Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Decision Document E95-04

Tribenuron methyl

The active ingredient tribenuron methyl and a formulated product EXPRESS® Dry Flowable 75%, for control of broadleaf weed in spring wheat, durum wheat and barley by ground application, were granted full registration in June 94.

This document provides a summary of data reviewed and the rationale for the registration decision concerning tribenuron methyl and EXPRESS® Dry Flowable 75%.

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.

(publié aussi en français)

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1.0 Summary

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

The Pest Management Regulatory Agency has completed a review of the available data supporting tribenuron methyl. The data base was considered sufficient for supporting the registration of the product for use on durum wheat, spring wheat, barley and on summerfallow in western Canada by ground application equipment only.

Acute toxicology studies indicate that technical tribenuron methyl and the end-use product EXPRESS® Dry Flowable 75% are virtually nontoxic via the oral and dermal routes. Acute inhalation testing with technical tribenuron methyl did not suggest a hazard by this route. Given the formulation type, spectrum of particle size, as well as the low acute toxicity for the technical active ingredient, the requirement for acute inhalation testing with EXPRESS® was waived. Technical tribenuron methyl is non-irritating to the eyes and skin and is not considered a skin sensitizer. EXPRESS® is minimally irritating to skin and slightly irritating to eyes. It is considered to be a potential skin sensitizer.

The range of toxicology studies on tribenuron methyl failed to demonstrate any major health hazard. The short-term toxicity studies were deemed to be the most relevant for occupational risk assessment due to the single application and short use season for this product. To this end, the No Observed Adverse Effect Level (NOAEL) of 5.3 mg/kg bw/day from the 90-day rat study was selected.

Based on the occupational exposure estimate of 0.003 mg/kg bw/day and the NOAEL of 5.3 mg/kg bw/day, there is a margin of safety of approximately 1700 for workers exposed to EXPRESS®, which the Agency considers adequate.

Crop residue studies indicated that wheat and barley treated at 7.5 g ai/ha/year and pre-harvest interval (PHI) of 30 days contained less than 0.02 ppm parent tribenuron methyl residues (grain, mature straw, and immature plants). The estimated Theoretical Daily Intake (TDI) would be 11.2% of the acceptable daily intake (ADI).

Review of environmental chemistry and fate data indicates that tribenuron methyl is non-persistent and is not likely to volatilize or leach under Canadian field conditions. Review of environmental toxicology data shows that this product should not present a hazard to honeybees, earthworms and soil microbial processes, and is unlikely to pose a significant direct acute risk to birds. Tribenuron methyl is not expected to pose a hazard to fish and aquatic invertebrates, such as *Daphnia magna*, which serve as

food for fish. Data submitted in response to concerns regarding the toxicity of a persistent transformation product, triazine amine, indicate that this compound should not be hazardous to fish and *Daphnia magna* at concentrations likely to occur in the environment. Toxicity of tribenuron methyl to the green algal species, *Selenastrum capricornutum*, was low. However, many terrestrial and aquatic broadleaf plantspecies are susceptible. The label restriction of no aerial application and a 15-metre buffer zone should mitigate the risk of spray drift to non-target plant species.

The end-use product EXPRESS® has been developed primarily for the brown soil zone of Saskatchewan and Alberta where the major weed species adapted to hot, dry summers are kochia and Russian thistle. EXPRESS®, which must be used in combination with 2,4-D, provides an additional alternative to weed management in this soil zone of the Canadian prairies. Based on a review of all available information, and in consideration of its benefits to the production of cereal crops, this herbicide was granted registration.

2.0 Pesticide Name and Properties

2.1 Pesticide Name

Common Name: tribenuron methyl; formerly DPX-L5300
Chemical Name: methyl 2-[[[[*N*-(4-methoxy-6-methyl-1,3, 5-triazin-2-yl) methylamino] carbonyl]amino]sulfonyl]benzoate
Trade Name: EXPRESS® Herbicide Dry Flowable 75%
CAS Registry No.101200-48-0

2.2 Physical and Chemical Properties

2.2.1 Tribenuron methyl Technical Active

Empirical formula:	$C_{15}H_{17}N_5O_6S$
Molecular weight:	395.39
Physical form:	solid
Colour:	light brown
Specific gravity:	1.5 g/cm^3
Melting point:	141^{o}C
Vapor pressure:	3.9 x 10^{-10} mm Hg at 25^{o}C
Octanol/water partition coefficient (K_{ow}):	0.3 at pH 7

Solubility, 25/C:

Solvent	**mg/L**
acetone	43.8
acetonitrile	54.2
carbon tetrachloride	3.12

ethyl acetate	17.5
hexane	0.028
methanol	3.39
water, pH 4.0	28
water, pH 5.0	50
water, pH 6.0	280

Hydrolysis Rate:

pH	Half-life (days)
5	< 1
7	3-6
9	32

2.2.2 Formulated Product

Product name:	EXPRESS® Herbicide Dry Flowable 75%
Guarantee:	75%
Bulk density:	0.668 g/cc
Flammability:	not applicable
Storage stability:	stable

3.0 Development and Use History

Tribenuron methyl is manufactured by DuPont Agrichemicals Caribe, Inc., Manati, Puerto Rico. The Canadian development program was conducted by DuPont Canada, Inc., the registrant for both the tribenuron methyl technical and the end-use products.

The Canadian field research and development program with tribenuron methyl was initiated in 1983. The submission for registration of tribenuron methyl was received in 1986. Submission for registration of EXPRESS® was received in 1987 and temporary registration was granted in December 1991 for tribenuron-methyl technical and in March 1992 for EXPRESS®.

EXPRESS® is marketed as a package with 2,4-D Ester LV 700 called EXPRESS® Pack.

Tribenuron methyl is currently registered for use in Austria, Belgium, Chile, China, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, Russia, Spain, Sweden, Switzerland, United Kingdom, and the U.S.

4.0 Regulatory Position and Rationale

Tribenuron methyl is a new member of the sulfonylurea family of herbicides which control a wide range of broadleaf weeds in cereal crops. Tribenuron methyl is less persistent compared to chlorsulfuron and metsulfuron-methyl and most rotational plants can be planted within 60 days following a postemergence

application at the recommended label rate. Research on the end-use product EXPRESS® started on cereal crops in the Prairie provinces in 1983. Since 1988, however, research efforts have focused on tank mixes of EXPRESS® with 2,4-D formulations to develop a product that would offer greater crop rotation flexibility and provide another alternative for weed resistance management. Crop tolerance data reviewed showed that spring wheat, durum wheat and barley exhibit satisfactory tolerance to tribenuron methyl (7.5 g ai/ha) when tank-mixed with 2,4-D amine or ester formulations at the recommended label rates.

Review of crop residue data indicated that when tribenuron-methyl is used on spring wheat, durum wheat and barley according to label directions with a pre-harvest interval of 30 days, the total residues at harvest are unlikely to exceed 0.05 ppm, and are not considered to pose a health hazard to consumers. This maximum residue limit (MRL) is published in Table II, Division 15 of the *Food and Drug Regulations*. An MRL of 0.01 ppm was established for tribenuron-methyl residues in milk to cover potential residues resulting from the feeding of treated green crop to dairy cattle. A seven-day pre-grazing interval for livestock was established.

Based on the review of the acute oral, dermal and inhalation toxicology data, no precautionary symbols were required on the main panel of the label.

Risks to the environment associated with the use of tribenuron methyl and its transformation products are minimal. When applied according to label directions, tribenuron methyl is not likely to leach under Canadian field conditions and the compound is nonpersistent and should not present a hazard to honeybees, earthworms, soil microbial processes, *Selenastrum capricornutum* and *Daphnia magna*. The octanol/water partition coefficient indicates that the compound has a low potential for bioaccumulation.

Review of the environmental chemistry and environmental toxicology data indicated that tribenuron methyl is practically nontoxic to rainbow trout, bluegill sunfish and daphnids. Its primary degradation product, triazine amine, is practically nontoxic to trout and daphnids. The toxicity of tribenuron methyl to aquatic vegetation, however, has not been addressed adequately by the registrant. Because the susceptibility of aquatic macrophytes to this product is not known, deposition of EXPRESS® on aquatic plants should be avoided.

It is unlikely that tribenuron methyl poses a significant direct acute risk to wildlife when used in accordance with the label directions.

Based on the outcome of the reviews of health, environmental and performance data and on the fact that the short persistence of this herbicide ensures flexibility of crop rotation options in the area of use, tribenuron methyl technical and the end-use product

EXPRESS® were registered under Section 13 of the *Pest Control Products Regulations*.

