Regulatory Note REG99-03

Triflusulfuron-Methyl

The active ingredient triflusulfuron-methyl and its formulated product UPBEET® 50 DF Herbicide have been granted limited term registrations under section 17 of the Pest Control Products Regulations. The review of these products was facilitated under the Pest Management Regulatory Agency's (PMRA) User Requested Minor Use Registration (URMUR) program.

UPBEET® 50 DF is intended to be used for control of broadleaf weeds in sugar beets in southern Alberta and southwestern Ontario.

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

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Foreword

The review of the active ingredient triflusulfuron-methyl and UPBEET® 50 DF Herbicide, which are DuPont products, was facilitated under the PMRA's URMUR program because of the following features/rationale:

- Triflusulfuron-methyl will be used for weed management in sugar beets, a small hectarage crop grown mainly in southern Alberta and southwestern Ontario.
- Triflusulfuron-methyl has already been registered in the U.S. and major European countries.
- Triflusulfuron-methyl provides effective control of velvetleaf, the major problem weed in sugar beet fields in Ontario, and supplements control of kochia, a hard-to-control weed in the arid regions of the Prairie provinces.
- Canadian sugar beet growers will have access to a new chemistry, a Group 2 sulfonylurea product, which will support the weed resistance management objective by offering an alternative mode of action.

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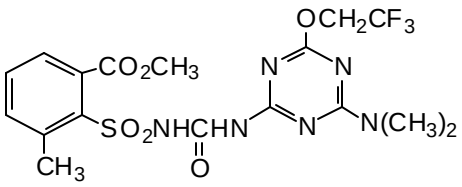
1.0 Product Chemistry

1.1 Identity of the active substance and preparation containing it

Active substance:	triflusulfuron-methyl
Function:	herbicide
Chemical name (International Union of Pure and Applied Chemistry):	methyl 2-[4-dimethylamino-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-ylcarbamoylsulfamoyl]-m-toluate
Chemical name (Chemical Abstracts Service [CAS]):	methyl 2-[[[[[4-(dimethylamino)-6-(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl]amino] carbonyl]amino]sulfonyl]-3-methylbenzoate
Other name:	DPX-66037
CAS Registry Number:	126535-15-7
Nominal purity of active:	97.9%
Identity of relevant impurities of toxicological, environmental and/or other significance:	Impurities of toxicological concerns are not expected to be present in the raw materials, nor are they expected to be generated during the manufacturing process.
Molecular formula:	$C_{17}H_{19}F_3N_6O_6S$
Molecular mass:	492.4
Structural formula:	

1.2 Physical and chemical properties of active substance

Table 1.1 Technical product: Triflusulfuron-Methyl (DPX-66037)

Property	Result	Comment
Colour and physical state	White crystalline solid	Not applicable (N/A)
Odour	Slight vinegar	N/A
Melting point/range	155–158°C	N/A
Boiling point/range	N/A	N/A
Density (g/mL)	1.45 absolute 0.56 (Bulk)	N/A
Vapour pressure	$<1 \times 10^{-7}$ mm Hg at 25°C.	A relatively non-volatile compound; low potential for losses due to volatilization.
UV/visible absorption spectrum in water	λ_{max} = 395 nm, absorption at $\lambda >$ 400 nm is not anticipated.	Potential to absorb sunlight in the UV/visible range of 290–400 nm.
Solubility in water at 25°C	pH — Solubility (parts per million [ppm]) 3 — 1.0 5 — 2.7 7 — 110 9 — 11 000	Low solubility at pH 3 and pH 5; soluble at pH 7; very soluble at pH 9. Solubility appears to increase with increasing pH.
Henry's law constant	$K = 4.123 \times 10^{-9}$ atm m^3/mole or $1/H = 5.83 \times 10^6$	This compound is non-volatile from moist soil and water surfaces.
Solvent solubility (mg/L)	Solvent — Solubility (mg/L) hexane — <0.0016 octanol — 0.026 toluene — 2.0 methanol — 7.0 ethyl acetate — 27 acetonitrile — 80 acetone — 120 chloroform — 160 methylene chloride — F580	N/A

Property	Result	Comment
Octanol/water partition coefficient (K_{ow})	pH / K_{ow} at 25°C 5 / 220 7 / 9.2 9 / 0.86	Low potential for bioaccumulation in biota.
Dissociation constant (pK_a)	pK_a = 4.4	This compound will dissociate and exist in its anionic form at most environmentally relevant pHs.
Stability (temperature, metals)	Not provided	N/A

Table 1.2 **End-use product:** UPBEET® 50 DF (DPX-66037 50DF)

Property	Result	Comment
Colour	Brown	N/A
Odour	Mild sweet odour	N/A
Physical state	Solid	N/A
Formulation type	Dry flowable granule	N/A
Guarantee	Triflusulfuron-methyl at 50%	N/A
Container material and description	Plastic jugs	N/A
Bulk density	560 kg/m^3	N/A
pH of 1% dispersion in water	8.3	N/A
Oxidizing or reducing action	Product does not contain oxidizing or reducing agents.	N/A
Storage stability	Stable. Supporting data were not provided.	N/A
Corrosive characteristics	Product is not corrosive to packaging material.	N/A
Explodability	The product is not potentially explosive.	N/A
Surfactants	Reax 80 Series (e.g., Reax 80C, 81A, 83A, 85A), sodium lignosulphonate, Aerosol OTB (sodium dioctyl sulfosuccinate) and Glacier 325 (magnesium silicate)	N/A

1.3 Details of uses and further information

Triflusulfuron is a sulfonylurea herbicide. Sulfonylureas are classified as Group 2 family of herbicides that inhibit acetolactate synthase. Triflusulfuron will be marketed as a 50% dry flowable (DF) product called UPBEET® 50 DF in 114 g plastic jugs. UPBEET® 50 DF may be used in combination with 0.25% volume per volume ratio (v/v) of a non-ionic adjuvant as a post-immergence application in sugar beets for control of velvetleaf. UPBEET® 50 DF may also be tank-mixed with 1.75–3.5 L/hectare (ha) (262–525 g active ingredient [a.i.]/ha) of BETAMIX (desmedipham 150 g/L + phenmedipham 150 g/L) for control of additional weeds such as redroot pigweed, lamb's quarters, kochia and green foxtail.

