+cyanazine tank mix was also examined for control of various weeds that were requested for labelling in view of the fact that the tank mix proposes a reduced rate of cyanazine compared to the rate of cyanazine used alone. The following results were obtained.

6.3.1 Redroot Pigweed (*Amaranthus retroflexus*)

Control of redroot pigweed was reported for 17 trials conducted in three years. The average control for an application of Ultim® alone was 97%.

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[2] *The number of field trials listed in this section may not represent the total number of research trials submitted by DuPont Canada Inc. in support of their application to register Ultim®; it represents the number of trials that were considered in the review.*

6.3.2 Fall Panicum (*Panicum dichotomiflorum*)

Control of fall panicum was reported for 14 trials conducted in four years. The average control value for Ultim® alone was 97%. The bromoxynil tank mix averaged 95% control in seven trials; the dicamba tank mix averaged 96% control in eight trials; and the cyanazine tank mix averaged 92% control in seven trials.

6.3.3 Proso Millet (*Panicum miliaceum*)

An application of Ultim® alone produced an average of 89% control of proso millet in 11 trials conducted in four years. This control level was maintained, or improved, in the tank mixtures with the bromoxynil tank mix providing 95% control (n=6), the dicamba mix provided 80% control in a single trial, and the cyanazine mix provided 94% control in a single trial.

6.3.4 Green Foxtail (*Setaria viridis*)

Twenty-five trials conducted with Ultim® alone over four years provided an average of 92% control of green foxtail. The bromoxynil tank mix averaged 89% control in 16 trials. The dicamba tank mix provided an average of 95% control in 14 trials. The cyanazine mix averaged 86% control in 14 trials. The lower control value for the cyanazine tank mix is due to a poor control value in one of the trials which reduced the average value.

6.3.5 Barnyard Grass (*Echinochloa crusgalli*)

Ultim® applied alone at 25 g a.i./ha provided an average of 94% control in 14 trials conducted over three years. Similar values were obtained from the tank mixtures: 94% control from the bromoxynil tank mix (n=7); 99% control from the dicamba tank mix (n=5); and 91% control from the cyanazine tank mix (n=5).

6.3.6 Yellow Foxtail (*Setaria glauca*)

Yellow foxtail control from an application of Ultim® by itself averaged 92% (21 trials over four years). Tank mixing with bromoxynil, dicamba, or cyanazine caused a reduction in yellow foxtail control. The antagonism in the tank mixtures reduced the control values to 79% with the bromoxynil mix (14 trials in four years), 84% with the dicamba mix (13 trials in four years); and 77% with the cyanazine mix (13 trials in four years). A label statement was added to the Ultim® label to indicate that reduced yellow foxtail control may result from tank mixing Ultim®.

6.3.7 Old Witchgrass (*Panicum capillare*)

Ultim® alone provided an average of 98% control of old witchgrass in nine trials conducted over four years. Ultim® tank mixed with bromoxynil averaged 91% control in six trials. The dicamba tank mixture provided an average of 96% control from six trials. Ultim® tank mixed with cyanazine averaged 99% control in four trials.

6.3.8 Quackgrass (*Agropyron repens*)

Since quackgrass is a perennial species, evaluations for weed control were taken early in the growing season (0-30 DAA) and later in the season (50-70 DAA) to examine regrowth effects. A total of 18 trials conducted over three years examined the control of quackgrass from an application of Ultim® alone. Evaluations for 0-30 DAA indicated an average of 87% control (n=12). Evaluations taken later in the season, 50-70 DAA, averaged 90% control (n=18).

6.4 Ultim®+Cyanazine Tank Mix

The proposed list of weeds to be labelled for the Ultim® and cyanazine tank mix included all of the weeds controlled by Ultim® alone at 25 g a.i./ha in addition to large crabgrass, smooth crabgrass, lady's thumb, cocklebur, common ragweed, lamb's quarters, and velvetleaf. Control for each of these species was evaluated separately since the proposed tank mixture involved a reduced rate of cyanazine. Insufficient data were provided by the applicant to allow for labelling of the following species: large crabgrass, smooth crabgrass, cocklebur, and velvetleaf. Results for the remaining species are as follows.

6.4.1 Lady's thumb (*Polygonum persicaria*)

Seventeen trials were reported examining control of this species with the Ultim® and cyanazine tank mix. An average of 93% control was obtained.

6.4.2 Common Ragweed (*Ambrosia artemisiifolia*)

An average value of 95% was reported for the 20 trials examining control of this species with the tank mix.

6.4.3 Lamb's quarters (*Chenopodium album*)

Thirty-four trials examining the tank mix of Ultim® and cyanazine reported an average control value of 86% for lamb's quarters. Almost half of these trials

reported having triazine-resistant populations of lamb's quarters. This accounts for the average value of 86% control. When the trials without triazine-resistant populations (18 trials) were examined, an average control value of 90% was obtained.

6.5 Recropping Effects

A total of 11 trials were conducted from 1987 to 1991 to examine the potential phytotoxic effects of Ultim® on rotational crops. Of the 11 trials, two tests examined recropping effects of rimsulfuron alone, five tests examined nicosulfuron alone, and four tests examined the formulated mixture of Ultim®.

The test sites, all in Ontario, included the locations of Iona Station, Guelph, Parkhill, Centralia, Varna, Blyth, and Huron Park. The soil types at these sites included loam, loamy sand, silt loam, clay loam, and fine sandy loam. Organic matter values ranged from 2.3-5.7% and pH values ranged from 6.0-7.8.

The requested recropping directions included the following: a four- month interval for winter wheat and a 10-month interval for spring barley, oats, canola, soybeans, white beans, red clover, alfalfa, sorghum, and corn (field and sweet). The data submitted supported these intervals except for the 10-month interval for oats, alfalfa and sweet corn.

6.6 Use Precautions

The data collected during the research program on Ultim® indicated that certain situations exist that may result in crop damage or reduced weed control when Ultim® is applied alone or in a tank mix. Since Ultim® is a postemergence graminicide used on a grass crop, some damage is possible and careful use of this product is required. As a result, the following label statements contain information necessary to maximize crop tolerance and efficacy:

- Corn hybrids with CHU ratings of 2500 or less have shown some sensitivity to Ultim®. Do not use Ultim® on corn hybrids with CHU ratings of 2500 or less or in geographic regions having 2500 or less average seasonal CHUs.

- Ultim® should not be applied to corn which has been treated with a highly systemic organophosphorus soil insecticide. DO NOT tank mix Ultim® with any organophosphorus insecticide. DO NOT apply a foliar organophosphorus insecticide within seven days before or after applying Ultim®.

- Because corn hybrids differ in their tolerance to herbicides, limit first use of Ultim® to a small area of each hybrid prior to adoption as a field practice.

- A slight reduction in yellow foxtail control may result with these tank-mix combinations.

- A rapid fluctuation in temperature (greater than 20°C difference within 24-36 hours) will stress the corn crop. For maximum crop safety, allow 48-72 hours for the corn to acclimatize before spraying Ultim®.

- For Ultim® used alone or in a tank mix, apply ONLY when the temperature in the 24 hours before **and** after application ranges between 5°C and 28°C. Temperatures beyond this range increase the potential for crop injury. Separate applications of Ultim® followed by a broadleaf herbicide (minimum 12 hours later) will reduce the potential for injury.

- Ensure that the boom is set at the proper height in relation to the corn plants to apply Ultim® accurately and uniformly, and to AVOID excessive application into the corn whorl.

- WARNING: Crop injury may result if application is made to corn that has been stressed by abnormally hot, humid or cold weather conditions, frost, low fertility, drought, water saturated soil, compacted soil, previous pesticide applications, disease or insect damage. If corn has been injured by frost, wait 48-72 hours before applying Ultim®.

6.7 Preharvest and Grazing Intervals

The Ultim® Herbicide label contains the following statements to address the issues of preharvest and grazing intervals:

- Ultim® Herbicide must not be applied within 30 days of harvest.