In view of the concerns about the potential impact of tribenuron methyl on nontarget aquatic and terrestrial plant species, registration was accepted for application by ground equipment only and subject to the following buffer-zone warning statement:

> OVERSPRAY OR DRIFT TO IMPORTANT WILDLIFE HABITATS SUCH AS SHELTERBELTS, WETLANDS, SLOUGHS OR DRY SLOUGH BORDERS, WOODLOTS, VEGETATED DITCH BANKS AND OTHER COVER ON EDGES OF FIELDS SHOULD BE AVOIDED. LEAVE A 15-METER BUFFER ZONE BETWEEN THE LAST SPRAY SWATH AND THE EDGE OF ANY OF THESE HABITATS.

After revew of remaining environmental toxicology and efficacy data, the technical active ingredient and the end-use product were determined to be acceptable for full registration on November 3, 1993.

5.0 Biological Properties

Tribenuron methyl is rapidly absorbed by plant foliage and roots and translocated throughout the plant. Susceptible weeds stop cell division and growth within hours after a postemergence application. Additional phytotoxicity symptoms develop over the next few days, including morphological changes, chlorosis and eventually necrosis of the leaf tissue. Susceptible broadleaf weeds succumb to the herbicidal action within 7 to 21 days after treatment. During this interval, the affected plants do not utilize soil moisture or nutrients and hence cannot compete with the crop. Like other sulfonylurea herbicides, tribenuron methyl acts by inhibiting the acetolactate synthase (ALS) enzyme system. ALS inhibitors arrest cell division in the meristematic regions of the plant. Since animals do not have a similar enzyme system, the plant specificity of sulfonylureas accounts in large part for the safety of these products to humans and wildlife.

6.0 Summary of Crop Tolerance Efficacy Data Reviewed

6.1 Crop Tolerance

Tolerance of spring wheat, durum wheat and barley to tribenuron methyl, alone and in combination with 2,4-D amine and ester formulations, was determined in Alberta, Saskatchewan, Manitoba and Quebec between 1983 and 1990. Visual assessments of crop injury were recorded at an early stage (0-20 days after treatment), and at a mature stage

of crop development (21-60 days after treatment). Crop yield data, submitted for some of the trials, and the Expert Committee on Weeds (ECW) (Western Section) Categories were also taken into consideration when assessing the overall tolerance of cereal crops to tribenuron methyl.

6.1.1 Spring Wheat (*Triticum aestivum*)

- Tribenuron at 15 g ai/ha (2x rate):
  Assessments recorded 0-20 days after the date of application showed that the resultant injury averaged over 16 trials, was 1% with a maximum value of 12% which did not have an adverse effect on crop yield.

- Tribenuron + 2,4-D amine at 7.5 + 560 g ai/ha:
  The resultant average injury for 31 applications to six common wheat cultivars was 0.4% with a maximum value of 2.5%.

- For 29 applications of tribenuron + 2,4-D ester formulations to five cultivars, the average injury was 0.4% with a maximum value of 5.5%.

Similarly, evaluations recorded later in the season showed that tolerance of spring wheat to tribenuron + 2,4-D amine or ester formulations was satisfactory.

6.1.2 Durum Wheat (*Triticum turgidum*)

- Tribenuron applications at 15 g ai/ha (two times the recommended rate) did not have any adverse effects on two durum cultivars as indicated by the early evaluations. Yield response from these trials was 107% of the check yield. Other trials evaluated later in the season showed that injury recorded for six cultivars did not exceed 10% and the resultant yield averaged 111% of the check yield.

- Similarly, satisfactory crop tolerance was observed when four common durum cultivars were treated with tribenuron + 2,4-D amine or ester formulations.

6.1.3 Barley (*Hordeum vulgare*)

- Tribenuron at 15 - 22.5 g ai/ha:
  Data submitted for the 0-20 day evaluations showed that no injury greater than 10% was observed for 31 applications to 19 cultivars. In the 21-60 day period, of 65 applications to 24 cultivars, no visual injury greater than 10% occurred.

- Tribenuron + 2,4-D at 7.5 + 560 g ai/ha:
  Of 19 applications of tribenuron + 2,4-D amine to seven cultivars, average crop injury was less than 1% with a maximum value of 5%. None of the 17 tribenuron + 2,4-D ester applications to 6 cultivars caused any injury.

6.1.4 ECW (Western Section) Categories

In the ECW Report of the Research Appraisal and Planning Committee, under the crop tolerance section on cereal crops, the use of tribenuron has been placed in the suggested category since 1988. Tank-mixes of tribenuron with 2,4-D amine or ester were placed on this list in 1991 for spring wheat, durum wheat and barley. The rate listed for tribenuron alone, 23 g ai/ha, is three times the current recommended rate. This would indicate a wide margin of safety.

6.2 Weed Control

Efficacy of tribenuron alone versus tribenuron + 2,4-D was determined over an eight year period on the following broadleaf weeds common to the Canadian prairies:

6.2.1 Lamb's-Quarters (*Chenopodium album* L.)

Control with tribenuron alone at a rate of 7.5 g ai/ha averaged at 92% (maximum 100%, minimum 68%) over 25 sites. When tank-mixed with 2,4-D amine, average control over four sites increased to 97% (maximum 100%, minimum 94%).

Similarly, tank-mixing tribenuron with 2,4-D ester increased average control to 98% over four sites.

There was no antagonism between tribenuron and the 2,4-D formulations.

6.2.2 Redroot Pigweed (*Amaranthus retroflexus* L.)

Average control across 23 sites with 7.5 g ai/ha of tribenuron alone was 75% (max. 100%, min. 42%). When tank-mixed with 2,4-D amine, the average control over eight sites increased to 85%. Similarly, tank-mixing tribenuron with 2,4-D ester at nine sites gave an average of 96% control. Consistency of control improved with the addition of 2,4-D. No antagonism occurred when the two herbicides were tank-mixed.

6.2.3 Stinkweed (*Thlaspi arvense* L.)

Tribenuron alone gave an average of 95% control (max. 100%, min. 70%) of the fall rosettes and spring seedlings. When tank-mixed with 2,4-D amine, the average control over eight sites did not change. When tank-mixed with the ester formulation of 2,4-D, average control over six sites increased to 99%.

6.2.4 Kochia (*Kochia scoparia* [L.] *Schrad.*)

Average control with tribenuron alone over 18 sites was 90%. Tank-mixing with 2,4-D ester did not improve the level of control appreciably; however, with the amine formulation, tested on two sites, control increased to 99%.

Although the number of trials with tribenuron + 2,4-D for Kochia is small, control achieved was more consistent where an adjuvant was used.

6.2.5 Wild Mustard (*Brassica kaber* [D.C.])

Tribenuron alone at 7.5 g ai/ha provided an average of 96% control at eight sites. The maximum and minimum control were, respectively, 100% and 75%. Addition of 2,4-D amine or ester improved the consistency of the control.

6.2.6 Russian Thistle (*Salsola kali* L.)

Average control with tribenuron alone at 31 sites across the prairies was 75%. When tank-mixed with 2,4-D amine, the average control over seven sites was 78%. Addition of an adjuvant to this treatment, however, improved the degree of control to 84%. Tank-mix treatments with 2,4-D ester at 420 to 560 g ai/ha further increased the level and consistency of control across eight sites to 94%.

6.2.7 Cow Cockle (*Saponaria vaccaria* L.)

Tribenuron alone at 7.5 g ai/ha provided 100% control at six sites. Tank-mix treatments with 5.0 to 7.5 g ai/ha of tribenuron and 420 to 560 g ai/ha of 2,4-D amine or ester also provided complete control with a high degree of consistency.

6.2.8 Canada Thistle (*Cirsium arvense* [L.] Scop.)

Tribenuron alone provided an average of 77% control (suppression of top growth) across 13 sites. Addition of 2,4-D amine or ester did not increase the extent of

suppression but improved the consistency of performance of tribenuron.

6.2.9 Wild Buckwheat (*Polygonum convolvulus* L.)

Average control over 15 sites was 62% with tribenuron alone. Tank-mixing with 2,4-D amine increased the level of control to 80%. Tank-mix treatment with 2,4-D ester resulted in 90% control. Addition of an adjuvant did not improve the extent of control.

The extent of control decreased as the weed growth stage advanced past the three-leaf stage. However, since wild buckwheat germinates relatively late in the season, the label claim was restricted to the one- to three-leaf stage.

