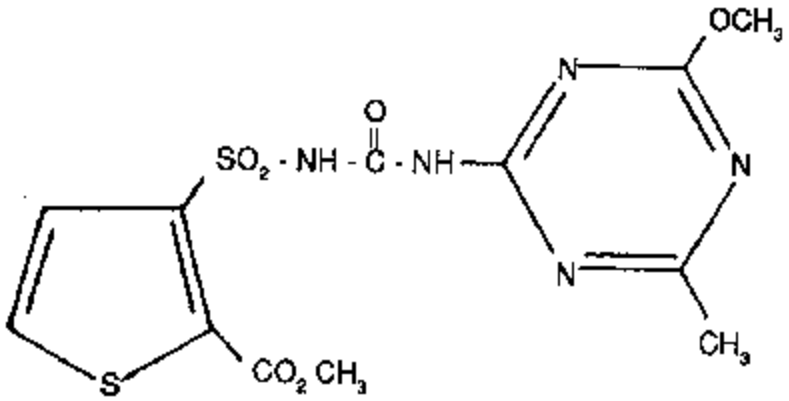
Agriculture Canada

Food Production and Inspection Branch
Direction générale, Production et inspection des aliments

Plant Industry Directorate
Direction de l'industrie des produits végétaux

Decision Document E90-01

REFINE - THIFENSULFURON



Herbicide

PRODUCT MANAGEMENT DIVISION AUGUST 1, 1990

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FOREWORD

THIFENSULFURON

As part of the ongoing efforts to provide a summary of the data received and to outline the regulatory action on the active ingredient thifensulfuron, a Decision Document has been prepared. This document reflects input from specialists within Agriculture Canada and from key departmental advisors. Based on the review of all available information and in consideration of the agronomic benefit to Canadian farmers, a regulatory decision has been made to grant registration for thifensulfuron and the end-use product Refine.

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1. SUMMARY

The purpose of this document is to provide a summary of the data reviewed and to outline the regulatory action on the active ingredient thifensulfuron.

Agriculture Canada, with the assistance of advisors from Environment Canada, Health and Welfare Canada, and the Department of Fisheries and Oceans has completed a review of the available data supporting thifensulfuron. The need for additional data to evaluate the toxicity to aquatic vascular plants has been identified. To mitigate potential risk, a 15-m buffer zone around bodies of water and wetland areas has been included on the label. The need for a buffer zone will be reconsidered once these data have been evaluated.

With regard to occupational hazard and safety, it is considered that an adequate margin of safety (MOS) exists for label uses with the dry flowable formulation.

With respect to environmental impact, the compound thifensulfuron has low toxicity to wildlife and soil microorganisms. Direct and indirect effects on wildlife should not occur. Acute toxicity studies using fish and aquatic invertebrates indicate that the compound is unlikely to produce toxic effects in aquatic biota. The proposed use pattern for the Refine formulation of thifensulfuron is unlikely to result in the accumulation of residues of the parent compound or its transformation products in fish. Algistatic testing indicated low toxicity to the single algal test species which was used as an indicator species to represent aquatic flora. Data indicate the likelihood of a high MOS for aquatic biota and minimal risk to fishery resources.

Data indicates that this compound has little potential for bioaccumulation. The environmental studies reviewed suggest that if the product is applied according to label directions, the levels of thifensulfuron found in the environment should not result in an adverse environmental impact. The routes for dissipation are hydrolysis, photolysis and microbial transformation.

Thifensulfuron is an effective herbicide for the control of various broadleaf weeds in spring, winter and durum wheat, barley and oats. The product has the advantage over other sulfonylurea herbicides already registered in that it has less carryover and residual to follow-up crops.

Based on a review of all available information and in consideration of the economic benefits to cereal management, this herbicide has been granted full registration status until December 31, 1990.

2. PESTICIDE NAME AND PROPERTIES

2.1 Pesticide Name

Common Name: thifensulfuron methyl
Chemical Name: Methyl 3-[[[[(4-methoxy-6-methyl-1,3,5-triasin-2-yl) amino]carbonyl]amino]-sulfonyl]-2-thiophenecarboxylate
Trade Name: Refine
CAS Registration No.: 79277-27-3

2.2 Physical and Chemical Properties

2.2.1 Technical Products

Empirical Formula: C12H13N5O6S2
Molecular Weight: 387.4
Melting Point: 186 C
Vapour Pressure: 1.3x10-10 mm Hg at 25 C
Ionization Constant: (pKa) = 4.0
Octanol/Water Partition Coefficient (Kow):
3.3 at pH 5
0.027 at pH 7