- CAUTION: Do not graze the treated crops or cut for hay; sufficient data are not available to support such use.

7.0 Toxicology and Occupational Exposure

Background

In the United States, Accent (the formulated product, nicosulfuron only) was approved for use on field corn at an MRL of 0.1 ppm for parent compound in corn grain, forage, fodder and silage. Nicosulfuron has not been petitioned for use as a separate product in Canada, since the mixture of rimsulfuron and nicosulfuron controls a broader spectrum of weeds and also permits a shorter recropping period than for nicosulfuron used alone.

Evaluation

Product Chemistry

All components of the technical material constituting more than 0.05% have been identified and are related to the manufacture of the parent compound.

The concentration of active ingredient in the technical product ranged from 88.5 - 94.5% for nicosulfuron and 96.0 - 100.0% for rimsulfuron.

7.1 Toxicology

Toxicokinetics - Technical

Radiolabelled nicosulfuron, radiochemical purity 99.0%, was administered to male and female rats as:

- single low oral dose (10 mg/kg bw; Pyridine-2-^{14}C);
- single high oral dose (1000 mg/kg bw; Pyridine-2-^{14}C);
- single high oral dose (1000 mg/kg bw; Pyrimidine-2-^{14}C);
- 14 daily oral low doses (10 mg/kg bw) of nicosulfuron followed by 10 mg/kg bw Pyridine-2-^{14}C; and
- 10 mg/kg bw Pyridine-2-^{14}C nicosulfuron by i.v.

The major portion of the test material was excreted via the feces, 80.2% to 92.2% for males and 85.1% to 95.2% for females following oral dosing. A lower percentage was eliminated in the urine, 8.8% to 19.9% for males, and 9.1% to 18.7% for females for the same dosing route. Following i.v. dosing, 76 to 80% of the administered dose (AD) was excreted in the urine and approximately 27 to 30% of the dose was excreted in feces.

The compound was rapidly eliminated, with more than 80% of the AD being excreted within the first 24 hours post-dosing in all groups. Elimination of ^{14}C-CO_2 was negligible (<0.01% of the AD). Therefore, a significant portion of the i.v. dose was eliminated via the bile.

Sex, dosing regime and dose level essentially had no effect on the excretion pattern or excretion half-lives (12 - 24 hours). Dosing with either Pyridine-2-^{14}C-nicosulfuron or Pyrimidine-2-^{14}C nicosulfuron did not affect the excretion pattern. None of the organ and tissue concentration data indicated selective retention or accumulation of dosed radioactivity. Radioactivity was undetectable in the gonadal tissue, body fat and bone in all treatment groups. Concentration of radioactivity in tissues was comparable between males and females. Tissue residues were higher in animals after a single oral

high dose, with approximately the same percentage of the AD being recovered in tissues. Three days after dosing, total recovery of radioactivity was greater than 97.9% of the AD.

Based on urinary and fecal metabolite profiles, the majority of nicosulfuron was excreted in unchanged form. A minor amount may be hydroxylated at the 5' carbon on the pyrimidine portion of the molecule then hydrolytically cleaved

to yield pyridine sulfonamide and 5'-hydroxy pyrimidine amine. Alternatively, pyrimidine amine may be hydroxylated at the 5 position following hydrolytic cleavage of nicosulfuron.

A metabolic profile and list of chemical names are shown in Figure 1 and Table 1 (p. 25, 26).

Acute Toxicity - Technical

Technical nicosulfuron (90.4 - 90.6% pure) is virtually nontoxic by the oral route in CD rats (LD_{50} >5000 mg/kg), the dermal route in New Zealand White (NZW) rabbits (LD_{50} >2000 mg/kg) and by the inhalation route in CD rats (4-hour LC_{50} >5.9 mg/L (gravimetrically determined). It was nonirritating to the skin of NZW rabbits and moderately irritating to the eyes of the same species. Results of sensitization testing in Dunkin Hartley guinea pigs utilizing the Buehler method suggest that the active ingredient has sensitization potential.

Acute Toxicity - Ultim® DF

DPX-79406 (Ultim® DF), comprised of the active ingredients rimsulfuron (12.5%) and nicosulfuron (12.5%), was virtually nontoxic by the oral route in CD rats (LD_{50} >5000 mg/kg) and the dermal route in NZW rabbits (LD_{50} >2000 mg/kg). The four-hour inhalation LC_{50} in CD rats exceeded 5.0 mg/L (gravimetrically determined).

It produced mild irritation when instilled into the eyes of NZW rabbits and was not irritating to the skin of this same species. Results of dermal sensitization testing with Dunkin Hartley guinea pigs employing the Buehler method were positive.

Short-Term Toxicity - Technical

Rats

Male and female Crl:CDBR rats (10/sex/group) were fed test diets containing 95.6% of a 1:1 mix of rimsulfuron (49.3%) and nicosulfuron (46.3%) at concentrations of 0, 100, 600, 3000 or 15000 ppm for 28 days. (NOTE: nicosulfuron is coformulated

with rimsulfuron and inert ingredients to yield an end-use formulation known as DPX-79406, "Ultim® DF". This study was conducted with the two constituent active ingredients minus the inert ingredients). The purities of the individual test agents were not provided. A No Observed Adverse Effect Level (NOAEL) was set at 15000 ppm (equal to 1136 mg/kg bw/day in males and 1267 mg/kg bw/day in females) on the basis of increased absolute and relative liver weights (males) and increased relative liver weights (females) at this level. The increases are consistent with

heightened liver metabolic activity, reflecting an adaptive response to treatment. The absence of microscopic or gross pathological changes in the liver supports selection of this dose level as a NOAEL.

Crl:CDBR rats (20/sex/group) were administered nicosulfuron (90.4% pure) in the diet for 90 days at levels of 0, 300, 1500, 7500, or 20000 ppm. At the end of this period, a subset of 10/rats/sex was retained for a reproduction study in which animals, continuing their respective diets, were mated and allowed to rear their offspring to weaning. (Summary of reproduction phase is contained in section on Reproductive Toxicity). For the 90-day feeding phase, a NOEL of 20000 ppm, equal to 1422 mg/kg bw/day in males and 1740 mg/kg bw/day in females, was established on the basis of no observed effects at this, the highest dose level.

Mice

Crl:CD-1(ICR)BR mice (10 females/group) and Crl:CDBR rats (6 males/group) received 10 daily doses (gastric intubation) of 0 or 2200 mg/kg bw of nicosulfuron (97.1% pure) as a suspension in corn oil over a two-week period. There were no effects which could clearly be attributed to the test material under the conditions of this test in either species.

Crl:CD-1(ICR)BR mice (15/sex/group) were fed diets containing nicosulfuron (90.4% pure) at concentrations of 0, 300, 1500, 7500, or 10000 ppm for 90 days. A NOEL of 10000 ppm (equal to 1441 mg/kg in males and 1925 mg/kg in females) was set on the basis of no treatment-related effects observed in this study.

Dogs

Beagle dogs (4/sex/group) were administered nicosulfuron (90.6% pure) in the diet for 90 days at concentrations of 0, 250, 5000 or 20000 ppm. A NOEL of 20000 (equal to 682 mg/kg bw/day in males and 656 ppm in females) was established on the basis of no observed treatment-related effects at dose levels up to and including this level.

Beagle dogs (5/sex/group) were administered nicosulfuron (90.6% pure) in the diet at levels of 0, 250, 5000 or 20000 ppm for one year. A NOEL of

5000 ppm (equal to 141 mg/kg bw/day) was determined for males on the basis of decreased body weights and increased liver and kidney weights while a NOEL for females was established at 20000 ppm (equal to 563.5 mg/kg bw/day) in the absence of any treatment-related findings.

Long-Term Toxicity/Carcinogenicity - Technical

Mice

Crl:CD-(ICR)BR mice (80/sex/group) received nicosulfuron (90.6% pure) in their diets for 18 months at levels of 0, 25, 250, 2500 or 7500 ppm. There were no treatment-related findings observed in either males or females, and hence the NOEL for chronic toxicity was set at 7500 ppm (equal to 953.3 mg/kg bw/day for males and 1259 mg/kg bw/day for females). Treatment with nicosulfuron was not associated with an increase in neoplasms in either sex.