6.3 Comparison of Efficacy of 2,4-D and Tribenuron used alone and in combinations

% CONTROL (NUMBER OF TESTS)						
Treatment	**Redroot Pigweed**	**Kochia**	**Russian Thistle**	**Cow Cockle**	**Canada Thistle**	**Wild Buckwheat**
2,4-D amine	85 (13)	65 (9)	80 (17)	37 (4)	62 (3)	67 (14)
2,4-D ester	90 (18)	77 (13)	85 (23)	55 (5)	70 (2)	78 (11)
Average both formulations	88 (31)	71 (22)	82 (40)	46 (9)	66 (5)	73 (25)
Tribenuron + 2,4-D (both formulations)	92 (29)	95 (17)	92 (40)	97 (15)	78 (5)	85 (27)
Tribenuron alone	75 (23)	90 (18)	75 (31)	100 (6)	77 (13)	62 (15)

In general, the ester formulation of 2,4-D, provided more effective control of the drought-adapted weed species such as kochia, Russian thistle, cow cockle, wild buckwheat and better suppression of Canada thistle.

In addition to the major weeds referred to above, a tank-mix of tribenuron + 2,4-D amine or ester provided satisfactory control of the following weeds which were found on fewer sites:

Prickly lettuce (*Lactuca scariola* L.)

Narrow-leaved hawk's-beard* (*Crepis tectorum* L.)
Volunteer sweetclover (*Melilotus alba* Desr., *Melilotus officinalis* [L.] Lam.)
Russian pigweed (*Axyris amaranthoides* L.)
Shepherd's-purse* (*Capsella bursa-pastoris* [L.] Medic.)
Wild radish (*Raphanus raphanistrum* L.)
Flixweed* (*Descurainia sophia* [L.] Webb)

* Fall rosettes and spring seedlings.

6.4 Crop Yield Response

In 168 treatments abstracted in the ECW Research Report (Western Section), yields of durum wheat and spring wheat were improved by 27% and 18%, respectively, over the weedy controls, as shown in the following table:

		Percent Yield Figures Compared to Weedy Control			Number of Trials Within Yield comparison Categories*				
Crop	**Total Number of Trials**	**Min**	**Max**	**Mean**	**>50% Yield increase**	**49-25% Yield increase**	**24-1% Yield increase**	**0-15% Yield decrease**	**>15% Yield decrease**
Durum	11	92	185	127	2	4	3	2	0
Wheat	125	74	190	118	16	17	69	21	2
Barley	32	76	122	102	0	0	17	11	4

* Comparison of treated crop vs weedy control

The lower yield response with barley probably reflects the stronger competitive nature of this crop, compared to spring wheat and durum.

6.5 Recropping Data

Crop rotation trials were conducted at 35 sites across the Prairie provinces representing major soil zones, soil types and climatic regions. Data were obtained on canola (*Brassica napus, Brassica campestris)*, flax (*Linum usitatissimum*), lentils (*Lens culinaris*) and alfalfa (*Medicago sativa*). These trials were conducted between 1983 and 1989 which includes the drought year of 1988.

The field trial sites selected represented a broad range of soil pH from a low of 5.4 at Veteran, Alberta, to 8.2 at Steinbach, Manitoba. The range in soil organic matter at these sites was from 2.3% at Hanley, Saskatchewan, to 12% at Crossfield, Alberta. The highest rate of tribenuron tested was 22.5 which is three times the recommended label rate. The recrop interval extended from as early as 6 days after application to as late as 401 days after the date of application.

The recropping data reviewed support the label claim that a minimum recrop interval of two (2) months should be left between the application of tribenuron and the seeding of canola, flax, lentils and alfalfa. The present data base is, however, inadequate to support the general statement initially requested by the registrant that "after two (2) months, there are no restrictions on the crops which may be planted." Only the four crops for which data were generated can be included on the label at this time.

The more general recropping statement that was proposed was not accepted in order to avoid potential injury to other rotational crops that could be seeded when a producer would be forced to replant in mid or late June because of a stand establishment failure due to hail, drying winds or severe insect attack.

7.0 Toxicology and Occupational Exposure: Health Evaluation Division

7.1 Acute Toxicity

7.1.1 Technical

Oral:

Rat: LD_{50} > 5000 mg/kg body weight (bw); virtually nontoxic

Dermal:

Rabbit: LD_{50} > 2000 mg/kg bw; virtually non-toxic

Inhalation:

Rat: LC_{50}(4-hr) > 6.7 mg/L of air (gravimetric concentration)

Primary Irritation:

Skin, Guinea pig: Not an irritant
Eyes, Rabbit: Practically non-irritating

Dermal Sensitization:

Guinea pig: Not a sensitizer

7.1.2 EXPRESS® Formulation 75% Dry Flowable

Oral:

Rat: LD_{50} > 5000 mg/kg bw; virtually non-toxic

Dermal:

Rabbit: LD_{50} > 2000 mg/kg bw; virtually nontoxic

Inhalation:

In consideration of the low acute inhalation toxicity associated with the technical, tribenuron methyl, the formulation type, and particle sizing data, a waiver for the acute inhalation study is supported.

Primary Irritation:

Skin, Rabbit: Minimally irritating
Eye, Rabbit: Slightly irritating

Dermal Sensitization:

Guinea pig: Potential skin sensitizer

7.2 Short-Term Toxicity - Technical

Mouse

In a 4-week range finding study Crl:CD-1 (ICR) BR mice were given tribenuron methyl at dietary levels of 0, 125, 500, 1250, 2500 and 5000 parts per million (ppm). A No Observed Effect Level (NOEL) of 500 ppm (equal to 70.0 mg/kg bw/day in males and 89 mg/kg bw/day in females) was determined based on body weight reductions in males, and increased liver weight (absolute and relative to body weight) at 1250 ppm or greater in both sexes.

A 90-day feeding study in Crl:CD-1 (ICR) BR mice with dose levels of 0, 125, 500 and 2500 ppm resulted in a NOEL of 125 ppm. Reduced actual concentrations of tribenuron methyl (68% of the nominal dose of 125 ppm) in the test diet (stored at room temperature for 10 days) was observed and thus, the adjusted NOEL would be 12.2 mg/kg bw/day in males and 16.3 mg/kg bw/day in females. A dose-related increase in absolute spleen weight and spleen to body weight ratios in females was statistically significant at dose levels of 500 ppm and greater. Absolute liver weights as well as liver to body weight ratios, were increased in a dose-

related manner in males at 500 ppm or greater and at 2500 ppm in females.

Rat

A 90-day feeding study was conducted with Crl:CD (SD) BR rats. Diets contained 0, 100, 1750 and 5000 ppm of tribenuron methyl. The No Observed Adverse Effect Level (NOAEL) set at 100 ppm (increased ratio of spleen to body weight at this dose level), adjusted for 75% dose reduction, was estimated to be 5.3 mg/kg bw/day in males and 6.0 mg/kg bw/day in females based on increased spleen to body weight ratios at this level. At 1750 and 5000 ppm body weight gains were significantly reduced (25% to 50% below control values) from weeks 1 - 13 in both sexes. Coloured nasal discharge was observed in males at 1750 ppm or greater.

Dog

In a three month feeding study, beagle dogs were fed diets containing tribenuron methyl at 0, 50, 500 and 2500 ppm. A NOEL of 500 ppm (equal to 15 mg/kg bw/day) was determined. Absolute thyroid/parathyroid weight in 2500 ppm males was nominally increased. Significantly increased thyroid/parathyroid absolute weight was observed at 2500 ppm in females; in males, only body weight and increased relative thyroid/parathyroid weight was observed at this dose level.

A one-year feeding study in beagle dogs was conducted with dose levels of 0, 25, 250 and 1500 ppm of tribenuron methyl. A NOAEL of 250 ppm (equal to 8.2 mg/kg bw/day) was determined based on an increase in aspartic aminotransferase in both sexes at this level but with no histopathological findings. At 1500 ppm, body weights were reduced in males and body weight gains reduced in both sexes. Increased serum creatinine levels were observed in males from 6 months and in females throughout treatment. Platelet counts were increased in both sexes at 1500 ppm.

7.3 Chronic Toxicity/Oncogenicity - Technical

Mouse

An 18-month feeding study was conducted using Crl: CD-1 (ICR)BR mice, given tribenuron methyl (purity not indicated) in the diet to achieve dose levels of 0, 20, 200 and 1500 ppm. A NOEL of 20 ppm was observed, equivalent to 1.6 mg/kg bw/day in males and 1.9 mg/kg bw/day in females after dose adjustment for 62% compound reduction when stored at room temperature. General weakness was observed in females at 200 and 1500 ppm and in males at 1500 ppm. At 1500 ppm, body weight reduction

(in excess of 20%), increased liver weight and increased incidence of age-related effects were observed in both sexes. In males, increased mortality, irregular respiration and tremors were also observed at 1500 ppm. There was no evidence for tumour induction in either sex.