Water Solubility:
Water solubility at controlled pH at 25 C

pH	Solubility of thifensulfuron(mg/L)
4.0	24
5.0	260
6.0	2400

Solvent Solubility:
Solubility in various organic solvents at 25 C

	mg/mL
Acetone	11.9
Acetonitrile	7.3
Ethanol	0.9
Ethyl acetate	2.6
Hexane	0.1
Methanol	2.6
Methylene Chloride	27.5
Xylenes	0.2

Thermal Stability: decomposes on melting (186 C)

Hydrolysis Rate: half-life 4-6 days @ ph 5

2.2.2 Formulated Product

Product Name: Refine
Guarantee: 75%
Flammability: Nonflammable
Storage Stability: Stable at room temperature

3. DEVELOPMENT AND USE HISTORY

Thifensulfuron is manufactured by I.E. Dupont de Nemours & Company. The Canadian development program was conducted by Dupont Canada Inc., the registrant for both the thifensulfuron, the technical and Refine, the end-use product.

The Canadian field testing program with thifensulfuron was initiated in 1984 and the original submission for registration was received in 1985.

Thifensulfuron is currently registered for use in many countries including the United States, the United Kingdom, France and Argentina.

4. REGULATORY POSITION AND RATIONALE

Thifensulfuron is one in a series of sulfonylureas whose herbicidal properties were first reported in 1966. These herbicides are inhibitors of plant growth and control a wide spectrum of broadleaf weeds. In comparison to other sulfonylureas, thifensulfuron provides for more crop rotation, with less residue carryover and residual, combined with a low application rate of 20g/ha (15g ai/ha).

Thifensulfuron has low acute, oral, dermal and inhalation toxicities in rats and/or rabbits. Studies indicate that thifensulfuron is not mutagenic or teratogenic and exhibits low toxicity to fish, wildflife and honeybees. Subchronic feeding and reproduction studies as well as chronic feeding studies in rats, mice, and dogs are also favourable. The data indicate that when thifensulfuron is used in barley, oats and wheat, in accordance with the label direction, residues are not considered to pose a hazard to consumers. Agriculture Canada has concluded that ground application of the end-use product, Refine, if used according to label directions, will not pose an unacceptable risk to the user or to the environment.

5. BIOLOGICAL PROPERTIES

Thifensulfuron is taken up by both plant leaves and roots. Once inside the plant it is translocated throughout the plant. Plant death usually occurs within a week or more following treatment. Crop tolerance is due to the rapid inactivation or detoxication of thifensulfuron by the crop.

6. USE SUMMARY AND BENEFITS

6.1 Cereal Use

Thifensulfuron herbicide has been field-tested extensively in Canada over the past five years, alone and in combination with other herbicides. Thifensulfuron, as a 75% Dry Flowable formulation, provides effective control of many broadleaf weeds in spring, winter and durum wheat, barley and oats not underseeded to legumes or grasses. The product is applied early post-emergence to the main flush of actively growing weeds. Warm, moist, growing conditions which promote weed growth enhance herbicidal activity by allowing maximum uptake. The end-use product Refine 75DF is only to be applied using ground application equipment. The use of a surfactant is recommended when applying the end-use product alone or in combination with other herbicides. The product is applied in the spring when the crop is in the two-leaf stage to flag-leaf stage.

6.2 Weeds Controlled or Suppressed:

Controlled:

Chickweed	Lady's thumb	Stinkweed
Corn Spurry	Lamb's-quarters	Volunteer rapeseed
Cow cockle	Redroot pigweed	Wild buckwheat
Green smartweed	Russian thistle	Wild mustard
Hemp nettle		

Suppressed:

Kochia

Refine may be tank-mixed with MCPA Amine 500 to control the above weeds and to control ragweed and suppress Canada thistle. In addition, Refine can be tank-mixed with Hoe-Grass for control of wild oats.

6.3 Time and Rate of Application

Refine is applied in the spring when the crop is in the two-leaf to flag-leaf stage, at the rate of 20\g/ha. For best results, applications of Refine should be made when weeds are actively growing and before the crop canopy closes. Weeds should be less than 10 cm tall or across. Weeds that emerge after treatment will not be controlled.

7. TOXICOLOGY AND OCCUPATIONAL EXPOSURE: HEALTH AND WELFARE CANADA INPUT

The technical material to be manufactured has a purity of 94-100%. All major impurities have been identified and are related to the active material. The major toxicity studies used technical material with a purity of 95.6-98.0%.