Rats

Crl:CD/BR rats (62 rats/sex/group) were fed test diets containing nicosulfuron at concentrations of 0, 50, 1500, 7500 or 20000 ppm for two years. At approximately 12 months of treatment, 10 rats/sex/group were sacrificed and examined. A NOEL of 20000 ppm (equal to 786 mg/kg bw/day in males, 1098 mg/kg bw/day in females) was established in the absence of treatment-related findings at any of the treatment levels. Treatment with nicosulfuron did not result in an increase in neoplasms in either sex.

Genotoxicity - Technical

An Ames mutagenicity in vitro assay was performed on *Salmonella typhimurium* using the following test strains and dose levels of nicosulfuron (90.4% pure):

TA1535, TA98: 0, 0.1, 0.25, 0.5, 0.75 and 1 ：g/plate,
TA97A: 0, 0.02, 0.04, 0.06, 0.08, 0.1 ：g/plate and
TA100: 0, 0.1, 0.5, 1, 5, 10 ：g/plate

Testing was conducted both in the presence and absence of metabolic activator. Nicosulfuron was not mutagenic under the conditions of this test.

An in vitro CHO/HPRT assay was performed on Chinese hamster ovary (CHO-K1 clone BH4) cells, using nicosulfuron (90.6% pure) at dose levels of 0, 4, 20, 40, 200 and 465 ：g/ml, both in the presence and absence of metabolic activator. Under the conditions of testing, nicosulfuron was not mutagenic.

An in vivo micronucleus assay was conducted using nicosulfuron (90.6% pure) as a suspension in corn oil. Male and female Crl:CD-1(ICR)BR mice were dosed once by oral gavage at dose levels of 0, 500, 2500 and 5000 mg/kg bw. Animals were sacrificed 24, 48 and 72 hours post-dosing, at which times bone

marrow slides were prepared and examined for micronucleus formation in polychromatic erythrocytes. Nicosulfuron was nonclastogenic under the conditions of this assay.

An in vitro unscheduled DNA synthesis assay was performed on rat primary hepatocytes using nicosulfuron (90.6% pure), at dose levels of 0, 0.04, 0.4, 1.2, 4.1, 12, 41, 122, 409 and 470 ：g/ml. Under the conditions of this assay, nicosulfuron did not induce unscheduled DNA synthesis.

An in vitro chromosomal aberration assay was conducted on human lymphocytes, using nicosulfuron (90.6% pure) at dose levels of 0, 40, 200, 400 and 470 ：g/ml, both in the presence and absence of metabolic activation. Cells were examined for chromosomal abnormalities following treatment. Nicosulfuron was not clastogenic under the conditions of this test.

Reproductive Toxicity - Technical

Rats

Crl:CD BR rats (10/sex/group), having received nicosulfuron (90.6%) in the diet at concentrations of 1, 300, 1500, 7500 or 20000 for 90 days, were continued on their respective diets for a one-generation reproduction study. A NOEL was set at 20000 ppm (equal to 1422 mg/kg bw/day in males, 1740 mg/kg bw/day in females) in the absence of treatment-related findings at any of the levels tested.

Nicosulfuron (90.5% pure) was administered to Crl:CD BR rats (30/sex/group) at dietary levels of 0, 250, 5000 or 20000 ppm in a two-generation reproduction study initially designed to produce one litter per generation. Due to low fertility in the second generation (F1), an additional mating was performed and a second litter produced. F0 rats were treated for 10 weeks before mating, during mating, gestation and lactation.

F1 rats were exposed through their lives including 17 weeks after weaning at 21 days and before mating to produce the F2A. F1A rats were mated one week after weaning of the F2A to produce F2B. Despite low fertility in all groups, including controls, for both the first and second matings of the F1 generation, sufficient litters were produced for an evaluation. The NOEL for parental and reproductive effects is 20000 ppm (equal to 1263 mg/kg bw/day for males, 1475 mg/kg bw/day for females) based on an absence of treatment-related effects at the dose levels tested.

Teratogenicity - Technical

Rats

Groups of 25 mated Crl:CD BR rats were administered nicosulfuron (90.6% pure) suspended in a 0.5% aqueous suspension of methylcellulose by gavage during gestation days 7 - 16 at doses of 0, 200, 1000, 2500 or 6000 mg/kg bw. The NOAEL for maternal toxicity was set at 6000 mg/kg on the basis of the clinical finding of light brown feces in animals of the 2500 and 6000 mg/kg group, considered to reflect the high level of dosing. There were no effects on any of the maternal reproductive parameters or on the incidence and type of fetal observations under the conditions of this test. A NOEL of 6000 mg/kg was therefore set for fetotoxicity and teratogenicity.

Rabbits

Groups of 20 mated Hra:NZW rabbits were administered nicosulfuron (90.6% pure) suspended in a 0.5% aqueous suspension of methylcellulose by gavage during gestation days 7 - 19 at doses of 0, 100, 500, 1000 or 2000 mg/kg bw. The NOEL for maternal toxicity of 100 mg/kg was based on clinical signs (altered fecal excretion and discharge) including abortions, and decreased body weights and food consumption at 500 mg/kg and above. A lack of any treatment-related effects on the fetuses was the basis of establishing a NOEL of 2000 mg/kg bw for fetotoxicity. In dams producing litters at scheduled sacrifice, nicosulfuron was not observed to be teratogenic at levels up to and including 2000 mg/kg bw.

Toxicology Summary

Oral metabolism studies in rats indicated that technical nicosulfuron is rapidly eliminated, primarily in unchanged form, with the majority appearing in the feces (81 - 95% of AD). Urinary excretion accounted for 9 - 20% of the AD. Elimination of ^{14}C-CO_2 was not significant. Position of radiolabel, sex, dosing regime and dose level essentially had no effect on the excretion pattern or excretion half-lives (12 - 24 hours). Following i.v. dosing, a significant portion of the AD was recovered in the bile. None of the organ and tissue concentration data indicated selective retention or accumulation of dosed radioactivity.

Toxicity testing results showed that technical nicosulfuron was generally of low toxicity following acute, short-term, and long-term dosing in rats, mice and dogs.

Technical nicosulfuron and the Ultim® DF formulated product were not acutely toxic to laboratory animals by the oral, dermal and inhalation routes. Both materials were not irritating to rabbit skin. The technical material was moderately irritating to the

rabbit eye, with the Ultim® DF product producing mild irritation. Both technical nicosulfuron and Ultim® DF were considered to possess sensitizing properties.

Short-term repeated oral dosing with technical nicosulfuron in rats, mice and dogs at relatively high doses failed to reveal any effects which could clearly be ascribed to treatment with the test compound. NOELs of 10000 ppm for mice, 10000 ppm for dogs, and a NOEL of 20000 ppm for rats were set. A 28-day oral dosing study in rats with a 1:1 mix of technical nicosulfuron and rimsulfuron (a similar sulfonylurea herbicide) resulted in a NOAEL of 15000 ppm based on increased liver weights in both sexes at this highest dosage level. The absence of histopathological findings in liver supported the contention that the liver weight increases likely reflected an adaptive response to increased metabolic activity.

Long-term oral dosing did not result in chronic toxicity at dose levels up to and including 7500 ppm in mice and 20000 ppm in rats. There was no evidence of oncogenicity/carcinogenicity in either species.

Results of a one-generation reproduction study (component of a 90-day rat feeding study) as well as those of a two-generation rat reproduction study did not indicate reproductive toxicity up to and including 20000 ppm.