Rat

In a 2-year chronic toxicity/oncogenicity study using Crl:CD(SD) BR rats, tribenuron methyl was administered in the diet at concentrations of 0, 25, 250 and 1250 ppm. At 25 ppm the content of tribenuron methyl in the diet was found to be 68% of nominal after storage for 10 days at room temperature. A NOAEL for chronic toxicity was set at 25 ppm (0.65 mg/kg bw/day in males and 0.82 mg/kg bw/day in females, adjusted for reduced actual concentration stability); in females, there was a minor decrease in body weight gain after one year. At 250 ppm and above, body weight gains and food efficiency were reduced in males, while organ to body weight ratios for brain, spleen and liver were increased in females at 24 months. At 1250 ppm terminal body weights were reduced by 29% in males and by 44% in females; histopathological changes observed included: mineralization of heart and aorta, pancreatic polyarteritis, decreased seminal vesicle secretion and splenic lymphoid depletion in males and, renal pelvis dilatation, uterus dilatation and bilateral retinal degeneration were observed in females. A statistically significant increase in mammary adenocarcinoma (a common occurring tumour in this strain) was observed in females at 1250 ppm only. Further discussion of the mammary adenocarcinomas is provided under the toxicology summary section.

7.4 Reproductive Toxicity - Technical

Rat

A one-generation reproduction study in Crl:CD(SD) BR rats fed diets containing tribenuron methyl at levels of 0, 100, 1750 and 5000 ppm was found to be inadequate, due to insufficient group size and protocol deficiencies.

In a 2-generation, 2-litter reproduction study, Crl: CD(SD) BR rats were fed diets containing tribenuron methyl at 0, 25, 250 and 1000 ppm. From this study a NOAEL was set at 25 ppm. Based on a 52% reduction in diet content of the test compound, the adjusted NOAEL was estimated to be 1.0 mg/kg/day in males and 0.91 mg/kg bw/day in females. At 250 ppm or greater, effects reported included: reduced body weight and low food consumption in parental animals; reductions in pup body weights and increases in organ to body weight ratios (testes, lungs) in male pups. The only observed toxicologically significant lesion was an increased incidence of decreased cytoplasmic clear space in hepatocytes of F2B weanlings.

7.5 Teratogenicity - Technical

Rat

A developmental toxicity study was conducted using pregnant Crl:COBS CD (SD) BR rats administered tribenuron methyl by gavage during days 6 to 15 of gestation, at dose levels of 0, 20, 125 and 500 mg/kg bw/day. A NOEL of 20 mg/kg bw/day for maternal and fetal toxicity was established. At 125 mg/kg bw/day or greater, excess salivation in dams during treatment was noted as well as reduced body weight gains and food consumption during treatment. Reduced maternal body weight plus gravid uterus weight and increased liver to body weight ratios were also noted. Fetal effects included reduced body weight and reduced ossifications (most likely reflecting maternal toxicity). No major malformations were observed.

Rabbit

A developmental toxicity study was conducted using New Zealand white rabbits. Groups of pregnant females were given tribenuron methyl at 0, 5, 20 and 80 mg/kg bw/day by gavage during days 6 to 18 of gestation. A NOEL of 20 mg/kg bw/day was determined for maternal toxicity, fetal toxicity and teratological effects. At 80 mg/kg bw/day, two treatment-related maternal deaths, seven abortions, body weight losses and reduced food consumption were reported. The number of live fetuses was decreased. An increased incidence of fetal malformations (7 malformations in 6 fetuses from 4 litters) was observed at the maternally toxic dose level, 80 mg/kg bw/day.

7.6 Mutagenicity - Technical

Tribenuron methyl did not demonstrate mutagenic activity in the following assays: microbial point mutation assay (Ames Test), mouse micronucleus test, unscheduled DNA synthesis in primary rat hepatocytes, Chinese Hamster ovary assay.

7.7 Absorption, Distribution, Metabolism and Excretion

Oral

Two metabolism studies were conducted. In each, the fate of ^{14}C-phenyl labelled tribenuron methyl was followed for 96 hours in Crl: CD(SD)BR rats, two per sex per dose level: 20 mg/kg bw (with or without preconditioning by feeding 5 mg/kg bw/day of unlabelled tribenuron methyl for 21 days) and 1800 mg/kg bw; and, ^{14}C-triazine labelled tribenuron methyl at 2000 mg/kg bw. In the second study excretion was followed for 168 hours in two groups of 5 females given 1700 mg/kg bw of either ^{14}C-phenyl or triazine labelled chemical.

Over 95% of radiolabel was recovered in excreta by 96 hours in both sexes following treatment at 20 mg/kg bw; there was no effect due to preconditioning. At 1800 mg/kg (phenyl label) or 2000 mg/kg (triazine label), males excreted over 98% of radiolabel by 96 hours but females excreted less: 67% (phenyl) to 80% (triazine). When the study was extended to 168 hours in 5 females per group, over 97% of label was excreted with both phenyl and triazine.

Biological half-life estimates at 96 hours were dose dependent. In the low-dose group (20 mg/kg bw) the half-life ranged from 26-33 hours and was independent of gender or preconditioning. At the high dose level the half-life for males ranged from 51 to 54 hours. A biological half-life could not be estimated for females due to significant retention of radioactivity in the carcass at 96 hours. In the 168-hour study the biological half-life for females was estimated to be 88-96 hours and there was no observed significant difference between phenyl and triazine labelled test material.

Radiolabel distribution in tissues and carcass was < 1.0% with or without preconditioning, following treatment at 20 mg/kg bw (both sexes) and males at 1800 mg/kg bw. At higher dose levels 26%-30% (phenyl label) or 10%-17% (triazine label) was retained in the gastrointestinal tract of females at 96 hours post administration versus 0.1% in males. By 168 hours, < 3.0% of label remained in the carcass of females, with < 1.0% in the gastrointestinal tract and other tissues following either phenyl label or triazine label treatment. These results indicate that at high doses, female rats metabolize and excrete tribenuron methyl much slower than male rats. The low residual radioactivity indicates that tribenuron methyl does not covalently bind to tissue macromolecules. Greater amounts of parent compound in some tissues (skin, fat) are consistent with the relative lipophilicity of tribenuron methyl.

Metabolites were identified with similar metabolites found in urine, feces and tissues (saccharin and metsulfuron-methyl with phenyl label; 0-demethyltriazineamine and metsulfuron-methyl with triazine label).

Dermal

The dermal absorption of formulated ^{14}C-tribenuron methyl was studied in CD(SD)BR rats. The product was applied to the backs of the animals at clipped, intact skin sites for 1, 4, 10 or 24 hours after which the animals were sacrificed for analysis of radioactivity. Dosed skin sites were washed at the above time periods. Excreta, carcass, blood, and dosed skin area were assayed for ^{14}C content to determine total dermal absorption. At dose levels of 0.03, 0.3 and 3.0 mg/rat, which correspond to dermal deposition of 2.5,

25 and 220 :g/cm^2, approximately 26%, 10% and 3% was absorbed after 24 hours of exposure.

Based on the results of the worker exposure study with EXPRESS®, the low dose (2.5 :g/cm2) best approximates deposition in the field. Accordingly, a penetration factor of 26% should be utilized as an estimate of dermal absorption in workers.

7.8 Toxicology Summary

In acute studies, tribenuron methyl was virtually non-toxic via the oral and dermal routes and an inhalation hazard was not indicated. It was non-irritating to eyes and skin and was not found to be a sensitizing agent. The formulation (EXPRESS® Herbicide) was not acutely toxic but was a minimal skin and slight eye irritant. It was considered to be a potential skin sensitizer.

Repeated short-term administration of tribenuron methyl at high dose levels resulted primarily in body weight reductions and increased organ weights in rats, mice and dogs. The rat was judged to be the most sensitive species and a NOAEL of 5.3 mg/kg bw/day was noted in the 90-day rat dietary study.

The long-term mouse study showed evidence of body weight reductions, irregular respiration and tremors, increased liver weights and an increased incidence of age-related effects. There was no evidence of tumour induction. A NOEL of 1.6 mg/kg bw/day was determined.

In the long-term rat study, a NOAEL of 0.65 mg/kg bw/day based on reduced body weight, food efficiency, and increased organ to body weights was noted. With respect to the increased incidence of mammary adenocarcinomas, the following considerations were made:

i) The increase is statistically significant for the trend ($p < 0.002$) and Fisher's Exact Test ($p < 0.001$) at the highest dose.

ii) The tumour incidence was increased only at the highest dose tested which was clearly toxic and exceeded the maximum tolerated dose.

iii) With the exception of one female of the control group where an adenocarcinoma was found during the first year of the study, tumours were observed generally at terminal sacrifice. An earlier onset of tumours was therefore not observed.

iv) There was no evidence of precancerous lesions in the high-dose females.

v) Tumours were observed in one sex (females) and one species (rat).

vi) Structural analogs such as thifensulfuron-methyl and ethametsulfuron-methyl, previously reviewed by the Health Protection Branch, showed little evidence of oncogenic potential.

vii) Metabolism data show that elimination was slower in females and that labelled tribenuron methyl was retained in the carcass (mostly fat, skin) at high dose levels, which is consistent with the lipophilicity of tribenuron methyl.

i) Results of mutagenicity tests were negative.