7.1 Toxicological Evaluation

Toxicology data submitted in support of the safety of this herbicide include the following:

a) Technical thifensulfuron has an oral LD50 value in rats in excess of 5000 mg/kg and a dermal LD50 value in rabbits in excess of 2000 mg/kg. It has an inhalation LC50 value in rats exceeding 7.9\mg/L (gravimetrically determined). It is minimally irritating to the rabbit eye and causes slight irritation to rabbit skin. The technical material is not a skin sensitizer when tested in guinea pigs.

b) Refine DF, a formulation with a guarantee of 75% thifensulfuron, has an oral LD50 value in rabbits in excess of 2000 mg/kg. Due to the low proportion of respirable particles in the DF formulation, it is not judged to pose an acute inhalation hazard. The DF product is not a skin irritant in rabbit but is minimally irritating to the rabbit eye. It did not elicit a skin sensitization reaction when tested in guinea pigs.

c) A 90-day rat feeding study with 10\rats/sex/dose level at 0, 100, 2500 and 7500 ppm resulted in a No\Observable Effect Level (NOEL) of 100 ppm (5\mg/kg\bw) based on treatment related decreases in body weight gains at the two highest dose levels of 2500 ppm (125 mg/kg bw/day) and 7500 ppm (375\mg/kg bw/day).

d) A 90-day dog feeding study with four\dogs/sex/dose level at 0, 75, 1500 and 7500 ppm resulted in a NOEL of 1500 ppm (37.5 mg/kg bw/day) based on decreased body weight gain in males at the next highest dose of 7500 ppm (187\mg/kg bw/day).
A 1-year dog feeding study with five\dogs/sex/dose level at 0, 50, 750 and 7500 ppm resulted in a NOEL of 750 ppm (18.7 mg/kg bw/day) based on decreased body weight gain in females and increased liver/body weight in males at the next highest dose of 7500 ppm (187 mg/kg bw/day).

e) A 2-year rat chronic toxicity/oncogenicity study with 72 rats/sex/dose level at 0, 25, 500 and 2500\ppm resulted in a NOEL of 25 ppm (1.25\mg/kg\bw/day) based on a decrease in body weight gain (males) and a decrease in serum Na+ concentrations (males and females) at 500 ppm (25\mg/kg bw/day) and decreased body weights and decreased Na+ concentrations at 2500 ppm (125\mg/kg bw/day) in both males and females. There were incidences of 21, 11, 29 and 32% of mammary adenocarcinomas in females in the 0, 25, 500 and 2500 ppm dose groups, respectively. The increases were not statistically significant. Furthermore, review of the in-house historical control data revealed that this is a common tumour. The mean incidence for 11 studies was 12.7% (range 1.5-23.4%). The incidence in the concurrent controls (21%) was considerably higher than the mean, suggesting that in this particular cancer study the overall incidence of mammary adenocarcinoma was in general higher. There were no treatment-related increases in the incidence of non-neoplastic or preneoplastic lesions of the mammary gland. There were no mammary tumours in any animals sacrificed at 12 months nor was there any indication of a decrease in latency period. Mean time to tumour (estimated by mean time of death of animals with this tumour) was 692, 669 and 655 days and the minimum time on test in any animal with mammary adenocarcinoma was 435, 501 and 379\days in the 0, 500 and 2500 ppm dose groups. Therefore, it is concluded that the slightly increased incidence in mammary adenocarcinoma in the two highest dose groups is spurious and unrelated to treatment. Therefore, thifensulfuron is not considered oncogenic or carcinogenic in the rat.

f) An 18-month oncogenicity study with 80\mice/sex/dose at 0, 25, 750 and 7500 ppm demonstrated a NOEL of 25 ppm (3.57 mg/kg bw/day). There was a slight decrease in body weight in females at the 750 ppm (107 mg/kg bw/day) and in both sexes at the highest dose level of 7500 ppm (1070 mg/kg bw/day). There was an increased incidence of benign liver cell tumors in male mice (9/80, 9/80, 12/80, 16/80 at 0, 25, 750, 7500 ppm, respectively) which exceeded historical control values. The incidence of hepatocellular carcinoma was comparable for all male groups, (4/80, 4/80, 2/80, 3/80 for control and treatment groups, respectively). When analysed, both separately and

combined, the incidences of both tumor types are not significantly different from controls (Chi-Square and Fischer's Exact, $P<0.05$). No increases in these tumors were observed in females. In view of the (1) common occurrence of these tumors in control mice, (2) lack of statistical significance, (3) lack of evidence suggesting a progression to malignancy, Health Protection Branch (HPB) does not feel that the increase in benign liver tumors is biologically significant and hence thifensulfuron is considered not oncogenic or carcinogenic in the mouse.

g) A complete battery of mutagenicity tests has been conducted and found to be negative. The tests were:

   i) point mutation in bacterial (Ames) and mammalian systems (CAO/HG-PRT/CHO cells)
   ii) DNA repair: UDS in rat hepatocytes
   iii) chromosomal aberrations in vivo mouse micronucleus test and in vivo rat bone marrow assay.

h) Pharmacokinetic and metabolism studies in rats demonstrated that thifensulfuron is rapidly excreted in the urine and feces. As the majority is excreted in the urine, one may conclude that it is absorbed, following oral dosing. Ninety-six hours after dosing, less than 1% is present in the tissues and 70-75% of the excreted radioactivity is the parent material. Several minor metabolites have been identified and a metabolic pathway was proposed.

i) A rabbit teratology study with 20 inseminated rabbits/dose level at 0, 30, 200 and 650 mg/kg bw demonstrated a NOEL of 200 mg/kg bw/day (actual level by analysis was 157.8 mg/kg bw) based on reduced maternal body weight gains at 650\mg/kg\bw. There was no indication of any teratological effects.