Dosing via oral gavage in a rat teratogenicity study at dose levels up to and including 6000 mg/kg bw failed to reveal any significant treatment-related findings. A NOAEL for maternal toxicity was established at 6000 mg/kg bw on the basis of clinical findings of light brown feces. A NOEL for fetotoxicity was set at 6000 mg/kg bw. Teratogenicity testing in rabbits indicated that this species was more sensitive than rats to the effects of nicosulfuron following oral gavage. A NOEL for maternal toxicity of 100 mg/kg bw was based on clinical signs (altered fecal excretion and discharge) including abortions, decreased food consumption and body weights at 500 mg/kg bw and above. A NOEL of 2000 mg/kg bw was established for fetotoxicity. Nicosulfuron was not teratogenic in rats or rabbits.

Nicosulfuron did not demonstrate genotoxic potential in a battery of mutagenicity assays.

7.2 Food Exposure

7.2.1 Acceptable Daily Intake (ADI)

Based on the results of the rabbit teratology study, the definitive NOEL was determined to be 100 mg/kg bw/day based on clinical signs including abortions, decreased food consumption and body weight. In view of these results, the standard safety factor of 100 is considered appropriate and the recommended ADI was calculated to be 1.00 mg/kg bw/day

7.2.2 Residue Levels

Label

Formulated product: Ultim® 25% DRY FLOWABLE,
nicosulfuron 12.5-13.2% (by weight)
+ rimsulfuron 12.5-13.2%

Mixed with water and a nonionic surfactant (either Citowett Plus, Agral 90 or Agsurf at 2 L/1000 L spray solution (0.2% v/v)).

Applied postemergence to field corn in Eastern Canada for control of various weeds (quackgrass, annual grasses and redroot pigweed).

Apply Ultim® (100 g product/ha or 12.5 g/ha nicosulfuron plus 12.5 g/ha rimsulfuron) as a single application per season as a broadcast spray with a recommended surfactant to corn up to the six-leaf stage. Applications of Ultim® after the six-leaf stage (30 cm leaf extended) must be delayed until after the eight-leaf stage when a height differential can be established between the corn and target weeds.

Ultim® herbicide must not be applied within 30 days of harvest.

Ultim® Tank Mixes
- Bladex 90 DF (cyanazine)
- Banvel (dicamba-dimethylammonium)
- Pardner (bromoxynil)

Ultim® must not be tank mixed with any organophosphorous (OP) insecticide; do not apply an OP insecticide within seven days before or after applying Ultim®.

Replanting of other crops on soil treated with Ultim® is detailed on the label.

The product is not to be used on sweet corn or seed corn.

CAUTION: Do not graze the treated crops or cut for hay; sufficient data are not available to support such use.

Metabolism - Plant

A metabolic profile for all plants and animals studied and the chemical names for all identified metabolites are given in Figure 1 and Table 1 (p. 25, 26).

Corn

A typical field corn was planted in pots maintained in a greenhouse and treated postemergence (four- to five-leaf growth stage) with either [pyridine or pyrimidine-^{14}C] nicosulfuron. The formulated labelled compounds were applied as a spray, at an application rate of 70 g a.i./ha (US rate) 5.6x the maximum use rate in Canada.

Whole plant samples of the crop treated with either ^{14}C-labelled parent solution were taken immediately after the spray dried and 7, 14, 30 (proposed preharvest interval), 49 (silage), and 113 days (maturity) after treatment. At maturity, the samples were separated into grain, cob, stover (stalk) and fodder (whole plant) for analysis.

These studies showed that the plant metabolism of nicosulfuron in field corn proceeds primarily by two pathways: hydrolysis of the sulfonylurea bridge resulting in the formation of pyridine sulfonamide and pyrimidine amine and hydroxylation at the 5'-position of the pyrimidine ring of the intact sulfonylurea followed by glucosidation.

For [pyridine-^{14}C]nicosulfuron-treated corn, the levels of total radioactivity (^{14}C) in 30-day forage sample, silage, mature grain, cob, fodder and stover were: 0.014, 0.005, 0.002, 0.004, 0.065 and 0.046 ppm (nicosulfuron equivalents), respectively. Grain and cob were not extracted due to their low total ^{14}C content. The concentration of nicosulfuron in each of the fractions that were extracted was less than 0.010 ppm. Pyridine sulfonamide, the hydrolysis product, was the major metabolite in silage, stover and fodder, comprising only 0.002, 0.058 and 0.021 ppm respectively (based on its own molecular weight). Individual metabolite concentrations in the 30-day whole plant and silage sample were each less than or equal to 0.005 ppm (nicosulfuron equivalents). Total ^{14}C-

residues in mature grain and in the cob were each less than 0.005 ppm (nicosulfuron equivalents).

For corn treated with [pyrimidine-^{14}C]nicosulfuron, the levels of total ^{14}C in the above fractions were 0.006, 0.003, 0.003, 0.004, 0.058 and 0.078 ppm (nicosulfuron equivalents), respectively. The concentration of nicosulfuron in each of the fractions that were extracted was less than 0.010 ppm except for fodder and stover at 0.021 and 0.028 ppm, respectively. The concentration of all other metabolites in all extracts were each less than 0.010 ppm (nicosulfuron equivalents). Samples taken prior to 30 days after application, contained nicosulfuron-5'-*O*-Glucoside and its aglycon, 5'-Hydroxy nicosulfuron. However, these compounds were not detected in any of the samples after 30 days.

In summary, the corn metabolism study shows that there are very low concentrations of ^{14}C-total terminal residues of nicosulfuron and its metabolites (0.002 and 0.003 ppm for the two labelled versions of nicosulfuron) in mature grain, and did not exceed 0.096 ppm in any other plant tissues harvested at 30 days to 113 days post-treatment. Since these metabolism studies were performed at 5.6 times the recommended Canadian use rate and under growing conditions representing a worst-case scenario (high transpiration rates and confined conditions in a greenhouse), field residues for nicosulfuron and its metabolites from plants treated at recommended use rate would be expected to be much lower.

Metabolism - Livestock

Goats

Goats were dosed with the equivalent of approximately 60 ppm [pyridine or pyrimidine-^{14}C]nicosulfuron in feed each day, for three consecutive days. This dose is approximately 600 times the total ^{14}C-residue levels found in any corn tissues treated at 5.6 times the maximum use rate.

Total terminal residues in tissues, milk and blood were too low to characterize (0.008-0.098 ppm). Radiolabelled metabolites identified in urine from the pyridine-labelled study included pyridine sulfonamide, N-desmethyl nicosulfuron, nicosulfuron cyclized ipso compound, N-desmethyl pyridine sulfonamide and pyridine sulfonamide carboxamide. The major metabolite from the pyrimidine-labelled study was a polar conjugate of 5-hydroxy pyrimidine amine.

Animal metabolism of nicosulfuron proceeds primarily by three pathways: hydrolysis of the sulfonylurea bridge, N-demethylation and loss of sulfur to form the nicosulfuron cyclized ipso compound and oxidation and conjugation at the 5-position of the pyrimidine ring.

The major metabolic pathway found in the rat, hydrolysis of the sulfonylurea bridge, is also found in the goat.

Hens

A hen metabolism feeding study was not submitted for nicosulfuron. The company requested a waiver of this study based on the following information.

Greenhouse corn metabolism studies which demonstrate total ^{14}C-residue levels in corn treated at maximum and at 5.6 times maximum use rate were less than 0.01 ppm (nicosulfuron equivalents) in grain and less than 0.07 ppm in fodder. Nicosulfuron levels in all samples (forage, silage and grain) from field corn treated at 1x and 2x maximum label use rates were below detection limits of 0.05 ppm by 15 days post-treatment (30 days PHI, label).

A hen metabolism study was provided for rimsulfuron, a close analogue of nicosulfuron, as a surrogate study. Hens fed rimsulfuron for 5 days, at 200x the anticipated dietary burden, eliminated up to 88 % of the dose via the excreta within about 24 hours after dosing. ^{14}C-Residues in muscle, fat and eggs were 0.016, 0.012 and 0.02 ppm, respectively. The metabolic pathways reported were consistent with those of the rat and goat studies for rimsulfuron.