UPBEET® 50 DF is to be applied at 35–75 g/ha (17.5–35.0 g a.i./ha) alone or in combination with BETAMIX. More than one application of UPBEET® 50 DF may be made to the same crop, provided the total amount applied does not exceed 100.0 g/ha (50.0 g a.i./ha). UPBEET® 50 DF is to be applied by ground equipment only.

A buffer zone of 23 metres is required between the downwind edge of the boom and sensitive terrestrial habitats. A buffer zone of 10 metres is required from sensitive aquatic habitats. Sugar beets may be harvested 60 days (d) after the last application of UPBEET® 50 DF.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

An isocratic reversed phase high performance liquid chromatographic (HPLC) method was used for the determination of the active substance and a solvent gradient HPLC method was used to determine significant impurities (content $ 0.1%) in the technical product. The methods have been shown to have satisfactory specificity, sensitivity, linearity, precision and accuracy.

2.2 Method for formulation analysis

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

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

According to the U.S. Environmental Protection Agency (EPA), analysis of triflusulfuron-methyl (DPX-66037) could be determined by the U.S. Food and Drug Administration multi-residue method.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) for sugar beet raw agricultural commodities (RAC) was defined as parent only.

A specific method was developed for the analysis of triflusulfuron-methyl residues in sugar beets (roots and tops). Samples were extracted with 20% acetonitrile/80% ammonium carbonate, similar to the solvent used in the sugar beet metabolism study, i.e., 50/50 mixture of acetone/0.1 molar ammonium carbonate. Residues were analyzed by HPLC and ultra-violet detection. The limit of quantification (LOQ) and limit of detection (LOD) are 0.02 ppm, 0.005 ppm, respectively. Recoveries and independent laboratory validation supported the method for the analysis of triflusulfuron-methyl residues in sugar beets. The method appears suitable as an enforcement method.

2.3.3 Methods for residue analysis of food of animal origin

No analytical method was submitted for livestock. Based on the results of the goat metabolism, residues of triflusulfuron-methyl are unlikely to be detectable in meat, milk and eggs as a result of feeding sugar beet commodities. On this basis, an analytical method for the analysis of food of animal origin is not required.

3.0 Impact on human and animal health

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

3.1.1 Absorption, distribution, metabolism and excretion

Four groups of 5–6 rats/sex were treated by gavage with the following single doses of radiolabelled triflusulfuron-methyl: group 1, 25 mg/kg body weight (bw) [triazine(U-14C)]; group 2, 25 mg/kg bw unlabelled triflusulfuron-methyl for 14 days, then a single dose, 25 mg/kg bw [triazine(U-14C)]; group 3, 250 mg/kg bw [triazine(U-14C)]; and group 4, 250 mg/kg bw [ester carbonyl-14C]. Triflusulfuron-methyl is well absorbed by the gastrointestinal tract when administered orally, and is rapidly excreted (78–96% of the administered dose [AD] within 48 hours) in the urine and faeces. Female rats excreted more radioactivity in the urine than male rats, regardless of dose or preconditioning. Urinary excretion of radioactivity in females was lower after repeat low-dose administration than after a single low-dose administration. Faecal excretion was higher in the 250 mg/kg bw groups than in the 25 mg/kg bw groups. Parent compound was a major component of the radioactivity in the faeces of male and female rats treated at 250 mg/kg bw. Since no detectable parent compound was found in the 25 mg/kg bw groups, it appears that 250 mg/kg bw overwhelmed the absorptive capacity of the rats. Triflusulfuron-methyl was extensively metabolized (see proposed pathway, Figure

3.1) and similar metabolites were found in the faeces, urine and liver in different proportions. The metabolites identified were N-desmethyl triflusulfuron-methyl (in urine), N-hydroxymethyl triflusulfuron-methyl (in urine), triazine metabolites (triazine amine, N-desmethyl triazine amine, N,N-bis-desmethyl triazine amine) (in urine and liver), methyl saccharin (in liver), and the unchanged parent compound (in faeces and liver).

3.1.2 Acute and dermal toxicity—technical and formulation

Triflusulfuron-methyl was of low acute toxicity by the oral, dermal and inhalation routes. It was minimally irritating to the eyes and skin of rabbits. It was not a dermal sensitizer in guinea pigs.

Triflusulfuron-methyl technical was considered to be of low acute toxicity by the oral and inhalation routes in rats (lethal dose 50% [LD_{50}] > 5000 mg/kg bw; lethal concentration 50% [LC_{50}] > 5.1 mg/L), and of low acute toxicity by the dermal route to New Zealand White (NZW) rabbits (LD_{50} > 2000 mg/kg bw). It was minimally irritating when applied to the skin of NZW rabbits, and minimally irritating when instilled into the eyes of the same species. Results of skin-sensitization testing using guinea pigs, employing the Maximization test, were negative.