It is therefore concluded that tribenuron methyl induced the development of mammary tumours only at dose levels which cause serious chronic toxicity. Based on this and the above considerations, tumorigenicity was not considered relevant to a safety assessment.

Effects on reproductive performance were not observed in rats receiving dietary doses up to 1000 ppm. A reduction in parental and pup body weights was the basis for a NOAEL of 0.92 mg/kg bw/day.

In rats, the NOEL for maternal and fetal toxicity was 20 mg/kg bw/day. No teratogenic effects were demonstrated. A rabbit study demonstrated a NOEL of 20 mg/kg bw/day for maternal and fetal toxicity and teratological effects.

7.9 Food Exposure

a) Acceptable Daily Intake (ADI)

The most sensitive species is the rat with body weight gains reduced and organ to body weight ratios increased in both sexes. In order to set an ADI based on the 2-year rat study, nominal concentrations were adjusted to account for the problem of reduced actual concentrations of tribenuron methyl in the diets at the low dose level with resulting NOAEL values of 0.82 mg/kg bw/day in females and 0.65 mg/kg bw/day in males. Using a 100-fold safety factor and the lowest NOAEL, an ADI of 6.5 :g/kg bw/day is estimated.

b) Food Residue Exposure

Label

The company label states that the product is to be used for weed control in wheat (spring and durum) and barley at a rate of 7.5 g ai/hectare (ha), at a preharvest interval (PHI) of 30 days, and that wheat or barley must not be grazed by or fed to livestock within 7 days of treatment.

7.10 Metabolism

Plant Metabolism

Field studies using 14C-labelled tribenuron methyl ([phenyl(U)-^{14}C] methyl 2-[[[[N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)-N-methylamino] carbonyl] amino] sulfonyl] benzoate) were performed on winter wheat at a rate of 75 g ai/ha (72 g ai/ha for the triazine label) and a PHI of 63 days (10 times the recommended label rate and 2 times the PHI). Immature wheat plants (4-28 days post-treatment) and mature grain and straw (63 days PHI) were analyzed for total ^{14}C-residues and metabolites.

Similar plant metabolism results were obtained using both the ^{14}C-phenyl and the ^{14}C-triazine labelled tribenuron methyl, therefore only the results from the ^{14}C-phenyl labelled study will be discussed. A proposed metabolic pathway is given in Figure 1.

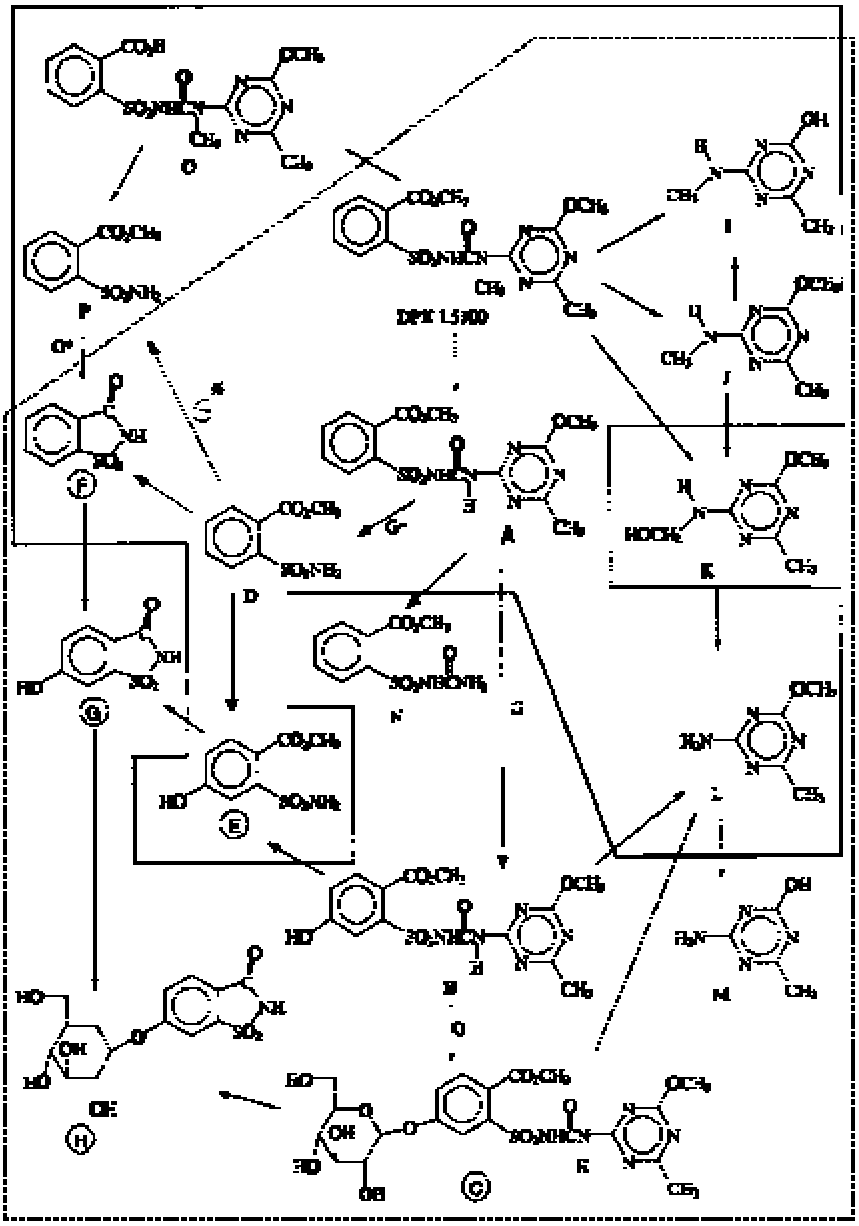
In the phenyl-labelled study, total terminal residues (TTRs) totalled 5.49, 2.84, 1.85, 1.11 and 0.75 ppm for forage (whole wheat plant) harvested at 0, 4, 8, 14 and 28 days post-treatment respectively. Total ^{14}C-residues in mature (63 day PHI) straw and grain were 0.55 and 0.05 ppm respectively.

The major grain metabolites were (% TTR); sulfonamide urea, 44.6% (methyl 2-[(aminocarbonyl)aminosulfonyl] benzoate); saccharin, 11.3% (1,2-benzisothiazol-3(2H)-one 1,1-dioxide); hydroxylated saccharin, 3.5% (1,2-benzisothiazol-3(2H)-one 6-hydroxy-1-dioxide); sulfonamide 1.9% (methyl 2-(aminosulfonyl)benzoate); glucose conjugate of OH-saccharin, 1.7%; unidentified, 5.2%; bound residues comprised 31.8% of the TTR; tribenuron methyl was not detected.

67% of the TTR in mature straw was extractable and was determined to contain 1.3% parent tribenuron methyl, 7.6% sulfonamide urea, 5.2% saccharin, 14.8% OH-saccharin, 3.2% sulfonamide, 7.1% glucose conjugate of OH-saccharin, 14.8% hydroxylated metsulfuron-methyl (the most prevalent metabolite), and 3.8% glucose conjugate of metsulfuron-methyl.

Forage harvested 8 days post-treatment contained 96.4 % extractable ^{14}C-TTR (1.85 ppm) with a metabolic profile similar to mature straw except for the glucose conjugate of metsulfuron-methyl at 11.3% of TTR; 3.6% of the TTR was identified as tribenuron methyl. The half-life for tribenuron methyl in plants is estimated to be approximately 1.5 days.

Figure 1. Proposed metabolic pathway for tribenuron methyl in plants and animals.



Animal profile bordered by _____
Plant profile bordered by ----------

All animal metabolites identified in rat metabolism, and those for goat metabolism (by analogy to metsulfuron-methyl, not performed for tribenuron methyl) are shown by a "G" and a "G*" for major metabolites (> 10%).

Plant metabolites were identified in a wheat metabolism study (straw & foliage); major plant metabolites are identified by a circle around the letter (> 6%).

Chemical Names of Compounds Shown in Figure 1.