In addition, rat and lactating goat studies (exaggerated feeding levels) showed that nicosulfuron was rapidly excreted with no selective retention or potential accumulation in any organ (0.047-0.098 ppm), meat (0.001-0.017 ppm) or milk (less than 0.0005-0.032 ppm). The major metabolic pathway found in rat, hydrolysis of the sulfonylurea bridge, is also prevalent in the goat, corn and soil metabolism studies. The data waiver request can therefore be supported.

These studies indicate that residues of nicosulfuron and its metabolites in meat and milk from livestock fed a diet of nicosulfuron-treated field corn, silage, grain, cob, fodder or stover are likely to be less than 0.1 ppm and would be covered under the General Regulation B.15.002(1).

Figure 1 (p. 25) shows the proposed metabolic profile for nicosulfuron and chemical names of all of the identified metabolites for all plants and animals studied.

Figure 1: Proposed Metabolic Pathway for Nicosulfuron(I).

[]=Proposed Intermediates, C=Corn, G=Goat and R=Rat.

Table 1. Trivial and chemical names for chemical structures shown in Figure 1

FIGURE #	TRIVIAL NAME	CHEMICAL NAME
I	(DPX-V9360) nicosulfuron	2-(4,6-dimethoxypyrimidin-2-yl) carbamoylsulfamoyl)-N,N-dimethylnicotinamide or 1-(4,6-dimethylpyrimidin-2-yl)-3-(dimethylcarbamoyl-2-pyridylsulfonyl)urea
II	(pyrimidinyl urea)	N-(4,6-dimethoxy-2-pyrimidinyl)urea
III	(N-demethyl nicosulfuron)	2-[[[[(4,6-dimethoxy-pyrimidin-2-yl)amino] carbonyl]amino]sulfonyl]-N-methyl-3-pyridinecarboxamide
IV	(N,N-didemethyl nicosulfuron)	2-[[[[(4,6-dimethoxy-pyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]-3-pyridinecarboxamide
V		2-(4,6-dimethoxy-pyrimidin-2-yl)urea-3-pyridinecarboxamide
VI	(nicosulfuron cyclized ipso compound)	1-(4,6-dimethoxy-pyrimidin-2-yl)pyrido[2,2-d] pyrimidine-2,4-(1H,3H)-dione
VII	(5'-OH nicosulfuron)	2-[[[[(4,6-dimethoxy-5-hydroxy-pyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]-N,N-dimethyl-3-pyridinecarboxamide
VIII	(5'-O-glucoside nicosulfuron)	2-[[[[(4,6-dimethoxy-5-glucosyl-pyrimidin-2-yl) amino]carbonyl]amino]sulfonyl]-N,N-dimethyl-3-pyridinecarboxamide
IX	(pyridine sulfonamide)	2-aminosulfonyl-N,N-dimethyl-3-pyridine carboxamide
X	(pyrimidine amine)	2-amino-4,6-dimethoxypyrimidine

XI		N-demethylpyridine sulfonamide
XII	(5-hydroxy pyridine amine)	2-amino-4,6-dimethoxy-5-hydroxypyridine
XIII	(pyridine sulfonamide carboxamide)	2-(aminosulfonyl)-3-pyridinecarboxamide
XIV	(pyridine acid sulfonamide)	2-(aminosulfonyl)-3-pyridinecarboxylate

Analytical methodology

Corn metabolism studies indicated that an analytical method for the analysis of the parent herbicide, nicosulfuron, would be required to monitor for residues in corn and its fractions, occurring as a result of potential misuse of the formulated product or from harvesting of immature crop for livestock consumption at less than the label recommended 30-day preharvest interval.

The analytical method developed for the determination of nicosulfuron residues in corn forage, silage, fodder and grain uses two HPLC columns with UV detection at 254 nm. One LC performs sample cleanup (Zorbax phenyl column) and the second allows sample analysis (Zorbax Rx column). The lower limit of quantitation (LLQ) was 0.05 ppm based on a 10 gram sample. Recoveries of samples spiked at 0.05 - 0.5 ppm ranged between 96 - 99% for forage, 94 - 102% for silage, 87 - 95% for fodder and 80 - 99% for grain; SDs ranged between 2 - 7% for all samples.

Accuracy and precision of the above analytical method are adequate for monitoring terminal residues of nicosulfuron for enforcement purposes.

Residues - Plant

Corn

Residue studies from 14 US field sites were conducted to determine the concentration of nicosulfuron in forage, silage (mid-dough), grain and fodder (stover) from corn treated with Accent (US formulated product). Formulated nicosulfuron was applied (single application, corn at the 5- to 10-leaf stage) to corn at each site either at the proposed US maximum label rate of 1.0 oz a.i./A (70 g a.i./ha) or at 2x rate. Samples of forage were taken at PHIs of 14-49 days post-treatment, silage (mid-dough) at PHIs ranging from 45-82 days, grain and fodder (stover) at PHIs of 72-128 days. No detectable

(LLQ=0.05 ppm) residues of nicosulfuron were found in any corn raw agricultural commodities (RACs) (grain, fodder or silage).

Residue data was reported for nicosulfuron and rimsulfuron in kernels and forage of sweet (two varieties) and field (four hybrids) corn, grown from treated (Ultim® formulation) crops in Ontario.

A 1:1 mixture of the two herbicides was applied as a foliar spray (10-13 leaf corn stage) and at a rate of 40 g a.i./ha total herbicides (1.6x the proposed maximum application rate). No residues of either herbicide were found above the LLQ of 0.05 ppm in any kernel or forage sample of sweet corn (PHI=28 and 29 days) and field corn (PHI= 28, 29, 89 and 102 days).

Corn and Processed Products

Field corn plots were treated with formulated nicosulfuron (0.25% nonionic surfactant) applied as a broadcast application at either 280 or 560 g a.i./ha (22 times and 45 times recommended maximum rate) postemergence when corn was at the 8-10 leaf stage. No nicosulfuron was detected (LLQ=0.05 ppm) in grain from samples treated at either 22 or 45 times the maximum label treatment rate and no nicosulfuron residues were detected in the processed fractions, corn oil or meal.

Rotational Crops

Greenhouse studies were conducted for rotational crops (soybeans, lettuce, wheat and radishes) grown in soil treated with nicosulfuron (^{14}C-labelled in pyridine or pyrimidine rings and formulated as Accent and applied with a label recommended surfactant) at the proposed maximum US label rate of 70 g a.i./ha and at 10x this rate or 700 g a.i./ha. Treated soils were aged 30 days, 120 days and 10 months. Nicosulfuron concentrations in crop fractions were very low, less than or equal to 0.006 ppm, and decreased with increased soil aging time. Data from these confined greenhouse studies indicated that nicosulfuron will not accumulate in rotational crops (soybeans, lettuce, wheat and radishes) grown in soil treated with nicosulfuron (Accent) at the proposed maximum US label rate of 70 g a.i./ha or at an exaggerated rate of 700 g a.i./ha.

Several other metabolites/degradates were detected at low concentrations in plant extracts (from the 10x treatment rate). N-Desmethyl nicosulfuron, for example, was detected in soybean forage/hay collected from the 30 and 120 day studies (0.024 and 0.020 ppm, respectively) but declined dramatically in the 10-month samples (0.001-0.002 ppm). Pyridine sulfonamide, a major soil

degradate of nicosulfuron, was detected in most extracts of plants grown in [^{14}C-pyridine]nicosulfuron treated soil. Concentrations were low and decreased with increased soil aging time. With the exception of soybean forage/hay from the 30-day and 120-day studies (0.081 and 0.071 ppm, respectively) and mature wheat straw from the 120-day and 10-month studies (0.056 and 0.038 ppm, respectively), pyridine sulfonamide levels were # 0.023 ppm in all crop fractions. Three other radiolabelled compounds, present at concentrations comparable to pyridine sulfonamide in soybean seed (0.01-0.04 ppm), were shown to be derived from degradation and/or metabolism of pyridine sulfonamide.