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

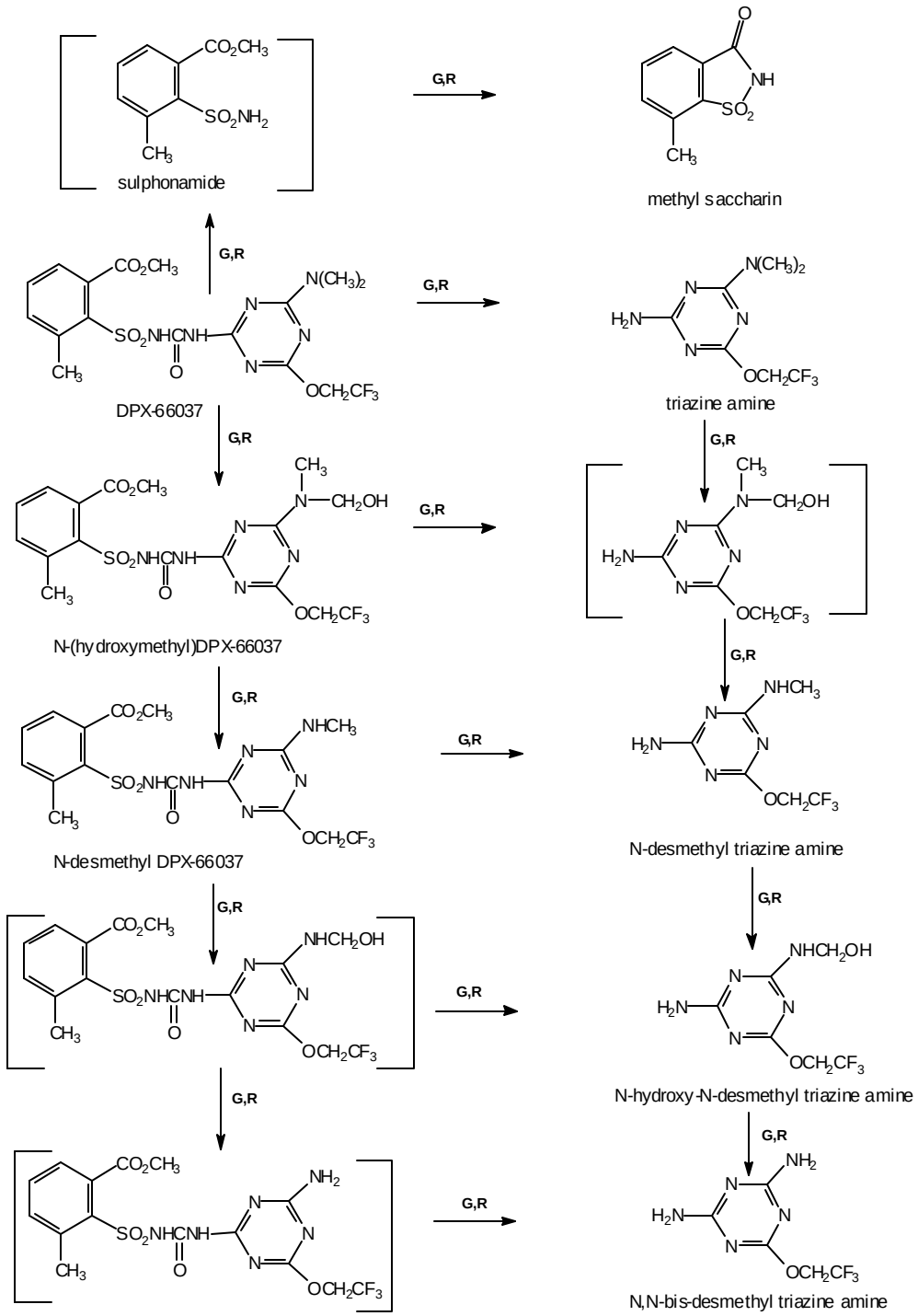
UPBEET® 50 DF Herbicide, containing 50% triflusulfuron-methyl, was considered to be of low acute toxicity by the oral (LD_{50} > 5000 mg/kg bw) and inhalation (LC_{50} > 6.1 mg/L) routes in rats and of low acute dermal toxicity in NZW rabbits (LD_{50} > 5000mg/kg bw). It was determined to be moderately irritating when instilled into the eyes of NZW rabbits (maximum average score of 28.32/110) and slightly irritating when applied to the skin of the same species (primary irritation score of 1/8). Results of skin sensitization testing using guinea pigs, employing the Maximization test, were negative.

Based on the evaluation of the acute toxicity data package on UPBEET® 50 DF Herbicide (DPX-66037), the signal words “WARNING - EYE IRRITANT” are recommended on the primary display panel.

Groups of five rabbits/sex were dermally exposed to a paste made of distilled water and 0, 50, 300, or 1000 mg/kg bw triflusulfuron-methyl (95.6% purity) for 21 days. No evidence of systemic toxicity was observed.

The no observed effect level (NOEL) for systemic toxicity was determined to be 1000 mg/kg bw/d, since there were no apparent signs of treatment-related systemic effects observed in male or female rabbits at any dose level tested.

Figure 3.1 Proposed metabolic pathways for triflusulfuron-methyl in the rat



3.1.3 Genotoxicity

A reverse mutation assay (Ames assay) was performed on *Salmonella typhimurium* strains TA98, 100, 1535, 1537, and 1538 with 62.5, 125, 250, 500 or 1000 micrograms (Fg)/plate DPX 66037 with and without metabolic activation. DPX 66037 was not mutagenic under the conditions of this test.

A Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase forward mutation assay was performed using 100, 500, 1000, 1500 or 2000 Fg/mL DPX 66037-24 with and without metabolic activation. DPX 66037 was not mutagenic under the conditions of this test.

A human lymphocyte cytogenetic assay was performed using 50, 100, or 200 Fg/mL DPX-66037-59 without metabolic activation, and 100, 200 or 400 Fg/mL DPX 66037-59 with metabolic activation. DPX 66037 was not clastogenic under the conditions of this test. This test was unacceptable due to technical difficulties with the cells and uncertainty regarding the test compound, which appeared to possess physical and biological properties that were different from the test compound used in other genotoxicity studies.

A human lymphocyte cytogenetic assay was performed using 0.5, 1.5, 1.7, 1.85, or 2.0 mg/mL DPX-66037-59 (98.7%) with and without metabolic activation. Cytotoxicity was observed at $1.85 mg/mL, indicated by a lower mitotic index than controls. Triflusulfuron-methyl, with metabolic activation, was clastogenic at 2.0 mg/mL under the conditions of this test.

A human lymphocyte cytogenetic assay was performed using 0.1–2.0 mg/mL DPX-66037-24 (95.6%) with and without metabolic activation. Cytotoxicity was observed at 2.0 mg/mL, indicated by a lower mitotic index than controls. Triflusulfuron-methyl, with metabolic activation, was clastogenic at $1.7 mg/mL in a dose-dependent manner under the conditions of this test.

An unscheduled deoxyribonucleic acid synthesis (UDS) assay was performed using 0.05–2.0 mg/mL DPX-66037-24 (95.6%) with primary rat hepatocytes. Cytotoxicity was observed at $1.5 mg/mL. Triflusulfuron-methyl did not induce UDS under the conditions of this test. This study was deemed unacceptable by the EPA because only 25 cells/culture were counted. The Organisation for Economic Co-operation and Development (OECD) guideline 482, which was the basis for this study, states that at least 50 cells/culture from two cultures should be counted.

Five Swiss OF1 mice/sex were treated by gavage with a single dose of 5000 mg/kg bw DPX-66037-59 (98.6%) in 0.5% methylcellulose. No clinical signs of toxicity were observed. Triflusulfuron-methyl did not induce micronuclei under the conditions of this test. This study was deemed unacceptable by the EPA because only two time points, 24 and 48 hours (h), were sampled. OECD guideline 474, which was the basis for this study, states that if only one dose is used, three time points must be tested.