A rat teratology study with 25 mated female rats/dose level at 0, 30, 200 and 800 mg/kg bw demonstrated a NOEL of 30 mg/kg bw/day (26.3 by analysis) based on decreased body weight in the dams and a decrease in the incidence of the number of male pups/litter observed at the next two higher doses of 200 and 800 mg/kg bw/day. Fetal body weights were decreased at 800 mg/kg bw/day. One fetus at 200 mg/kg bw/day and two fetuses at

800\mg/kg bw/day exhibited microphthalmia; however, the incidence was within the range of historical control values. Abnormalities of the renal papillae (absent or small) occurred with a combined incidence of 1/1, 1/1, 1/1, 9/9 (fetuses/litters) for control and treatment groups, respectively. The incidence at 800 mg/kg bw/day is slightly higher than historical control values. In view of the occurrence of these renal findings at a level which was also associated with maternal and fetal toxicity, HPB considers the data to be indicative of a fetotoxic rather than a teratogenic effect. The increased kidney weights in weanlings recorded in the rat reproduction study are supportive of the sensitivity of the kidney in young animals.

j) A two-generation, four-litter reproduction study conducted with 20 rats/sex/dose level at 0, 25, 500 and 2500 ppm showed a No Observable Adverse Effect Level (NOAEL) of 500 ppm (25 mg/kg bw); decreased body weight of dams and increased kidney weights of weanlings occurred at the 2500 ppm dose level (125\mg/kg bw).

7.2 Food Exposure

Plant metabolism studies indicate rapid absorption and degradation in cereal plants, with total radioactivity less than 0.005 ppm in grain. Even at four times the recommended application rates, levels of radioactivity in treated plants were so low that no attempt was made to identify the radioactivity. Extensive residue studies show that, when applied during early growth stages at recommended application rates (two-leaf stage but before flag-leaf or shot-blade stage), no residues of parent compound are detected above the sensitivity of the analytical method (0.02 ppm) in wheat, oats and barley grain at harvest. No residues are detected in cereal straw (<0.05 ppm). A residue decline study indicates that even at 4 times the maximum proposed rate, residues in green cereal foliage will be very low (<0.1 ppm) 7 days after application.

HPB estimates that the maximum total theoretical daily intake (TDI) of residues from wheat, barley and oats, assuming residues at 0.1 ppm at all times, would not exceed 0.0004 mg/kg/day. HPB has estimated the acceptable daily intake (ADI) to be 0.01\mg/kg bw/day based on the lowest NOEL of 1.25\mg/kg bw/day in the rat chronic/oncogenicity study and using a 100-fold safety factor. Therefore, the TDI is well below the

estimated ADI of 0.01\mg/kg/day. Furthermore, it is expected that residues would be below the limit of detection, namely 0.02 ppm and thus intake should not exceed 0.00007\mg/kg/day.

7.3 Occupational Exposure

An exposure study on thifensulfuron was not submitted. However, HPB had agreed to utilize the exposure study submitted by the registrant for a similar product, DPX-W4189 (Glean or chlorsulfuron), unless problems were identified as a result of their review of the toxicology data or circumstances regarding the use of the new product changed. The HPB agreed to use the surrogate exposure data because the two products are structurally similar, they are both dry flowables, similar crops are treated and similar application equipment is used. The study was also conducted at twice the application rate recommended on the label for thifensulfuron.

In the exposure study, three farmers mixed and applied DPX-W4189 (Glean) by ground rig to 16 ha each. Two farmers used open cab tractors and one used a closed cab. The operations were between one and two hours in duration. Applicators wore coveralls, boots and two wore hats. Both dermal deposition and inhalation exposure were monitored. The dermal deposition ranged from 0.004 to 0.005 mg/kg-bw/lb ai. The inhalation exposure was negligible, all samples were less than the limit of detection. To estimate exposure to a 70\kg farmer wearing long pants, short sleeves, boots and no gloves, and treating 80 ha (200 acres) at the maximum application rate (0.020 lb ai/acre) for thifensulfuron (Refine) the dermal deposition estimate from the Glean study was used. This resulted in an estimate of dermal deposition of 0.019\mg/kg-bw/day for workers using Refine. Since a dermal penetration study was not submitted, HPB has assumed 100% absorption. These figures must be viewed with some caution since they are based on only three workers who were monitored for 1 to 2 hours each during mixing/loading and application. Exposure during cleanup and repair was not considered. Furthermore only one inside chest patch was used to estimate exposure to all covered areas of the body and no field recovery studies were conducted. It should also be noted that exposure to all body regions other than hands and forearms was less than the limit of detection.