The experimental design employed in these studies (greenhouse confined conditions, low organic matter and high sand content of soil and direct application to the soil) tends to maximize uptake of pesticide residues. Under "Good Agricultural Practices" using field conditions and maximum label rate, concentrations of nicosulfuron and related metabolites/degradates in rotational crop would be expected to be even lower.

Based on results from these confined greenhouse studies, significant accumulation of nicosulfuron and or its degradates in rotational crops, resulting from the proposed use of nicosulfuron on corn, would not be anticipated.

Soil Residues

Nicosulfuron and rimsulfuron (Ultim®) were applied to field sites in Nova Scotia and Ontario to determine the mobility, dissipation and degradation in a sandy loam and loamy sand soil. Ultim® (25% dry flowable of rimsulfuron and nicosulfuron as a 1:1 mix) was applied at a rate of 400 g a.i./ha (plus 0.2% nonionic surfactant), 16 times the proposed maximum application rate. Soil cores were collected at various intervals post- treatment at depths of 1-10, 10-20 and 20-30 cm. Cores were extracted and analyzed by LC/MS to determine residues of nicosulfuron, rimsulfuron and soil degradation products IN-70941 [N-(4,6-dimethoxy-2-pyrimidinyl)-N-((3-ethylsulfonyl)-2-pyridinyl)urea] for rimsulfuron and pyridine sulfonamide for nicosulfuron; LLQ for each compound was 0.02 ppm.

Rimsulfuron degrades rapidly with calculated half-lives of 3.3-9.4 days. Parent residues decreased from 0.063 to 0.102 ppm on day 0 to <0.02 ppm in a one-month period. Nicosulfuron also degrades rapidly, $t_{1/2}$ = 9.9-12.8 days and parent decreased from 0.075-0.140 ppm on day 0 to <0.02 ppm in a one-month period. Residues of IN-70941 (primary metabolite of rimsulfuron)

were <0.02 ppm in Cambridge samples and <0.02-0.043 in London and Somerset soils in the early weeks of the study (up to two months post-treatment) and decreased to <0.02 ppm after two months.

Pyridine sulfonamide (primary metabolite of nicosulfuron) residues were <0.02 ppm in all soil samples, except for the 28-day London samples which contained 0.028 ppm. Most parent residues and their degradation products were in the 0-10 cm layer; no residues were found in the 20-30 cm soil segments indicating negligible soil mobility of parents and metabolites.

7.2.3 Dietary Risk Assessment

Based on data submitted, residues in corn, processed corn fractions, meat, milk and eggs will be <0.1 ppm and can be covered under General Regulation B.15.002(1). Based on 0.1 ppm, the potential daily intake (PDI) was calculated to be 0.00111 mg/kg bw/day which is 0.11% of the ADI (ADI = 1.00 mg/kg bw/day) for adults and 0.0125 mg/kg bw/day or 1.25% of the ADI, for preweanling children. Residues are expected to be much lower than this general regulation level and therefore the PDI will also be much lower.

7.3 Drinking Water and Risk Assessment

Based on the ADI of 1.00 mg/kg bw/day, an objective concentration of nicosulfuron can be calculated as approximately 9.3 mg/L, assuming an adult consumer with a 20% allocation to drinking water. At this concentration the intake of a bottle fed infant would be less than 60% of the ADI.

No monitoring data were found on residues of nicosulfuron or related compounds in surface and drinking water.

Nicosulfuron is very soluble in water and is unstable at acidic pH hydrolyzing to pyrimidine amine and pyridine sulfonamide. In aerobic soil under laboratory conditions nicosulfuron was moderately persistent at 25ºC (half-life of approximately 3.5 weeks) and persistent at 5ºC (half-life 1.7 years). Under anaerobic conditions, it degrades at a slower rate with a half-life of 9 weeks at 25ºC. In field tests in Nova Scotia and Ontario, the parent residues of a 1:1 mixture of nicosulfuron:rimsulfuron and primary metabolites decreased to less than 0.02 ppm in a one-month period. Adsorption of nicosulfuron was low to moderate in different soils and indicated that potential mobility in soil would be high to very high for nicosulfuron and its major transformation products. However, in field tests, no residues were reported in the 20 to 30 cm soil segments indicating negligible soil mobility of parents and metabolites.

Concerns regarding ground water contamination by nicosulfuron have been alleviated based on Canadian and American terrestrial dissipation studies. The risk of exceeding the suggested objective concentration of 9 mg/L is low.

7.4 Occupational Exposure

Ultim® DF

7.4.1 Qualitative Exposure Assessment

Potential users of this product would be farmers growing field corn in Eastern Canada. Application of this postemergence herbicide would be carried out using ground boom equipment. The application rate specified on the label is 100 g Ultim®/ha and it is anticipated that approximately 48 hectares would be treated during a typical workday. Workers would be exposed during mixing, loading, application and spray tank clean-up. The label specifies that gloves must be worn during mixing/loading and clean-up operations and when making repairs and adjustments.

7.4.2 Quantitative Exposure Assessment

An exposure study on Ultim® DF has not been submitted. The registrant provided a rationale to support the use of an exposure study conducted with tribenuron methyl (EXPRESS®) as a surrogate study. This study has been previously reviewed and has been used as a surrogate for two other products, metsulfuron-methyl (ESCORT®) and ethametsulfuron-methyl (MUSTER®).

Based on similarities in active ingredients (both sulfonylureas), formulations (both dry flowables), use scenarios (contact herbicide for ground boom application on grain/corn crops), application rates (25 g a.i./ha for Ultim® and 17.5 to 27.3 g a.i./ha in the EXPRESS® exposure study), and the overall acceptability of the EXPRESS® exposure study, it is felt that the EXPRESS® exposure data can be used as surrogate data for Ultim®.

The EXPRESS® exposure study was carried out with eight workers monitored at three sites during both mixing/loading and application (M/L/A) job functions (seven of the workers were also monitored during spray tank clean-up). Ground boom equipment (both open and closed cabbed tractors) was used to apply EXPRESS® to winter wheat plots (6.4 to 21.2 ha). Each worker completed one M/L/A cycle, which took between 2 and 3 hours.

Dermal deposition (except hands) was monitored using patches and face and neck swabs. Hand deposition was measured using cotton gloves or hand

rinses, on alternate hands. Inhalation monitoring was also carried out. Recoveries were acceptable: laboratory (78 - 90%), storage stability (78 - 110%) and field (77 - 108%).

The following limitations have been identified with the EXPRESS study:

- The total monitoring time per worker (2 - 3 hours) may not represent the typical time required under actual use conditions.

- Analysis of the innermost layer of a multilayer patch as opposed to analysis of patches placed inside the workers' clothing does not account for deposition through seams, etc. This procedure may, therefore, have underestimated dermal exposure.

Using the total exposure estimate (dermal + inhalation) from the EXPRESS study (0.0021 mg/g a.i.), exposure to each of the two active ingredients in Ultim® (e.g., rimsulfuron, nicosulfuron) was calculated based on a maximum application rate of 25 g a.i./ha (e.g., 12.5 g a.i./ha for each active ingredient as they are present in equal concentrations), a typical daily treatment of 48 ha with ground boom equipment and assuming dermal absorption of 100% as a dermal absorption study was not conducted for Ultim®.

Exposure to a 70 kg worker wearing long pants, short-sleeved shirt and no gloves is estimated to be 0.018 mg/kg bw/day (range = 0.0043 to 0.038) for rimsulfuron and 0.018 mg/kg bw/day (range = 0.0043 to 0.038) for nicosulfuron. Given that Ultim® will be packaged in water-soluble bags and that chemical-resistant gloves are a label requirement, these values are thought to be overestimated.

7.4.3 Risk Assessment

The range of toxicology studies indicate that nicosulfuron is generally of low toxicity. Rabbits appeared to be the most sensitive species with a NOEL of 100 mg/kg bw established in the teratology study on the basis of clinical signs of toxicity to the dams (altered fecal excretion and discharge, abortions) and reduced body weights and food consumption at 500 mg/kg bw and above.