DPX-L5300 methyl 2-[[[[(N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)methylamino]carbonyl]amino]sulfonyl]benzoate

A "metsulfuron-methyl"
methyl 2-[[[[(N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate

B "hydroxylated metsulfuron-methyl"
methyl 2-[[[[(N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl] -4-hydroxybenzoate

C glucoside of B

D "sulfonamide"
methyl 2-(aminosulfonyl)benzoate

E "hydroxylated sulfonamide"
methyl 2-(aminosulfonyl) 4-hydroxybenzoate

F "saccharin"
1,2-benzisothiazol-3(2H)-one, 1,1-dioxide

G "hydroxylated saccharin"
1,2-benzisothiazol-3(2H)-one 6-hydroxy 1,1-dioxide

H glucoside of G

I "O-desmethyl triazine amine"
4-methylamino-6-methyl-1,3,5-triazino-2-ol

J "triazine amine"
4-methoxy-N, 6-dimethyl-1,3,5-triazine-2-amine

K N-hydroxymethyl derivative of J

L "N-demethyl triazine amine"
4-methoxy-6-methyl-1,3,5-triazin-2-amine

M 4-hydroxy-6-methyl-1,3,5-triazin-2-amine

N "sulfonamide urea"
methyl 2-[(aminocarbonyl)aminosulfonyl]benzoate

O "free acid of DPX-5300"
2-[[[[(N-(4-methoxy-6-methyl-1,3,5-triazin)-2-yl)methylamino]carbonyl]amino]sulfonyl]benzoate

P "acid sulfonamide" 2-(aminosulfonyl)benzoic acid

Animal Metabolism

Large animal metabolism studies were not performed for tribenuron methyl, however metsulfuron-methyl (^{14}C-phenyl labelled) animal metabolism studies can be used as a faithful model; structurally the herbicides are identical except for the absence of a methyl group at the 2-N of the urea. Metsulfuron-methyl is registered for use on wheat and barley at negligible residue levels (0.1 ppm). A lactating goat study involved dosing 5 mg (3.4 ppm) metsulfuron-methyl for 5 days; only 0.2% (0.01 ppm) of the total dose was reported in tissues and blood. Metabolites identified in liver (0.003 TTR) included those reported in plants i.e., saccharin (55%), metsulfuron-methyl (20 %), sulfonamide (10 %), and one metabolite not reported in plants the acid sulfonamide (10%, 2-(aminosulfonyl)benzoic acid). A proposed metabolic pathway for animal metabolism is also given in Figure 1.

Analytical Methodology

Residues of parent tribenuron methyl were extracted, centrifuged (20 K), cleaned up using HPLC and analyzed using a second HPLC with UV detection (254 nm). The lower limit of quantitation for grain was 0.01 ppm and for whole plant tissues (straw or immature plants) 0.02 ppm. Recoveries for samples spiked at 0.01 to 0.17 ppm ranged between 71% to 107% +/- 11% (standard deviation). Although no analytical methodology was presented for meat or dairy products, due to the similarity in structure to metsulfuron-methyl, a lower limit of quantitation of 0.01 ppm in meat and dairy products is expected.

Analytical methodology was not developed for the major terminal residues (metabolites described above) in plant and animal tissues and this may be important due to the short half-life of the parent tribenuron methyl. Tribenuron methyl and metsulfuron-methyl metabolites are identical thereby precluding the development of an analytical method to differentiate between these two compounds. The determination of the source of any potential violative residues may not be possible.

7.11 Residues

Crop Residues

An evaluation of all Canadian data indicated that parent tribenuron methyl residues in wheat or barley grain are unlikely to exceed 0.01 ppm when crops were treated at the recommended rate of 7.5 g ai/ha/year and at a recommended PHI of 30 days. A ^{14}C metabolism study utilizing ten times the rate reported 0.75 ppm TTR for forage (whole plant) harvested 28 days PHI and 0.05 ppm TTR for grain harvested at 63 days PHI.

Straw residues were below the lower limit of quantitation (LLQ) for parent tribenuron methyl of 0.02 ppm for plants treated as recommended, while the ^{14}C study done at ten times the rate reported 0.55 ppm TTR in mature straw tissues (63 days PHI).

Immature plants treated with unlabelled tribenuron methyl (7.5 g or 15 g ai/ha) and harvested 7 days post-treatment combined < 0.02 ppm (LLQ) parent tribenuron methyl residues. The ten times the rate ^{14}C metabolism study reported 1.85 ppm TTR for immature plants at 8 days post-treatment.

In summary, wheat and barley crops treated at recommended rates and PHI contained less than 0.02 ppm parent tribenuron methyl residues (grain, mature straw, immature plants); however, greater than 96% of the TTR was shown to be present as extractable metabolites in wheat and barley plants. Consequently, although it is unlikely that the TTR of tribenuron methyl in treated wheat and barley will exceed 0.05 ppm, a precise qualitative and quantitative evaluation of the terminal residues in plant tissues was not possible since these metabolite residues were not determined for the 30 day PHI residues and the ^{14}C metabolism study used a treatment time of 63 days PHI as compared to the PHI of 30 days proposed for the label.

Animal Residues

Animal feeding studies were not reported for tribenuron methyl but metsulfuron-methyl studies may be used as a model to indicate bioavailability and disposition.

A lactating goat study for metsulfuron-methyl (dosing regime: 5 mg ^{14}C-phenyl labelled/day for 5 days; equivalent to 3.4 ppm in the goat diet) reported the following disposition of total ^{14}C-residues. Tissues and blood contained less than 0.01 ppm TTR (0.02% of the total dose); total ^{14}C in milk plateaued rapidly, remaining constant at 8 to 9 parts per billion (ppb) (80% of which was identified as metsulfuron-methyl).

A lactating cow study reported the following disposition of unlabelled metsulfuron-methyl residues (dosing regime: 0, 5, 20 or 100 ppm in the diet for 4 weeks). Fat and meat tissues were < 0.01 ppm (LLQ), except for one cow (100 ppm feeding study) with meat residues of 0.014 to 0.02 ppm. Liver and kidney tissues from cows fed 5 ppm were not greater than 0.053 ppm.

Metsulfuron-methyl residues in milk samples from cows fed 5 ppm were less than 0.011 ppm; 20 ppm feeding resulted in residues that reached a plateau at day 7 post-treatment with residues at 0.016-0.033 ppm over the 4 week period.

Metsulfuron-methyl was rapidly excreted in the urine and feces.

Tribenuron methyl residues (by analogy with metsulfuron-methyl) of up to 5 ppm in total diet may be fed to cattle with residues in meat and dairy products expected to be less than 11 ppb in milk, meat, and liver, and less than 53 ppb in kidney.

Avian feeding studies were not performed for either metsulfuron-methyl or tribenuron methyl but considering the very low levels of TTR expected in grain (< 0.01 ppm), residues in poultry products are not expected be significant.

Dietary Risk Assessment

When the general regulation level of 0.1 ppm in wheat, barley, meat, and dairy products was used to estimate the Theoretical Daily Intake (TDI), the intake was calculated to be 1.4 :g/kg bw/day or 21.5% of the ADI. The TTRs of tribenuron methyl, however, are not expected to exceed 0.05 ppm in harvested wheat or barley grain and therefore a maximum residue limit (MRL) is proposed at this level.

The use of a milk residue at the general Regulation level of 0.1 ppm may however result in unacceptable residues for certain segments of the Canadian population, i.e., young children, and therefore a lower residue limit is considered necessary. The extrapolated metsulfuron-methyl feeding studies data along with the day 0 residue data from tribenuron methyl forage residue studies and the proposed label restrictions, i.e., do not feed within 7 days of treatment, indicates that the residues that may occur from this proposal in green forage and straw are expected to result in residues in whole milk of less than the detection limit of the analytical method, i.e., < 0.01 ppm, and therefore a residue limit of 0.01 ppm in whole milk is proposed.

The estimated TDI using the proposed MRL for wheat and barley of 0.05 ppm and the proposed MRL for whole milk of 0.01 ppm would therefore be 11.2% of the ADI.

7.12 Occupational Exposure

7.12.1 Exposure Assessment

An occupational exposure study for EXPRESS® formulation was submitted by the registrant. Eight workers each mixed and applied tribenuron methyl to wheat using ground boom equipment to areas spanning 13-21 hectares. Seven of the workers were also monitored during cleanup of spray equipment. Each complete spray cycle (mix/load, apply, cleanup) took between 2-3 hours. Two workers employed

open-cab tractors; the other six utilized closed cabs. Dermal deposition and inhalation exposure were monitored.

A description of the workers' clothing was not provided because the estimate of skin deposition was based on analyses of the different layers of the patches. Inhalation exposure was negligible with all samples less than the limit of detection. Little difference in exposure was noted for those workers using open- or closed-cab tractors. Exposure was estimated for a 70 kg farmer wearing long pants, short sleeves, boots, and no gloves and treating 48 hectares at the label application rate (7.5 g ai/ha) for EXPRESS®. The results of the rat dermal absorption study with EXPRESS® (26% absorbed) were taken into account.