The most prominent toxicological effect was a reduction in body weight with the lowest NOEL being 1.25 mg/kg/day in the rat chronic/oncogenicity study. The estimated exposure for workers using Refine is 0.019 mg/kg/day based on dermal deposition in the Glean worker exposure study. Although some caution should be exercised in viewing this figure because of the study limitations noted previously, a conservative assumption of 100% absorption has been made in the absence of dermal absorption data for Refine. Based on the dermal deposition value and the NOEL of 1.25\mg/kg-bw/day, there is a MOS of approximately 60 for workers exposed to Refine. In view of the toxicological end-point and the assumption of 100% absorption, HPB considers the MOS to be adequate for occupational exposure.

8. ENVIRONMENTAL ASPECTS:
ENVIRONMENT CANADA INPUT

8.1 Overall Summary

When used according to label instructions, Refine is unlikely to be acutely or chronically toxic to non-target organisms. The toxicity of the parent compound and the transformation products to aquatic and terrestrial invertebrates was judged to be very low. Direct and indirect impacts, through food removal, on wildlife should not occur.

Regarding the impact of Refine on vegetation, the algal growth inhibition study indicates that the use of Refine should not lead to an impact on fresh water algae even under a worst-case scenario. However, the impact of Refine on vascular plants remains to be addressed. Therefore, because of concerns regarding the likelihood of entry of the compound into bodies of water and the lack of data on its toxicity to aquatic vascular plants, a 15-m buffer zone is recommended around bodies of water and wetland areas until further data are provided.

8.2 Environmental Chemistry and Fate

i) Summary

The parent compound has a short persistence in soil and although the results of laboratory studies suggest a potential for leaching, its fast transformation under field conditions mitigate the risks associated with groundwater contamination. Because of the high water solubility of

thifensulfuron, there is no risk with bioaccumulation. Under both aerobic and anaerobic conditions, thifensulfuron is rapidly transformed into several transformation products. The data submitted by the applicant indicate that the toxicity of these transformation products to non-target organisms from both terrestrial and aquatic ecosystems is minimal.

ii) Mobility

Thifensulfuron has a very low vapour pressure, which minimizes potential for volatilization under field conditions. Both laboratory studies on mobility, i.e., adsorption-desorption and leaching studies, indicate that thifensulfuron may leach in soils. The mobility of thifensulfuron was inversely correlated with the organic matter content of the soils. However, the potential for groundwater contamination was not confirmed by the results of field studies. Most of the radioactivity did not leach to more than 12 to 23 cm (5 to 9 inches). Biotransformation is responsible for this situation.

iii) Persistence

Thifensulfuron is stable to hydrolysis at pH's 7 and 9. At pH 5, the DT50 was approximately 5 days. Photolysis, either in aqueous solutions or on soil, does not constitute a significant route of transformation.

Under laboratory conditions, biotransformation studies in soils and aquatic systems (natural water and sediment) indicate that microbial degradation, under both aerobic and anaerobic conditions, is the major route of dissipation of thifensulfuron in the environment. The following half-lives were reported: 2-6 days in non-sterile soils, 24-32 days in sterile soils; in aquatic systems under anaerobic conditions 2.5 weeks and 2.5 months in non-sterile and sterile aqueous solutions, respectively.

Results from field studies conducted under Canadian and American conditions do not indicate any potential for groundwater contamination. The reported half-lives for the parent compound were between 5.8 and 16.5 days.

8.3 Environmental Toxicology

i) Summary

When used according to label instructions, Refine is unlikely to be acutely or chronically toxic to birds or mammals as well as terrestrial and aquatic invertebrates. It should be mentioned, however, that some of the transformation products of environmental breakdown have not been identified as mammalian metabolites and are thus of unknown mammalian toxicity.

No data were available to adequately evaluate the risk to amphibians and reptiles. The toxicity to aquatic and terrestrial invertebrates was judged to be very low, thus impacts on wildlife due to food removal should not occur. Regarding the impact on algae, the algal growth inhibition study indicates that the use of Refine should not lead to an impact on freshwater algae even under a worst-case scenario.