Five Crl:CD-1(ICR)BR mice/sex were treated by gavage with doses of 1250 or 2500 mg/kg bw DPX-66037-24 and six mice/sex/groups were treated with 5000 mg/kg bw DPX-66037-24 (95.6%) in corn oil. Two males and one female in the high-dose group died within 48 hours of treatment. Clinical signs of toxicity were observed at all doses. Lethargy and abnormal gait persisted to 48 hours in the high-dose group, and lasted 24 hours in the low and mid-dose groups. Lower body-weight gain (bwg) than controls was also observed at the high dose. Triflusulfuron-methyl did not induce micronuclei under the conditions of this test.

3.1.4 Sub-chronic and chronic toxicity

The sub-chronic and chronic toxicity of triflusulfuron-methyl were investigated in mice (chronic only), rats and dogs. Ninety-day studies were conducted, which were used to establish appropriate dose levels to be used in the long-term studies.

3.1.4.1 Chronic toxicity in the mouse

Groups of 80 mice/sex were fed diets containing 0, 10, 150, 2500 or 7000 ppm DPX-66037-24 (95.6% purity) (equal to 1.37, 20.9, 349 or 1024 mg/kg bw/d for males, and 1.86, 27.7, 488 or 1360 mg/kg bw/d for females) for 18 months (mo).

The NOEL for this study was 150 ppm (20.9 mg/kg bw/d). Absolute and relative liver weights were increased in the males and females at $2500 ppm. Histopathological changes in the liver were also observed in males and females at $2500 ppm (foci of cellular alteration, intrahepatocellular hematopoesis, individual cell necrosis).

Triflusulfuron-methyl was not oncogenic under the conditions of this study.

3.1.4.2 Sub-chronic and chronic toxicity in the rat

Groups of 10 rats/sex were fed diets containing 0, 100, 2000, 10 000 or 15 000 ppm triflusulfuron-methyl (adjusted for 97.8% purity, sponsor later changed purity statement to 95.8%) (equal to 6.2, 127, 646 or 965 mg/kg bw/d for males and 7.54, 150, 774 or 1070 mg/kg bw/d for females) for 90 days. The NOEL for this study was 100 ppm (6.2 mg/kg bw/d). At doses $2000 ppm, lower body weight, body-weight gain, food consumption, feed efficiency, and regenerative hemolytic anemia were observed. Serum glucose and phosphate, and absolute heart weights were statistically significantly lower than controls, and relative heart weights were higher than controls at $10 000 ppm. Relative liver weights were increased in the males at 15 000 ppm and in the females at $2000 ppm, in spite of lower absolute liver weights in males at $10 000 ppm. Renal hemosiderosis was found in both sexes at $2000 ppm, which was due to the hemolytic anaemia. At 15 000 ppm in males, small testicles were observed grossly along with testicular atrophy/degeneration and oligospermia. Decreased absolute and increased relative kidney weights were found at $2000 ppm in males and $10 000 ppm in females. At 15 000 ppm in females, renal tubular epithelial cell atrophy was observed.

This study (HLR 528-92) was conducted using DPX-66037-59 synthesized by a cyanate process; the other 90-day rat study (HLR 523-90) used technical active synthesized by a carbamate process. The cyanate process is being registered for use in Canada, not the carbamate process. The objective of this study was to assess the short-term toxicity potential of the technical grade active ingredient (TGAI) produced by the cyanate process and compare it to that of the TGAI produced by the carbamate process. Groups of 10 rats/sex were fed diets containing 0, 100, 2000, 10 000 or 15 000 mg/kg bw DPX-66037-59 (adjusted for 97.8%) (equal to 6.56, 133, 658 or 1036 mg/kg bw/d for males and 7.71, 153, 783 or 1124 mg/kg bw/d for females) for 90 days. The NOEL for this study was 100 ppm (6.56 mg/kg bw/d). At doses of 2000 ppm and higher, lower body weight, body-weight gain, food consumption, feed efficiency, and regenerative hemolytic anaemia were observed. Relative liver weights were increased in the males and females at $10 000 ppm. Splenic extramedullary hematopoiesis was observed in males at $10 000 ppm and in females at $2000 ppm. Renal hemosiderosis was observed in males and females at $10 000 ppm, which was likely due to the hemolytic anaemia.

Groups of 62 rats/sex were fed diets containing 0, 10, 100, 750 or 1500 ppm DPX-66037-24 (95.6% purity) (equal to 0.406, 4.06, 30.6 or 64.5 mg/kg bw/d for males and 0.546, 5.47, 41.5 and 87.7 mg/kg bw/d for females) for 22 months. The NOEL for this study was 100 ppm (4.06 mg/kg bw/d). At $750 ppm, body weights and body-weight gains were lower than controls in both sexes and males had lower erythrocyte counts than controls at most time points and an increased incidence of Leydig cell hyperplasia compared to controls. The incidence of myelin/axonal degeneration of the sciatic nerve was increased compared to controls in the 1500-ppm group of females (25/48 versus [vs] 42/49).

Triflusulfuron-methyl was oncogenic in male rats under the conditions of this study, with an increased incidence of Leydig cell adenomas in the 750- and 1500-ppm groups compared to controls.

Possible mechanisms of Leydig cell tumour development induced by triflusulfuron-methyl were studied. Ten Crl:CD®BR male rats/group were treated by gavage for 15 days with 0, 1000, 1500 or 2000 mg/kg bw DPX-66037-24 (95.6% purity) in corn oil. An additional group of 10 control rats were pair-fed to the 2000 mg/kg bw group. Satellite groups of 10 rats treated with 0 or 2000 mg/kg bw DPX-66037 were given human chorionic gonadotropin (hCG) one hour before sacrifice. All treated groups had lower body weights and food consumption than controls. Absolute and relative weights of the prostate, seminal vesicles and coagulating glands were lower than controls. Serum estradiol was statistically significantly lower than controls. There were slight, but not statistically significant, increases in luteinizing hormone (LH), follicule-stimulating hormone (FSH) and prolactin in the treated groups compared to controls. In the rats treated with hCG, the 2000 mg/kg bw/d group had increased testosterone and lower estradiol than the controls.