The estimated mean exposure is 0.003 (range 0.0008 - 0.007) mg/kg bw/day for workers using EXPRESS®. Performing this study at application rates 3-4 times that appearing on the label may contribute to an overestimation of exposure. However, there were factors which may result in an underestimation of exposure. The total monitoring time/worker was only 2-3 hours and it is expected that the full range of exposure encountered during a work day would not be captured. Furthermore, determination of skin deposition was based on an analysis of the innermost layer of the multi-layer patch as opposed to analysis of patches placed inside the workers' clothing. This may underestimate exposure occurring at seams, up cuffs and through worn areas of clothing. The extent to which these factors offset each other cannot be assessed, however, the study is considered adequate for use in the risk assessment for EXPRESS®.

7.12.2 Risk Assessment

The range of toxicological studies on tribenuron methyl failed to demonstrate any major health hazard. The short-term toxicity studies were deemed to be the most relevant for risk assessment due to the single, short use season for this product. The adverse effects noted in the rat reproduction study (25, 250 and 1000 ppm) and the 90-day dietary study (100, 1750 and 5000 ppm) were similar though the reported NOAEL was higher in the latter study due to selection of the dose range. Therefore, the most relevant endpoint for occupational exposure is the reduction in body weight in the 90-day oral rat study with a NOAEL of 5.3 mg/kg bw/day (100 ppm).

Exposure was estimated for a typical 70 kg farm worker wearing a short-sleeved shirt, long pants, no gloves and applying EXPRESS® at the label rate of 7.5 g ai/ha to 48 ha/day. The estimated daily exposure was 0.003 (0.0008 - 0.007) mg/kg bw/day. This value takes into consideration 26% dermal absorption as observed in a dermal absorption study in rodents.

Based on the exposure value and the NOAEL of 5.3 mg/kg bw/day, there is a margin of safety of approximately 1700 (range 757 - 6625) for workers exposed to EXPRESS®, which Health Protection Branch considers adequate.

8.0 Environmental Aspects: Environment Assessment Division

8.l Summary

The submitted information indicated that, when applied according to label directions, tribenuron methyl is nonpersistent and is not likely to volatilize or to leach under Canadian field conditions.

Tribenuron methyl should not present a hazard to honeybees, earthworms and soil microbial processes. Based on the limited data available, tribenuron methyl is unlikely to pose a significant direct acute risk to birds. Some of the estimates of risk to wild mammals approach a level of concern. However, the studies on which these estimates were based involved repeated exposure which would overestimate risk since tribenuron methyl is proposed for single applications and is not persistent.

Tribenuron methyl is not expected to pose a hazard to fish and aquatic invertebrates, such as *Daphnia magna*, which serve as food for fish. Data supplied in response to concerns regarding the toxicity of a persistent transformation product, triazine amine, indicated that this compound should not be hazardous to fish and *Daphnia magna* at concentrations likely to occur in the environment.

No data were available from which to evaluate the risk posed to amphibians and reptiles from the use of tribenuron methyl.

Toxicity of tribenuron methyl to the green algal species, *Selenastrum capricornutum*, was low. Plant-screening data submitted by the registrant on 50 terrestrial and aquatic species indicated that tribenuron methyl was toxic to many broadleaf species at the rate estimated for spray drift (l0% of previous label rate of 10 g ai/ha = 1.0 g ai/ha). An additional study was conducted in the field on selected nontarget terrestrial plants. The two annual species were greatly

affected during and at the end of the season. Although the four perennial species were damaged at low doses during the growing season, they showed recovery. In another study, three aquatic plant species were tested under laboratory conditions; however, the data from the study were inadequate and highly variable. In the absence of reliable aquatic plant toxicity data, and given the toxicity of tribenuron methyl to a wide range of terrestrial species, the label restrictions of no aerial application and a 15-metre buffer zone are recommended.

8.2 Environmental Chemistry and Fate

8.2.1 Physicochemical Properties

Tribenuron methyl was shown to have a pK_a of 4.7, a vapour pressure of 5.3×10^{-8} Pa, and a solubility in water of 28, 50 and 280 mg/L at pH 4, 5 and 6, respectively. Based on the values for Henry's Law Constant over the range of pH of 4-6, tribenuron methyl has a low potential for volatilization from moist soil and water.

The octanol/water partition coefficient (K_{ow}) of 0.3 at pH 7 indicated a low potential for tribenuron methyl to bioaccumulate.

8.2.2 Transformation

Rates and Mechanisms of Transformation

The predominant means of transformation in sterile water was acid-catalyzed hydrolysis; half-lives were < 1, 3-6 and 32 days at pH 5, 7 and 9, respectively. Evidence was also presented that biotransformation may occur at low rates under alkaline conditions.

In phototransformation studies, the rate of tribenuron methyl transformation in sterile water and on a soil surface was not influenced by exposure to sunlight. DT_{50}s for tribenuron methyl in these studies were 1, < 13-16 and > 30 days at pH 5, 7 and 9, respectively (in water) and < 5.1 days (on a silt loam soil surface, pH 7.5, 5.4% organic matter).

In aerobic soil biotransformation studies, tribenuron methyl DT_{50}s were 3 and 12 days in nonsterile silt loam soils of pH 4.3 and 7.5, respectively, and organic matter contents of approximately 5%. Tribenuron methyl transformation rates in corresponding sterile soils were slightly faster, which was attributed to a lowering of soil pH following sterilization.

In anaerobic aquatic sediment/water study systems, tribenuron methyl transformed rapidly under nonsterile conditions; half-lives were 2-3 and 11 days in study systems which were slightly acidic (pH 6.1) and slightly basic (pH 7.4), respectively. In sterile systems, tribenuron methyl transformation rates were similar to those in nonsterile systems under slightly acidic conditions, but were lower under slightly basic conditions.

In terrestrial field studies conducted at four sites in the Canadian prairies, on soils of pH ranging from 6.2-7.9 and organic matter contents ranging from 2.9-9.2%, the DT_{50}s of tribenuron methyl were $\leq$ 11 days. Concentrations of tribenuron methyl in soil 1 and 4 months post-application were $\leq$ 11 and $\leq$ 6% of the amount applied, respectively (i.e., $\leq$ 5 and $\leq$ 3 ppb, respectively). In similar studies conducted in Illinois, Idaho and Delaware, DT_{50}s for tribenuron methyl in soils of pH ranging from 5.1 - 8.3 and organic matter contents ranging from 1.7 - 5.0% were comparable to those observed in Canadian field studies.

These data indicate that tribenuron methyl will be of low persistence in the soil environment following application according to label directions.

Products of Transformation

Transformation products of tribenuron methyl included carbon dioxide, tribenuron methyl acid, sulfonamide, acid sulfonamide, saccharin, triazine amine, O-demethyl triazine amine and N-demethyl triazine amine. Of these transformation products, triazine amine, saccharin and sulfonamide were major (i.e., they occurred at concentrations > 10% of the applied tribenuron methyl) and persistent.

Triazine amine did not transform under most of the conditions encountered in terrestrial field studies in Canada and the U.S., and generally accounted for the majority of recovered radioactivity. At one field site in the U.S., triazine amine concentrations were observed to decline from 97% of the applied radioactivity at two weeks post-treatment to 55% at 52 and 78 weeks post-treatment. It was unclear if this decline was due to leaching or transformation, or if it was an artifact of poor recoveries during the latter stages of the study. The dissipation of triazine amine did not occur in other studies.

Sulfonamide was transformed to saccharin under certain (basic) extraction conditions, thus relative

expected concentrations of each of these transformation products could not be firmly established. Both compounds dissipated over time in laboratory and field studies. In one terrestrial field study in the U.S., concentrations of saccharin plus

sulfonamide accounted for 78% (by four weeks post-treatment) of applied ^{14}C-phenyl-labelled tribenuron methyl, but declined to 8% (by 20 weeks post-treatment).

Mobility

The results of soil-column leaching, soil thin-layer chromatography and adsorption/desorption studies indicated that tribenuron methyl may leach in soil under field conditions. However, the rapid transformation of tribenuron methyl under both aerobic and anaerobic conditions would minimize this potential for leaching as was seen under the environmental conditions of the Canadian and American terrestrial field studies. It is expected that the potential for leaching would also be minimal under rainfall conditions higher than those reported for the submitted field studies. Based on these considerations, field studies in Eastern Canada are not considered necessary at this time for the proposed use pattern.

8.3 Environmental Toxicology

Fish and Aquatic Invertebrates

Assuming a direct application of tribenuron methyl at the maximum label rate of 7.5 g ai/ha to a 15-cm-deep body of water, the expected environmental concentration (EEC) would be 0.005-mg tribenuron methyl/L.