The high water solubility of the compound, its hydrolytic stability at a pH of 7 or above and its potential for leaching in soil suggest there is a potential for exposure of aquatic vascular plants in water bodies and wetlands adjacent to treated fields following runoff events. In addition, the high herbicidal activity of Refine, the lack of data on the effects of sulfonylurea herbicides on aquatic vascular plants and the potential for off-target drift during application underline this concern.

To mitigate potential risk to aquatic plants the label has been amended to include a 15-m buffer zone around bodies of water and wetland areas until data are provided and evaluated on the toxicity of Refine to aquatic vascular plants. The need for a buffer zone will be reconsidered once these data have been evaluated.

ii) Estimated Environmental Exposure

Estimating the risk posed by a pesticide to wildlife involves examining laboratory-derived toxicity data in light of exposure scenarios. The latter are developed from information on the use pattern of the compound and its intended effects, and on the biology of species of concern and their habitat. With regard to the herbicide Refine two

potential routes of impact on wildlife are identified: 1) a direct toxic effect, either acute or chronic, via consumption of contaminated food, and 2) an indirect effect through an impact on wildlife habitat by way of the elimination of food sources or vegetative habitat.

iii) Estimated Environmental Concentrations

In this review, environmental concentrations are estimated using the limited data available and simple worst-case scenarios where it is assumed that habitats of concern are directly oversprayed.

Maximum plant residues immediately following application of 15 g ai/ha are estimated to be 4.5\mg ai/kg (dry weight). Assuming that surface residues on small insects would be of the same order of magnitude as those on plants of similar surface mass ratios, maximum arthropod residues of 3.1\mg ai/kg (dry weight) are expected for an application rate of 15 g ai/ha.

Thifensulfuron is not lipophilic (Kow 0.027) and thus bioconcentration in prey such as soil invertebrates is unlikely. Maximum soil residues immediately following application of 15 g ai/ha are predicted to be 0.008\mg ai/kg (dry weight), assuming a soil bulk density of 1.2 g/cm3 (dry weight) and a sampling depth of 15 cm.

The worst-case estimated environmental concentration (EEC) that could result from direct overspray of a water column 0.5 m deep, at 15\g\ai/ha is 0.003 mg ai/L (assuming uniform mixing).

8.4 Toxicity to Wild Birds

The acute oral toxicity of thifensulfuron has been studied in the mallard duck. The acute dietary toxicity has been studied in the mallard duck and the bobwhite quail. Based on these data, the acute LD50 of the technical product in mallard ducks is greater than 2510 mg ai/kg-bw and the acute NOEL is 1000\mg\ai/kg-bw. The only statistically significant sublethal effect reported was reduced bodyweight gain at doses of 1590 mg ai/kg bw and above.

In the dietary studies, the NOEL and LC50 were greater that 5620 mg ai/kg diet in both the mallard duck and bobwhite quail.

No data were available on the metabolism or pharmacokinetics of thifensulfuron in avian species. No avian reproduction studies were submitted.

Risk estimates (i.e., ratio of expected exposure level to level causing toxic effect) for a bobwhite quail consuming 8.9% of its bodyweight daily in vegetation and for a Carolina wren ingesting 34% of its body weight in insects per day were calculated. The estimates are in the order of 10-4 and indicate that thifensulfuron is unlikely to pose a direct hazard to birds when used as proposed. The risk posed by environmental transformation products is unknown.

8.5 Toxicity to Wild Mammals

The results of metabolism studies in the rat indicate that the compound is excreted mostly unchanged (70 to 94%) and mainly in the urine. At low doses, 71 to 92% is excreted in the urine while more than 94% is excreted in the urine at higher doses. At the high dose, there is sex variation in the urinary/fecal excretion ratio.

High dose excretion was delayed relative to excretion of the low dose. All tissue levels were low at 96\hours post-dose (<0.1 ug/g for the low dose and <15\ug/g for the high dose). There was no indication of significant selective retention of thifensulfuron or metabolites. Each of these metabolites constituted <3% of the administered dose.

The LD50 of the technical product in male and female rats is >5000 mg ai/kg bw. Sublethal effects at this dose included crusts on genitalia, diarrhea, stained perineum and very slight, sporadic weight loss. In rabbits, the dermal LD50 of the technical product was >2000 mg ai/kg bw.

In a two-week (10-dose) short-term rat study with the technical product, the LD50 and the NOEL were >2200\mg ai/kg bw/day.

Reproduction and developmental studies on rats and rabbits with the technical product indicated no reproductive effects of significant concern. In the rat study, the incidence of small renal papilla was increased at 800 mg ai/kg bw/day but maternal toxicity was also evident at this dose.

The acute oral LD50 of the formulated product, Refine (75% ai), in rats was >3750 mg ai/kg bw.