In an in vitro study, ammonium perfluorooctanate-induced or phenobarbital-induced rat liver were exposed to levels of 0.01 to 0.5 micromolars (FM) DPX-66037-24 to measure aromatase activity, or to determine the cytochrome P450 binding spectra, respectively. There was a dose-dependent decrease in aromatase activity, starting at the lowest dose tested. The cytochrome P450 showed a type II binding spectra. Blood samples from the one-year sampling in the chronic study were retained for hormonal analysis. No statistically significant changes were observed; however, trends were seen at 750 and 1500 ppm toward increased testosterone and FSH and decreased estradiol.

Isolated Leydig cells from 11-week old male rats were exposed to 0, 0.1, 0.5, 1.0, 10, 100 or 1000 FM DPX-66037-24 for two hours. Three cultures from each dose were then exposed to two international units of hCG. No effect on hormone levels was observed in the hCG-treated cultures. In the triflusulfuron-methyl-only cultures, testosterone was significantly increased (198%) compared to controls, and estradiol was decreased. Triflusulfuron-methyl appears to inhibit the conversion of testosterone to estradiol by aromatase in vitro; the in vivo results are inconclusive.

3.1.4.3 Sub-chronic toxicity in the dog

Groups of five beagle dogs/sex were fed diets containing 0, 35, 875, or 3500 ppm DPX-66037-59 (95.6% purity) (equal to 1.0, 26.9 or 95.5 mg/kg bw/d for males, and 1.2, 27.7 or 95.5 mg/kg bw/d for females) for 90 days. The NOEL for this study was 875 ppm (26.9 mg/kg bw/d). At 3500 ppm, lower body weight, body-weight gain and slight decreases in hematology parameters (erythrocytes, hemoglobin, hematocrit) were observed. Absolute and relative (to body and brain) liver weights were increased in the males and females at 3500 ppm. Minimal centrilobular hepatocellular hypertrophy was observed in 3/4 males and 2/4 females at the high dose. One male and one female in the 3500 ppm group were sacrificed moribund, the deaths did not appear to be treatment-related.

3.1.5 Reproductive and developmental toxicity

Groups of 30 rats/sex were fed diets containing 0, 10, 100, 750 or 1500 ppm DPX--6037-24 (95.6% purity) (equal to 0.588, 5.81, 44.0 or 89.5 mg/kg bw/d for males and 0.764, 7,75, 58.0 or 115 mg/kg bw/d for females) for a two-generation (one litter/generation) reproduction study. The NOEL for systemic toxicity was 100 ppm (5.81 mg/kg bw/d). At $750 ppm, body weights and body-weight gains were lower than controls in both sexes during the premating periods of both generations. Body weights, but not body-weight gains were statistically significantly lower than controls in the 750 ppm and higher groups during gestation and lactation. The no observed adverse effect level (NOAEL) for reproductive toxicity was 750 ppm (44.0 mg/kg bw/d) based on lower F1 male pup body weights on day 14 at that dose, and in both sexes on days 14 and 21 at 1500 ppm.

Groups of 25 mated female rats/group were treated by gavage with 0, 30, 120, 350 or 1000 mg/kg bw DPX-66037-24 (95.6% purity) on days 7–16 of gestation. The NOEL for maternal toxicity was 120 mg/kg bw/d. At $350 mg/kg bw/d, body weights and body-weight gains were lower than controls during the treatment period. Food consumption was also lower than controls in the 350 and 1000 mg/kg bw/d groups. The NOEL for developmental toxicity was 120 mg/kg bw/d based on delayed ossification at $350 mg/kg bw/d.

There was no evidence of any teratogenic effects related to treatment with triflusulfuron-methyl at any dose level tested.

Groups of 20 artificially inseminated female rabbits were treated by gavage with 0, 15, 90, 270 or 800 mg/kg bw/d DPX-66037-24 (95.6% purity) on days 7–19 of gestation. The NOEL for maternal toxicity was 15 mg/kg bw/d. At $90 mg/kg bw, body-weight gains were lower than controls at the beginning of the treatment period. Clinical signs of toxicity were observed at $270 mg/kg bw/d (stool absent or reduced, small stool), abortions and evidence of gastrointestinal effects were found at gross necropsy (ulceration of gastric mucosa, gaseous distension). Food consumption was also lower than controls in the 270 and 800 mg/kg bw/d groups. At 800 mg/kg bw/d, there was also increased mortality (9/20 vs 0/20 in controls). The NOEL for developmental toxicity was 90 mg/kg bw/d based on abortions at $270 mg/kg bw/d.

There was no evidence of any teratogenic effects related to treatment with triflusulfuron-methyl at any dose level tested.

3.1.6 Neurotoxicity (acute, delayed and sub-chronic)

Ten Crl:CD®BR rats/sex/group were treated with a single gavage dose of 0, 500, 1000 or 2000 mg/kg bw DPX-66037-24 (95.6% purity) in 0.5% methylcellulose. Behavioural examinations (functional observational battery [FOB] and motor activity) were performed the week before treatment, two hours after treatment (day 1) and on days 2, 8 and 15. Six rats/sex/dose were anaesthetized and perfusion fixed for examination of the nervous system. The remaining rats were sacrificed and examined grossly.

The NOAEL for this study was 2000 mg/kg bw, the highest dose tested. At this dose, body weight, body-weight gain and food consumption in the 2000 mg/kg bw males was lower than controls on days 1 and 2. The changes were slight and only statistically significant for food consumption. No evidence of neurotoxicity was observed at any dose.

Data on delayed neurotoxicity have not been generated, and are not considered relevant for compounds such as triflusulfuron-methyl.

Eleven Crl:CD®BR rats/sex/group were fed diets containing 0, 100, 750, 1500 or 3000 ppm DPX-66037-24 (95.6% purity) (equal to 6.1, 46.1, 92.7 or 186.2 mg/kg bw/d) for 92 days.

Behavioural examinations (FOB and motor activity) were performed before treatment, and on weeks 4, 8 and 13. Six rats/sex/dose were anaesthetized and perfusion fixed for examination of the nervous system. The remaining rats were sacrificed and examined grossly.

The NOEL for this study was 100 ppm (6.1 mg/kg bw/d). At $750 ppm, body weight, body-weight gain and food consumption in females was lower than controls. Similar effects were observed in males at 3000 ppm. No evidence of neurotoxicity was observed at any dose.