Acute toxicity data indicated that tribenuron methyl was practically nontoxic to fish and aquatic invertebrates. There was no mortality during 96-hour exposure studies with rainbow trout, *Oncorhynchus mykiss* and bluegill sunfish, *Lepomis macrochirus*. The 48-hour EC_{50} for immobility with *Daphnia magna* was 720 mg ai/L. The primary degradation product, triazine amine, was also practically nontoxic, having EC_{50}s of 172 mg ai/L (trout) and > 1000 mg ai/L (*Daphnia magna*). Although there were no specific studies on bioconcentration/depuration of tribenuron methyl in fish, its physicochemical properties, along with data for other sulfonylurea herbicides, indicate that tribenuron methyl would not be expected to accumulate in aquatic food webs.

Based on the information provided, the use of tribenuron methyl in accordance with the label directions is not

expected to pose a hazard to fish and the aquatic invertebrates which serve as food for fish.

Wild Birds

Wild birds could be exposed to tribenuron methyl by direct overspray, spray drift or consumption of sprayed vegetation. The probability of exposure of birds through direct overspray is reduced as long as only ground application methods are used. However, it is possible that the eggs of ground nesting species could be sprayed at field rates.

No data are available on the metabolism or pharmacokinetics of tribenuron methyl in avian species.

The acute oral LD_{50} for technical tribenuron methyl in six-month-old bobwhite quail, *Colinus virginianus*, was > 2250 mg ai/kg bw. A NOEL was not established, as sublethal symptoms were observed at the lowest dose administered (292 mg ai/kg bw). In the acute dietary studies with technical tribenuron methyl fed to both bobwhite quail and mallard duck, *Anas platyrhynchos*, the LC_{50}s were > 5620 mg ai/kg diet. The NOELs were reported as 1780 (bobwhite quail) and 562 (mallard duck) mg ai/kg diet. The estimated risk factors for avian species are in the order of 10^{-4} to 10^{-3}, indicating that tribenuron methyl is unlikely to pose a direct acute hazard to birds when used at label rates. These values are well below the level of concern of 0.2. No avian reproduction studies were submitted.

Wild Mammals

The most likely exposure routes for wild mammals are through consumption of contaminated vegetation or consumption of contaminated prey.

The acute oral LD_{50}s of tribenuron methyl in female and male rats were > 5000 (technical) and 3750 (75DF formulation) mg ai/kg bw. The acute dermal toxicity of tribenuron methyl technical in male and female New Zealand white rabbits was > 2000 (technical) and > 1500 (75DF formulation) mg ai/kg bw. A 90-day dietary study conducted with the Charles River mouse indicated a NOAEL of 500 mg ai/kg diet, equivalent to 70 (females) and 89 (males) mg ai/kg bw/d.

In the rat teratogenicity study, the NOEL for maternal toxicity and developmental effects with tribenuron methyl was 20 mg ai/kg bw/d. The NOAEL for maternal or fetal effects in the rabbit teratogenicity study was 5 mg ai/kg bw/d. The NOAEL in the two generation rat reproduction study was 25 mg ai/kg diet, equivalent to 1.9 (females) and 1.75 (males) mg ai/kg bw/d.

Worst-case acute risk factors for tribenuron methyl, estimated on the basis of small mammal acute toxicity data, were low (i.e., < 10^{-4}). Risk factors based on other mammalian studies were higher, ranging from $l0^{-3}$ to 10^{-1} (teratogenicity studies) and 0.01-0.1 (rat reproduction study). It is acknowledged that these risk factors likely overestimate probable exposure scenarios, as tribenuron methyl is not persistent in the environment. However, the observation of toxic effects at relatively low doses (NOEL = 5 mg ai/kg bw/d) challenges the premise that tribenuron methyl is specifically toxic only to plants.

Amphibians and Reptiles

No data were available with which to evaluate the risk posed to amphibians and reptiles from the use of tribenuron methyl.

Terrestrial Invertebrates

Tribenuron methyl was of low acute toxicity to the earthworm, *Eisenia foetida* (LD_{50} = 1299 mg ai/kg soil). No contact toxicity to the honeybee, *Apis mellifera*, was observed at rates up to 100 :g/bee. No data on the effects of tribenuron methyl on predatory and parasitic insects were found in the submission.

Soil Microbial Processes

Results indicate that when applied according to label directions, tribenuron methyl should not affect soil ammonification, nitrification, respiration and asymbiotic nitrogen fixation.

Algae

A five-day static algal assay was conducted by exposing the green alga, *Selenastrum capricornutum*, to technical tribenuron methyl. The E_bC_{50} (using area under the curve) was 67 mg ai/L, the E_rC_{50} (using growth rate) was > 100 mg ai/L, and the No Observable Effect Concentration (NOEC) was 6.5 mg ai/L. With an EEC of 0.005 mg ai/L (based on the maximum label rate of 7.5 g ai/ha applied to a 15 cm-deep body of water), the risk factor of 7.7 x $l0^{-4}$ is very low.

Aquatic and Terrestrial Macrophytes

Tribenuron methyl, like other sulfonylurea herbicides, acts through inhibition of acetolactate synthase (ALS), which participates in the biosynthesis of the branch-chain amino acids, valine, leucine and isoleucine. This inhibition leads to a rapid cessation of plant cell division and growth.

The metabolism of phenyl- and triazine-labelled tribenuron methyl in field-grown winter wheat was studied. Tribenuron methyl was rapidly degraded with a half-life < 4 days.

Results of toxicity studies with tribenuron methyl, based on plant-screening data routinely developed during product development, were presented for 42 terrestrial and eight aquatic species. Of these, there were 23 dicotyledonous species from 17 families and 27 monocotyledonous species from three families. Plants were sprayed post-emergence, in accordance with the use pattern requested for tribenuron methyl, at doses ranging from 1.0 - 125 g ai (most species) and from 0.25 - 1000 g ai (two of the aquatic species). The EC_{25} was calculated for each species. The results showed that 12 species (i.e., 43% of broadleaf species tested) from nine families (i.e., 56% of broadleaf families tested) would be harmed by drift occurring at l0% of the previous label rate of 10 g ai/ha (EC_{25} < 1.0 g ai/ha). Grasses were very resistant to tribenuron methyl.

In another study, three aquatic plant species were tested under laboratory conditions; these were two submerged species, *Potamogeton pectinatus* and *Myriophyllum spicatum* and one floating species *Lemna minor*. No emergent species, (e.g., *Eleocharis acicularis, Sagittaria latifolia* or *S. cuneata*) were tested. The data from these studies were inadequate and highly variable. Consequently, the toxicity of tribenuron methyl to aquatic vascular plants cannot be adequately estimated at present.

An additional field study was conducted on selected nontarget terrestrial species in Saskatchewan. Two annual species (*Lentilla lens* and *Helianthus annuus*), two herb perennials (*Sonchus arvensis* and *Melilotus alba*) and two woody perennials (*Symphoricarpos occidentalis* and *Rosa acicularis*) were investigated. Dose-response data on several endpoints indicated 25% growth reduction (GR25) at rates ranging from 0.44 - 4.23 g ai/ha. The annual species were greatly affected throughout the growing season (GR25 = 0.44 - 2.02 g ai/ha). Although the perennial species were damaged at low doses during the growing season (GR25 = 1.4 - 4.23 g ai/ha), they recovered at doses < 8-120 g ai/ha.

Aquatic and Wildlife Habitat Considerations

Tribenuron methyl has a low application rate, it persists briefly and its toxicity to fish, aquatic invertebrates, birds and mammals is low. However, tribenuron methyl is toxic to a wide range of terrestrial broadleaf species at l0% of the previous label rate and many of these species are important to wildlife for food and cover. Furthermore, given the limited information on its toxicity to aquatic plants, it must be assumed that the risk to aquatic plants is high.

No significant indirect effects on wildlife through habitat damage are forseen, providing the following conditions are met during applications:

1) Care should be taken that slough margins and other non-target areas are not sprayed.
2) No aerial application should be permitted.
3) As wildlife habitat and farmland overlap considerably in the prairies where this product will be used, spray drift should be avoided.

To ensure that these conditions are met, the following warning should be added to the label:

> OVERSPRAY OR DRIFT TO IMPORTANT WILDLIFE HABITATS SUCH AS SHELTERBELTS, WETLANDS, SLOUGHS OR DRY SLOUGH BORDERS, WOODLOTS, VEGETATED DITCH BANKS AND OTHER COVER ON THE EDGES OF FIELDS SHOULD BE AVOIDED. LEAVE A 15-METRE BUFFER ZONE BETWEEN THE LAST SPRAY SWATH AND THE EDGE OF ANY OF THESE HABITATS.