Nicosulfuron is not formulated on its own as an end-use product. It is coformulated with another Dupont technical active ingredient, rimsulfuron, in equal amounts. Both active ingredients belong to the same chemical class (sulfonylurea) and both display similar toxicology profiles.

Overall, the NOELs for the rimsulfuron toxicology data package were slightly lower than those for nicosulfuron. A short-term repeated oral dosing study in rats performed with a 1:1 mix of both active ingredients did not indicate synergistic effects; the spectrum of toxicity and NOEL were consistent with the toxicology profile of rimsulfuron.

For purposes of the risk assessment, therefore, the contribution of both active ingredients was considered. Given the lack of evidence for increased toxicity resulting from the combination of active ingredients, as well as the similar chemical and toxicology profiles, it was decided to conduct the risk assessment for Ultim® DF on the basis of the rimsulfuron component.

The lowest definitive NOEL from the rimsulfuron toxicology data package was 9.6 mg/kg bw/day from the combined results of the 90-day and one-year dog studies. This NOEL was established on the basis of decreased bodyweights and increased absolute and relative liver and kidney weights.

Exposure to each of the two active ingredients in Ultim® DF was calculated on the basis of the results of the tribenuron methyl (EXPRESS®) exposure study. Exposure was estimated for a typical 70 kg worker wearing long pants, short-sleeved shirt and no gloves and applying Ultim® DF at the maximum label rate (25 g a.i./ha) to 48 ha/day. The estimated exposure was 0.018 mg/kg bw/day for either active ingredient.

Based on the exposure value and the NOEL of 9.6 mg/kg bw/day, there is an MOS of 533 which is considered adequate.

8.0 Environmental Aspects

8.1 Summary

Nicosulfuron is highly soluble in water and is not expected to volatilize from moist soil and water surfaces. Bioaccumulation/bioconcentration of nicosulfuron is not expected, based on its low octanol/water partition coefficient. Biotransformation of nicosulfuron would be the major pathway of transformation in the environment. Nicosulfuron hydrolysis was significant only under acidic conditions. Nicosulfuron phototransformation in the environment is not expected to be significant. Under laboratory conditions, nicosulfuron was moderately persistent in aerobic and anaerobic soil, but was biotransformed rapidly in anaerobic pond sediment/water. The stability of nicosulfuron in natural water under aerobic conditions and the potential persistence of major nicosulfuron transformation products under anaerobic aquatic conditions, however, raised concerns regarding persistence of nicosulfuron residues in natural aquatic systems.

The review of laboratory data identified the mobility of nicosulfuron, and the potential mobility of several major transformation products, as concerns. The review of Canadian and American dissipation data from terrestrial field studies, however, alleviated concerns regarding potential contamination of groundwater by nicosulfuron residues. Also, the concentrations of transformation products persisting in soil under field conditions would be very low.

Application of nicosulfuron at the rate recommended on the Ultim® 25 DF label would not be expected to present a direct hazard to wild birds and mammals, fish, aquatic and terrestrial invertebrates, soil microbial processes and algae. Direct adverse effects would be expected from exposure of diatoms and nontarget aquatic and terrestrial vascular plants to nicosulfuron applied at the label-recommended rate. These effects on wildlife habitat and the consequent indirect impacts on wildlife should be mitigated by observance of label statements establishing 5- and 10-metre buffer zones between the treatment area and terrestrial and aquatic habitats, respectively.

In addition, observance of buffer zones is expected to sufficiently mitigate against the introduction of nicosulfuron into aerobic/anaerobic environments. Should the use pattern for this herbicide be expanded to include sites that are likely to be or become anaerobic, however, empirical data characterizing the persistence, mobility and environmental toxicology of the major anaerobic nicosulfuron transformation products in greater detail would be required to permit a more complete scientific assessment of environmental fate and effects. The submission of such data is not being requested for the present use pattern of Ultim® 25 DF.

8.2 Use Pattern

Ultim® 25 DF is intended for the postemergent control of quackgrass, annual grasses and redroot pigweed in field corn in eastern Canada, when applied as a broadcast ground spray at a rate of 100 g formulation/ha in a minimum of 100 L water/ha. This is equivalent to an application rate of 12.5 g nicosulfuron/ha.

According to the 6 December 1993 draft label, Ultim® 25 DF is not to be applied during periods of intense rainfall, to soils saturated with water, to standing or running water, or to areas where surface water from the treatment site can run off into adjacent cropland or into streams, irrigation water or wells. The statement “DO NOT APPLY BY AIR” appeared on the draft label.

8.3 Identity of Major Transformation Products

The DuPont code and the chemical name for the major transformation products of nicosulfuron and rimsulfuron are presented in Table 2. IN-37740, IN-H9235, IN-V9367 and IN-W9807 are transformation products of nicosulfuron.

IN-E9260, IN-70942 and IN-70941 are transformation products of rimsulfuron. IN-J290, or *pyrimidine amine*, is a common transformation product of both nicosulfuron and rimsulfuron. IN-V9367 and IN-E9260 are **pyridine sulfonamide *derivatives***, both of which are referred to as *pyridine sulfonamide* in submitted reports, although they are different compounds that arise from transformation of nicosulfuron and rimsulfuron, respectively.

Table 2. Summary of the identities of the major nicosulfuron and rimsulfuron transformation products

DuPont Code	Chemical Name		Parent Compound
	Full	Short	
IN-37740	--	*O*-desmethyl nicosulfuron	Nicosulfuron
IN-H9235	--	*O*-desmethyl pyrimidine amine	
IN-V9367	2-aminosulfonyl-N,N-dimethyl-3-pyridinecarboxamide	Pyridine sulfonamide **derivative**	
IN-W9807	--	*N*-desmethyl nicosulfuron	
IN-J290	2-amino-4,6-dimethoxypyrimidine	Pyrimidine amine	Nicosulfuron Rimsulfuron
IN-E9260	3-(ethylsulfonyl)-2-pyridine-sulfonamide	Pyridine sulfonamide **derivative**	Rimsulfuron
IN-70941	N-(4,6-dimethoxy-2-pyrimidinyl)-N-((3-ethylsulfonyl)-2-pyridinyl)urea	--	
IN-70942	N-((3-ethylsulfonyl)-2-pyridinyl)-4,6-dimethoxy-2-pyrimidineamine	--	

8.4 Environmental Chemistry and Fate

Based on laboratory results, biotransformation would be the major route of nicosulfuron transformation in the environment. In aerobic soil under laboratory conditions, nicosulfuron was moderately persistent at 25°C and persistent at 5°C. Microbial activity was a significant factor in the transformation of nicosulfuron in aerobic soil. Nicosulfuron was also moderately persistent under anaerobic soil conditions at 25°C, and biotransformation occurred at a slower rate than under aerobic conditions. Nicosulfuron hydrolysis was pH-dependent and was significant under acidic (pH 5), but not neutral (pH 7) or basic (pH 9) conditions. Nicosulfuron was shown to be persistent in aerobic natural water (pH 6.6 - pH 8.7) at 25°C over a one-year period. Phototransformation of nicosulfuron is not expected

to be a major pathway of transformation on soil and is not expected to be significant in water. Nicosulfuron was biotransformed rapidly in anaerobic pond sediment/water.

IN-V9367 (pyridine sulfonamide derivative) and IN-J290 (pyrimidine amine) were the major transformation products of nicosulfuron identified in the soil biotransformation studies. In aerobic soil at 25°C, their concentrations increased steadily to very high levels [> 80% of the initial radiolabel] over the 240-d study period. At 5°C, their concentrations increased and then remained stable at lower levels [12 - 25% of the initial radiolabel]. Under anaerobic soil conditions, the major transformation products were also IN-V9367 and IN-J290 and their concentrations increased with time over the 90-d study period. It was evident from the anaerobic aquatic data that the major transformation product, IN-H9325, would be classified as moderately persistent under anaerobic aquatic conditions, whereas the persistence of the other major transformation products, IN-37740 and IN-W9807, could not be determined. These results raise concerns regarding the potential for persistence of nicosulfuron residues in soil and sediments.