3.1.7 **Overall toxicological summary** (refer to Appendix I)

A detailed review of the toxicity data base available for the new herbicide triflusulfuron methyl has been completed. Data submitted were complete and well presented, and included the full battery of studies required for registration purposes. Studies were well conducted and conformed with acceptable international testing protocols.

Triflusulfuron-methyl is well absorbed by the gastrointestinal tract when administered orally, and is rapidly excreted (78–96% of the AD within 48 h) in the urine and faeces. Female rats excreted more radioactivity in the urine that male rats, regardless of dose or preconditioning. Faecal excretion was higher in the 250 mg/kg bw groups than the 25 mg/kg bw group and parent compound was a major component of the radioactivity. No detectable parent compound was found in the 25 mg/kg bw groups, suggesting that 250 mg/kg bw overwhelmed the absorptive capacity of the rats. Triflusulfuron-methyl was extensively metabolized (see proposed pathway, Figure 3.1) and similar metabolites were found in the faeces, urine and liver in different proportions. The metabolites identified were N-desmethyl triflusulfuron-methyl (in urine), N-hydroxymethyl triflusulfuron-methyl (in urine), triazine metabolites (triazine amine, N-desmethyl triazine amine, N,N-bis-desmethyl triazine amine) (in urine and liver), methyl saccharin (in liver), and the unchanged parent compound (in faeces and liver).

Triflusulfuron-methyl technical was of low acute toxicity by the oral, dermal and inhalation routes. It was minimally irritating to the eyes and skin of rabbits. It was not a dermal sensitizer in guinea pigs.

UPBEET® 50 DF Herbicide, containing 50% triflusulfuron-methyl, was considered to be of low acute toxicity by the oral and inhalation routes in rats and of low acute dermal toxicity in NZW rabbits. It was determined to be moderately irritating when instilled into the eyes of NZW rabbits and slightly irritating when applied to the skin of the same species. UPBEET® 50 DF was not a skin sensitizer in guinea pigs.

Repeated short-term oral administration of triflusulfuron-methyl technical to rats (90 d) and dogs (1 year [yr]) resulted primarily in a regenerative hemolytic anemia (rats), liver effect (dogs) and lower body weights. The NOELs were 6.2 mg/kg bw/d in rats based on lower body weights and regenerative hemolytic anemia at the lowest observable effect level (LOEL)

of 127 mg/kg bw/d, and 26.9 mg/kg bw/d in dogs based on lower body weights, slight anemia and centrilobular hepatocellular hypertrophy.

In long-term rodent dietary studies, the NOEL for chronic (18-mo) systemic toxicity in mice was 20.9 mg/kg bw/d, based on increased absolute and relative liver weights along with histopathological changes in the liver at the LOEL of 349 mg/kg bw/d. Triflusulfuron was not oncogenic in the mouse. The NOEL for chronic (2-yr) systemic toxicity and oncogenicity in rats was 4.06 mg/kg bw/d, based on lower body weight and erythrocyte counts, and an increased incidence of Leydig cell tumours (adenomas) in males at $30.6 mg/kg bw/d. A study was performed that attempted to determine the mechanism of tumour formation. The results indicated that triflusulfuron-methyl appears to inhibit the conversion of testosterone to estradiol by aromatase in vitro, the in vivo results are inconclusive. Disruption of the hypothalmic-pituitary-testicular (HPT) axis is a well-recognized mechanism of Leydig cell adenoma formation in the rat by non-genotoxic compounds. Aromatase inhibition is one of the established mechanisms of disruption. A threshold for this effect exists; doses that do not disrupt the HPT axis should not cause tumours. The relevance of these tumours to humans is questionable, as they are extremely rare in humans.

Triflusulfuron-methyl was adequately tested for genotoxicity in a range of in vitro and in vivo assays. It was not mutagenic in mammalian or microbial systems under the conditions of the studies. It was genotoxic in mammalian in vitro chromosomal aberrations assays (same assay performed twice), but not in a mammalian in vivo assay.

In a rat reproduction study (2-generation, 1 litter/generation), the NOEL for systemic (parental) toxicity was 5.81 mg/kg bw/d based on lower body weights and food consumption. The NOEL for reproductive toxicity was 44 mg/kg bw/d (750 ppm) based on lower pup body weights and histopathological effects on the cerebellum consistent with undernutrition (decreased cellularity in the internal granular layer and increased cellularity in the external germinal layer) in the 2500 ppm group. In the rat developmental toxicity study, the NOEL for maternal toxicity was 120 mg/kg bw/d (based on reduced body-weight gain during dosing period at 350 and 1000 mg/kg bw/d) and for developmental toxicity was 120 mg/kg bw/d (based on delayed ossification). There was no evidence of teratogenicity. In the rabbit developmental toxicity study, the NOEL for maternal toxicity was 15 mg/kg bw/d based on decreased body-weight gain during the treatment period at $90 mg/kg bw/d and clinical signs of toxicity at 270 mg/kg bw/d. The NOEL for developmental toxicity was 90 mg/kg bw/d, based on abortions at $270 mg/kg bw/d. There was no evidence of any teratogenic potential of triflusulfuron-methyl in the rabbit up to 800 mg/kg bw/d.

Table 3.2 Summary of the sub-chronic and chronic toxicity studies with triflusulfuron- methyl

Type of study	Species	NOEL/NOAEL (mg/kg bw/d)
Oral route, 90 d	rats	6.2 in males, 7.54 in females
Oral route, 90 d	rats	6.56 in males, 7.71 in females
Dermal route, 21 d	rabbit	1000 for both sexes
Oral route, 1 yr	dogs	26.9 for males, 27.7 for females
Oral route, 22 mo	rats	4.06 for males, 5.47 for females
Oral route, 18 mo	mice	20.9 for males, 27.7 for females
Multi-generation	rats	Systemic: 5.81 for males, 7.75 for females Reproductive: 44 for males, 58 for females Maternal, fetotoxic: 120 Teratogenic: 1000
Teratogenicity	rats	Maternal: 15 Fetotoxic: 90
Teratogenicity	rabbits	Teratogenic: 800 Systemic, neurotoxic: 2000 for both sexes Systemic: 6.1
Acute oral neurotoxicity	rats	Neurotoxic: 188
Neurotoxicity, 13 wk	rats	

3.2 Determination of acceptable daily intake

The lowest NOEL was 100 ppm, equal to 4.06 mg/kg bw/d, established in the two-year rat feeding study, based on lower body weight and erythrocyte counts, and an increased incidence of Leydig cell tumours (adenomas) in males at $30.6 mg/kg bw/d. This is considered an appropriate study for determination of the acceptable daily intake (ADI), since there was evidence of treatment-related oncogenicity in rats.