Sublethal effects included wet or stained perineum and slight sporadic weight loss in the females and diarrhea in both sexes.

The acute dermal LD50 of Refine was >1500\mg\ai/kg\bw, tested on abraded skin in rabbits. Dermal erythema was observed which cleared in seven days.

It is of some concern that acute toxicological testing has focused on only one species, the rat. A dermal test was conducted on rabbits but dermal absorption was not determined and may be low for a compound with such a low Kow. Based on the report summaries for 90-day studies on rats, mice and dogs, as well as maternal toxicity data in developmental studies with rats and rabbits, the rat appears to be the most sensitive species tested.

Therefore, based on the available toxicology data on thifensulfuron, the risk factors estimated for a rat feeding on vegetation (5% bw/day) are very low (<\l\x\10-3). The risk posed by environmental degradation products, however, is unknown.

8.6 Toxicity to Amphibians and Reptiles

No data are available to evaluate risk to amphibians and reptiles from the use of thifensulfuron.

8.7 Toxicity to Aquatic Invertebrates

The 48-hour LC50 study conducted on Daphnia magna clearly indicates that the technical compound is not toxic to Daphnia magna. The LC50 as estimated at greater than 1000 mg/L which is at least five orders of magnitude greater than the estimated worst case concentration of 0.003 mg ai/L. The toxicity to Daphnia of transformation products found in aquatic environment has been tested at 100 times the EEC and no mortalities were reported after 48-hour exposure.

8.8 Toxicity to Terrestrial Invertebrates

The data submitted demonstrate the low toxicity of Refine and its transformation products to honeybees. The data presented indicate that the contact LD50 is greater than 12.5 ug/bee.

Concerning earthworms, no mortality is reported after the 14-day exposure period at the concentration of 2000 mg/kg (approximately 200,000 times the expected

environmental concentration). The 14-day exposure time allowed the transformation of the parent product and therefore the results of this test can also be used to demonstrate the low toxicity of the transformation products found under aerobic soil conditions to earthworms.

8.9 Habitat Considerations

i) Aquatic Invertebrates

The differences between expected concentrations in water and the LC50 for D. magna is so large that secondary effects on wildlife due to food deprivation in aquatic habitats are not likely.

ii) Terrestrial Invertebrates

Little impact is expected on terrestrial invertebrates and, consequently, secondary effects on wildlife are unlikely.

8.10 Plants

Algal Growth Inhibition Study: The study provided by the registrant dealt with the toxicity of the technical compound thifensulfuron to the green alga Selenastrum capricornutum. The endpoints reported were:

- *EbC50 (72 hours) = 14.5 mg/L using area under the curve
- *ErC50 (0-24 hours) = 17.0 mg/L using growth rates
- NOEL - 5.0 mg/L

*EbC = reduction of biomass by 50%
*ErC = reduction of growth by 50%

The expected environmental concentration under a worst-case scenario of a direct overspray of a 0.5-m deep pond at maximum recommended rate is 0.003\mg\ai/L. Under these circumstances, the risk factor using the NOEL, is 0.0006. It, therefore, appears that the use of thifensulfuron should not lead to an impact on freshwater algae under normal use conditions.

Other Non-target Plants: No other data were provided to assess the potential impact of Refine on either terrestrial or aquatic non-target plants. This raises concerns about the potential impact of Refine on aquatic plants. The high water solubility of the

compound, its hydrolytic stability at a pH of 7 or above, and its potential for leaching suggest that contamination of water bodies following runoff events is possible. In light of the lack of toxicological data and the added potential of off-target drift, a 15-m buffer zone is recommended around bodies of water and wetland areas to mitigate the risk.

9. EFFECTS ON FISH, FISH HABITAT AND FISHERY RESOURCES: FISHERIES AND OCEANS CANADA INPUT

9.1 Fish

Acute toxicity of thifensulfuron to fish has been demonstrated to be very low with 96-hour LC50 values greater than 100 mg/L for both rainbow trout (Oncorhynchus mykiss) and bluegill sunfish (Lepomis macrochirus) generated under static, unaerated test conditions.

The octanol:water partitioning coefficient (Kow) for thifensulfuron was reported to be 0.027 (pH 7 and 25 C). However, no confirmatory data report was available to the Department of Fisheries and Oceans for review. This value indicates a very low potential for accumulation in biota, which was confirmed by a correspondingly low bioconcentration factor, demonstrated for bluegill sunfish, in which a BCF of _1.0 was reported for all tissues (edible, inedible and whole fish) at all sampling times.

The Department of Fisheries and Oceans has received no data relating to chronic exposure toxicity testing of fish using Refine, its active ingredient thifensulfuron, or any of its transformation products.