Nicosulfuron is highly soluble in water. Although the vapour pressure was determined by an inappropriate method, the potential for nicosulfuron volatilization from moist soil and water surfaces is expected to be low. Nicosulfuron is a weak acid and would be an anion at pH > 4.3. Adsorption of nicosulfuron was low to moderate in four types of soil, was not strongly correlated with the soil organic-matter content and indicated that the potential mobility of nicosulfuron in soil would be "high" to "very high". Soil thin layer chromatography (TLC) indicated that the mobility of nicosulfuron in soil would be "intermediate". The mobility of the transformation product, IN-V9367, was greater than that of the parent material, whereas the mobility of IN-J290 was less. IN-V9367 was "mobile" in all soils studied, while the mobility of IN-J290 ranged from "immobile" in medium-textured soil to "low" in coarse-textured soil. The persistence and mobility of nicosulfuron and its major transformation products, particularly IN-V9367, raised concerns regarding the potential for residues to leach through soil.

Dissipation data collected after application of Ultim® 25 WP to *coarse-textured* soil at three eastern Canadian sweet and field corn sites indicated that nicosulfuron was nonpersistent in soil under field conditions. At each field site, nicosulfuron was recovered mainly from the 0 - 10 cm depth of soil. There was some evidence of movement of *minor* amounts of the transformation product, IN-V9367, into soil at the 20 - 30 cm depth. The Canadian field data alleviated concerns (based on laboratory data) regarding the persistence and mobility of nicosulfuron and its *primary* transformation product, IN-V9367, as well as the potential for groundwater contamination.

As the soil samples were not analyzed for IN-J290, the common major transformation product of rimsulfuron and nicosulfuron, concerns regarding the persistence of this compound could not be addressed by the Canadian soil field data. Based on laboratory data, however, potential mobility of this compound in soil is not a concern.

American field data developed following application of ^{14}C-labelled nicosulfuron to silt loam soil in Delaware confirmed the persistence and relative immobility of the major transformation product, IN-J290, but also indicated that the concentrations of this compound persisting in soil under field conditions would be very low.

8.5 Environmental Toxicology

Bioaccumulation/bioconcentration of nicosulfuron is not expected, based on its low octanol/water partition coefficient.

Wild birds

Nicosulfuron was practically nontoxic when administered either orally to Bobwhite Quail (*Colinus virginianus*) or in the diet to Bobwhite Quail and Mallard Duck (*Anas platyrhynchos*). An acute risk to birds from the ingestion of contaminated material is not expected. Based on a worst-case exposure scenario and the lowest NOEL from the avian toxicity studies, the risk factor is well below the level of concern. The effects of nicosulfuron on avian reproduction and the risk to birds from long-term exposure to its transformation products are unknown.

Wild mammals

Based on mammalian toxicology and metabolism studies and on the proposed use patterns, application of nicosulfuron at the rate recommended on the Ultim® 25 DF label is not expected to present a direct hazard to wild mammals.

Amphibians and Reptiles

No data were available for review.

Fish

Nicosulfuron was practically nontoxic to bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (*Oncorhynchus mykiss*). Comparison of toxicity data with the worst-case expected environmental concentration (EEC) in water (13.3 ：g nicosulfuron/L) indicated that direct toxic effects to fish would not be expected from exposure to nicosulfuron applied at the label-recommended rate.

Aquatic Invertebrates

Nicosulfuron and the major transformation products, IN-V9367 and IN-J290, were practically nontoxic to the water flea, *Daphnia magna*.

Comparison of toxicity data with the worst-case EEC in water indicated, however, that direct toxic effects to aquatic invertebrates would not be expected from exposure to nicosulfuron applied at the label-recommended rate.

Terrestrial Invertebrates

Nicosulfuron was practically nontoxic to the honeybee (*Apis mellifera*) on oral and contact bases, and to the earthworm (*Eisenia foetida*). A mixture of five major (nicosulfuron and rimsulfuron) transformation products, IN-V9367, IN-J290, IN-E9260, IN-70941 and IN-70942, had no effect on earthworms. Therefore, application of nicosulfuron at the label-recommended rate is not expected to pose a hazard to these nontarget organisms.

Soil Microbial Systems

The treatment of soils with nicosulfuron had no effect on microbial respiration (i.e., CO_2 evolution), but slightly stimulated nitrification. Application of nicosulfuron at the label-recommended rate is not expected to significantly affect soil microbial processes.

Algae

Investigations of the acute toxicity of nicosulfuron to the growth of the algae, *Selenastrum capricornutum* or *Anabaena flos-aquae*, demonstrated no significant effects on cell growth, biomass, cell counts and cell morphology. Comparison of toxicity data with the worst-case EEC in water indicated that toxic effects to these algae would not be expected from exposure to nicosulfuron applied at the label-recommended rate.

In contrast, nicosulfuron is toxic to the growth of the diatom, *Navicula pelliculosa*. Statistically significant inhibitory effects were observed in the growth rate and cell counts of *N. pelliculosa* exposed to nicosulfuron over a 120-h period. Comparison of toxicity data with the worst-case EEC indicated that an adverse effect on diatom populations in freshwater could occur from exposure to nicosulfuron applied at the label-recommended rate.

Nontarget Aquatic Vascular Plants

Nicosulfuron is highly toxic to the growth of duckweed, *Lemna gibba*. When this aquatic macrophyte was exposed to nicosulfuron for a 14-d period, there were statistically significant reductions in frond density, growth rates and biomass. Comparison of toxicity data with the EEC indicated that substantial negative impacts on populations of *L. gibba* in freshwater could occur from exposure to nicosulfuron applied at the label-recommended rate, or even at 10% of this rate.

Nontarget Terrestrial Vascular Plants

Field data on the effects of Ultim® 25 DF application on eight species of terrestrial vascular plants indicated the following: Fall Panicum, Barnyard Grass and Green Foxtail would be adversely affected with no recovery, if situated at distances # 10 m from the edge of the treated field; Redroot Pigweed and Quackgrass would be slightly affected with some recovery occurring with time, if situated at distances # 5 m from the edge of the treated field; and Lady's Thumb, Common Ragweed and Lamb's Quarters (*Chenopodium album* L.) would not be affected, if situated at distances $ 5 m from the edge of the treated field.

Field data on the growth of nontarget Timothy (*Phleum pratense*) and Goldenrod (*Solidago canadensis*) after ground spray application of Ultim®
25 DF indicated that no serious effects should be expected, if these species are situated at distances $ 5 m from the edge of the treated field.

From screening data developed under greenhouse conditions, it was concluded that direct overspray of nicosulfuron would pose an unacceptable risk to most of the indicator plant species (from several families) tested, especially when applied postemergence. Consideration of exposure of nontarget plants only via drift of ground spray, however, reduced the risk to most species to an acceptable level.

Comparison of greenhouse and field data indicated that, in most cases, plants demonstrated slightly more sensitivity in the field than in the greenhouse.

Wildlife Habitat Considerations

In aquatic environments, an adverse impact of nicosulfuron on diatoms (e.g., *N. pelliculosa*) could disrupt the food chain in freshwater aquatic ecosystems. Furthermore, a negative impact on duckweed (*L. gibba*) could affect aquatic invertebrate populations and the waterfowl that feed on these organisms. Duckweed is an important source of plant material in the diet of ducklings such as the Gadwall (*Anas strepera)* and the American Widgeon (*Mareca americana*).

In terrestrial environments, exposure of nontarget plants through direct overspray or spray drift could adversely affect wildlife habitat.

These potential environmental impacts should be mitigated by the inclusion of the following statements on the Ultim® 25 DF label:

> "DO NOT APPLY BY AIR" and
>
> "Overspray or drift to important wildlife habitats, such as ponds, wetlands, streams, woodlots and shelterbelts, should be avoided. Leave a 10-metre buffer zone between the last spray swath and bodies of water or wetlands. Leave a 5-metre buffer zone between the last spray swath and the terrestrial habitats listed above."