For the calculation of the ADI, a safety factor (SF) of 100 is proposed.

The ADI proposed is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOEL}}{\text{SF}} = \frac{4.06 \text{ mg/kg bw/d}}{100} = 0.04 \text{ mg/kg bw/d of triflusulfuron-methyl}$$

The maximum acceptable intake for a 60-kg person, calculated according to the formula, ADI × 60 kg, is 2.4 mg/d.

This provides a margin of exposure (MOE) of 765 for the Leydig cell tumours observed in male rats. This ADI applies to triflusulfuron-methyl produced by either the carbamate or cyanate process.

3.3 Acute reference dose

Acute toxicity was observed in the rabbit teratology study. Thus, the findings observed in this study are used in the determination of the acute reference dose (ARfD). The NOEL for acute effects was 90 mg/kg bw/d. Clinical signs of toxicity were observed at $270 mg/kg bw/d (stool absent or reduced, small stool), abortions and evidence of gastrointestinal effects were found at gross necropsy (ulceration of gastric mucosa, gaseous distension). At 800 mg/kg bw/d, there was also increased mortality (9/20 vs 0/20 in controls). Three of the rabbits died during the treatment period, the remaining six died post-dosing.

For the calculation of the ARfD, a SF of 100 is proposed.

The ARfD proposed is calculated according to the following formula:

$$\text{ARfD} = \frac{90 \text{ mg/kg bw/d}}{100} = 0.9 \text{ mg/kg bw/d of triflusulfuron-methyl}$$

3.4 Toxicology endpoint selection for occupational and bystander risk assessment

The formulation is considered to be of low acute toxicity by the oral, inhalation and dermal routes. It is a slight skin irritant and a moderate eye irritant. Results of skin sensitization studies were negative.

Given the short-term nature of the exposure for farmers (one to two days per year), and the predominantly dermal exposure route, a dermal toxicity study is considered to be the most relevant to use in the risk assessment. A 21-day dermal rabbit study with triflusulfuron-methyl technical was well conducted and did not demonstrate any systemic toxic effects at 1000 mg/kg bw/d, the highest dose tested.

Although a NOEL for oncogenicity of 4.06 mg/kg bw/d was found in the chronic study in rats, based on an increased incidence of Leydig cell tumours (adenomas) in males at $30.6 mg/kg bw/d, it was concluded that it should pose no carcinogenic hazard to humans provided the dose is below the threshold concentration required to disrupt the HPT axis. The HPT axis is a well-recognized mechanism of Leydig cell adenoma formation in the rat by non-genotoxic compounds. The relevance of these tumours to humans is also questionable, as they are extremely rare in humans.

Triflusulfuron-methyl was adequately tested for genotoxicity in a range of in vitro and in vivo assays. The weight of evidence in the genotoxicity assays (in vitro and in vivo) suggested that triflusulfuron-methyl was not mutagenic.

There was no evidence of reproductive, teratogenic or neurotoxic effects.

3.5 Drinking water limit

See Section 4.2.

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

Two different manufacturing methods have been used to produce technical triflusulfuron-methyl. The carbamate process was used to produce lot DPX-66037-24, which was used for most of the toxicity studies, including the long-term studies. An improved cyanate process (lot DPX-66037-59) was developed and is the method that will be used for the commercial production of triflusulfuron-methyl for use in Canada. The cyanate method results in greater purity (97.8%) for the technical than the carbamate method (95.8%). Two 90-day rat studies were performed with technical triflusulfuron-methyl, one with each manufacturing process, and demonstrated that there is no change in toxicity. Since the 90-day studies had very similar results, the toxicity database generated with the TGAI produced by the carbamate method is acceptable to support the registration of triflusulfuron-methyl produced by the cyanate method. A comparison of the impurities produced by the two processes revealed one impurity resulting from the cyanate method not found with the carbamate method. The acute studies and mutagenicity studies along with the 90-day study all using the cyanate process technical active do not indicate any toxicological concerns for this impurity.

3.6.1 Operator exposure and risk assessment

A farmer applying UPBEET® 50 DF by ground equipment would typically treat 45 ha/d and be exposed for one or two days per season.

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

To estimate total dermal and inhalation exposure for groundboom application, appropriate subsets of A and B grade data were created from the mixer/loader and from the applicator PHED database files. There were no relevant data available in the mixer/loader/applicator database file. The mixer/loader file was subset for open mixing, dry-flowable formulations and

to exclude replicates for packaging in water-soluble packets. The applicator file was subset for application by groundboom tractor or truck with open cabs. The number of replicates for inhalation and dermal data were acceptable (range 16–40). In the PHED subsets, the mean and range of pesticide mixed and applied and the sampling time were of the same order of magnitude as the estimated 1.6 kg a.i./d handled by a farmer treating 45 ha with 35 g ai/ha in an eight-hour work day.

Protective clothing specified on the label for mixer/loaders are waterproof gloves, long- sleeved shirt, long pants, shoes and socks for mixing/loading/clean up and repair operations. Exposure was estimated for mixer/loaders wearing long pants, long-sleeved shirts and gloves, and for applicators wearing long pants, long-sleeved shirts and no gloves. PHED Version 1.1 uses actual data and does not assume clothing penetration factors.

All data were normalized for kilograms per active ingredient handled. Exposure estimates are presented on the basis of the "best-fit" measure of central tendency, i.e., on summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part (arithmetic mean if normal distribution, geometric mean if lognormal distribution, median if any other distribution). Exposure estimates and MOE calculations were based on farmers mixing/loading and applying UPBEET® 50 DF at 35 g a.i./ha to 45 ha/d, on a few days per growing season. Custom applicators were not considered in this assessment, as it has been noted that the vast majority of herbicide applications to sugar beets are performed by farmers. Exposure was predominantly dermal.

Although PHED does not include data from which to estimate exposure during cleanup/repair activities, PHED data provide an adequate basis for estimating occupational exposure for the proposed use.