9.2 Fish Habitat

Acute toxicity of thifensulfuron to Daphnia magna (a\representative fish food species) has been shown to be extremely low, as demonstrated by a 48-hour LC50 value of greater than 1000 mg/L which was generated under static, unaerated conditions. Major transformation by products have also shown to be not acutely toxic to D.\magna under similar test conditions.

Algistatic testing of thifensulfuron indicated low toxicity to the algal test species Selenastrum capricornutum, with EC50 values of 14.5 and 15.0 mg/L (50% biomass reduction at 72 and 120 hours,

respectively) and of 17.0 mg/L (50% reduction in growth rate over 0 to 24\hours).

The Department of Fisheries and Oceans has received no data relating to toxicity testing conducted on aquatic macrophytes.

9.3 Movement into and Transformation in Aquatic Environments

The mobility of thifensulfuron has been demonstrated to range from intermediate mobility (EPA Class 3) to very mobile (EPA Class 5), based upon the results of a soil thin-layer chromatography study. Thifensulfuron was found to be poorly adsorbed into sandy loam soils and only weakly adsorbed onto silt loam soils. In addition, the chemical was readily desorbed from the silt loam soils but more tightly retained on the sandy loam. Ease of adsorption and desorption appeared to be related to the organic matter content of the soils.

Under field conditions, typical leaching depths were reported to be less than 12.5 cm, with a maximum of 22.5 cm observed with well-aged samples. This indicated limited mobility in the soils investigated.

Water-solubility of thifensulfuron was demonstrated to be strongly pH dependent, increasing rapidly from 24 to 2400 mg/L over a pH range of 4 to 6 (25 C). This high water solubility at environmental pH's, combined with a reportedly low vapour pressure of 1.3\x\10-10 mm Hg (at 25 C), would result in this compound having a low fugacity in water and a limited tendency to dissipate from aquatic systems into the atmosphere.

Hydrolysis of thifensulfuron was shown to be moderately rapid under acidic conditions (half-life of 4-6 days at pH 5), but to be very slow above pH 7 (82-92% remaining after 30 days).

Photolysis in water was relatively constant over a tested pH range of 5 to 9, using sterile, buffered, aqueous solutions of thifensulfuron. A photolytic half-life of 4 to 5 days was reported for thifensulfuron, although discrepancies in the results of the study indicate that the compound may be much more photolytically stable.

As in the hydrolysis and photolysis studies, laboratory aquatic anaerobic studies using thifensulfuron showed increasing concentrations of

polar transformation products over time. Partitioning of parent thifensulfuron into sediments could be rapid (a\correlation with soil percent organic matter was observed, especially in sterile systems). However, the resulting transformation products subsequently moved into the overlying water. Sterile and non-sterile test conditions both yielded qualitatively similar transformation products. However, the rate of formation of these products was 4 to 5 times faster under non-sterile conditions. The DT50 for thifensulfuron determined to be approximately three weeks in non-sterile systems, was about three months in sterile test systems, thereby indicating the importance of anaerobic microbial metabolic activity in the initial step in the transformation process. At the conclusion of the test, the percent recovery of originally applied 14C (applied as 14C-thifensulfuron) remained high in both sterile (95% at day 280 vs 103% at day 0) and non-sterile systems (89% at day 280 vs 105% at day 0), confirming that dissipation through volatilization or C02 formation is unlikely under aquatic anaerobic conditions.

The Department of Fisheries and Oceans has received no data relating to aquatic aerobic studies using thifensulfuron.

9.4 Impact Assessment

Thifensulfuron, the active ingredient in Refine herbicide, represents a new class of compounds known as sulfonylureas. As a group, these chemicals are capable of high levels of selective herbicidal potency at relatively low doses, due primarily to their specific mode of action. This mode of action involves inactivation of acetolactate synthese, an enzyme responsible for the synthesis of certain amino acids which are essential to some plants.

Refine is recommended for ground application only, at a rate of 15 g ai/ha, for the selective post emergence control of broadleaf weeds in wheat, barley and oats. The predicted maximum environmental concentration, resulting from the hypothetical application of Refine (at the label rate) as a direct overspray of a water body of 0.5-m depth, is 3 ug ai/L, thereby indicating the likelihood of a considerable MOS for aquatic biota. The limited potential for movement of Refine into aquatic ecosystems, its low acute toxicity to aquatic organisms and its low potential for concentration through aquatic food chains indicate

that minimal aquatic impact can be expected from the use of this product. These conclusions are based, however, upon data generated only through laboratory studies and soil field trials, and are supported by a predicted maximum environmental concentration which has been estimated from the label application rate of Refine to typical fish habitat. No data from field aquatic studies were available to the Department of Fisheries and Oceans for review, which would provide confirmation of the fate, persistence and effects of Refine in aquatic ecosystems.