Table 3.3 Estimated operator exposure and resulting margins of exposure

Operator Exposure Scenario		**Daily exposure (dermal + inhalation) 70 kg operator (mg/kg bw/d)**	**MOE (NOEL/ exposure)**
Application at 35 g a.i./ha. Mixer/loaders wearing long pants, long- sleeved shirts and gloves. Applicators wearing long pants, long- sleeved shirts and no gloves.	Farmer: Mixer/loader/ applicator treating 45 ha	0.005	200 000[a]

[a] Based on a NOEL of 1000 mg/kg bw/d from a 21-day dermal rabbit study.

The MOE, calculated on the basis of typical Canadian use patterns, is acceptable for farmers.

3.6.2 Bystanders

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

3.6.3 Workers

Data are not available to make a quantitative estimate of re-entry exposure. However, the proposed use pattern is such that re-entry exposure should be minimal. Workers may re-enter treated fields to perform monitoring tasks such as scouting; however, these tasks would involve little foliar contact and thus minimal exposure and risk.

4.0 Residue

4.1 Definition of the residues relevant to maximum residue limits

4.1.1 Definition of the residues in sugar beet relevant to maximum residue limits

Sugar beet metabolism

In a field study, sugar beets were treated post-emergence with ^{14}C-triflusulfuron-methyl. The test compound was applied by spraying at a rate equivalent to 1.9× the proposed rate, in a 50% dry flowable formulation with a surfactant.

The concentration of total radioactivity in sugar beets declined rapidly. Total radioactive residues (TRRs) in whole plants ranged from 4.10–4.98 ppm at day 0 and at 56 days post-treatment (preharvest interval [PHI] 60 d), TRRs in sugar beet roots and tops ranged from <0.01–0.038 ppm, and 0.07–0.28 ppm, respectively. At 56 days, the parent and metabolites in the roots were all less than 0.01 ppm. While in tops, the parent and metabolites ranged from <0.01–0.06 ppm. By maturity (199-d post-treatment), residues of the parent and metabolites were all less than 0.01 ppm in roots and tops.

Since the parent and metabolites were less than 0.01 ppm in roots at 56 days (PHI 60 d) and all processed commodities (sugar, molasses, dried pulp) are derived from this matrix, the ROC for sugar beets was defined as parent only.

Confined crop rotation

In a confined rotational crop study, ^{14}C-triflusulfuron-methyl was applied to a sandy loam soil at a rate of 100 g a.i./ha (1.9× proposed Canadian good agricultural practice). Wheat (group 15), beet root (red beet, group 1), and lettuce (group 4) were sown 30, 120, and 300 days post-application and grown to maturity.

Residues were not translocated into the edible portions of plants to any appreciable extent. TRRs in wheat grain, beet root "root" and lettuce ranged from <0.01–0.03 ppm, <0.01–0.02 ppm, and <0.01–0.04 ppm, respectively.

Residues in matrices that can be used as animal feeds were significantly higher. At the 30-day plant-back interval, TRRs in wheat forage, straw and beet root foliage ranged from 0.07–0.27 ppm, 0.30–1.39 ppm and 0.02–0.22 ppm, respectively. Analysis of these fractions revealed the presence of several metabolites that ranged from 0.03–0.26 ppm.
In order to ensure that potential residues in meat, milk and eggs would not be detectable if wheat forage, straw and beet root foliage were fed to livestock, it was concluded that a 120-day plant-back interval should be placed on the label for all rotation crops.

Environmental chemistry and fate

Environmental chemistry and fate studies indicated that biotransformation and hydrolysis in soil and water were the major transformation processes for triflusulfuron-methyl.

In a soil study conducted in the laboratory under aerobic conditions, triflusulfuron-methyl was shown to be non-persistent with a half-life of 50 days. This result was confirmed in a field study, in which a half-life of approximately three days was achieved.

Triflusulfuron-methyl was shown to have half-lives of 3.7 days, 32 days, and 36 days at pH 5, pH 7, and pH 9, respectively, indicating that hydrolysis was a major route of transformation of triflusulfuron-methyl.

The results of the environmental chemistry fate studies indicated triflusulfuron-methyl was readily broken down in the environment. The metabolites resulting from abiotic and biotic transformation of triflusulfuron-methyl were the same as those seen in the plant and animal metabolism studies.

Storage stability

All sugar beet samples were stored at -20ºC and analyzed within eight months. Storage stability data indicated that triflusulfuron-methyl was stable for periods of up to 18 months when stored frozen at -20ºC.

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

When two lactating goats were dosed orally with ^{14}C-triflusulfuron-methyl (DPX-66037) for five consecutive days at a 10 ppm feeding level, a majority of the total radioactive dose (75–95%) was excreted in the urine and faeces. Maximum TRRs in milk, kidney, liver, and muscle were 0.09 ppm, 0.66 ppm, 0.61 ppm, and 0.17 ppm, respectively. In addition to the parent, N-desmethyl triazine amine, N,N-bisdesmethyl triazine amine, triazine amine, and methyl saccharin were identified as the metabolites. N-desmethyl DPX-66037 was identified as a minor metabolite.

The metabolism of triflusulfuron-methyl in the rat was essentially the same as in the goat. Triflusulfuron-methyl was extensively metabolized and similar metabolites were found in the faeces, urine and liver in different proportions. The metabolites identified were N-desmethyl DPX-66037 (urine), N-hydroxymethyl DPX-66037 (urine), triazine amine, N-desmethyl triazine amine, and N,N-bisdesmethyl triazine amine (urine and liver), methyl saccharin (liver), and the unchanged parent compound (faeces and liver).

The anticipated residue levels in treated sugar beet are expected to be under the LOQ. TRRs in all edible livestock commodities were <0.005 ppm when extrapolated from the 500× feeding level (10 ppm) to the anticipated 1× feeding level (0.02 ppm); therefore, an animal feeding study was not required. Maximum residue limits (MRLs) are not required for meat, milk and eggs.

4.2 Residues relevant to consumer safety

The results of supervised residue trials conducted in the U.S. (from zones common to the U.S. and Canada) and Europe indicated that when sugar beet was treated with triflusulfuron-methyl at 0.9–8× the proposed rate, and harvested 7–160 days (PHI 60 d), residues of triflusulfuron-methyl in sugar beet foliage and roots were less than the LOQ (0.02 ppm).

In a processing study, there was no concentration of triflusulfuron-methyl residues in sugar, molasses or dried pulp at an application rate equivalent to 8× the proposed rate.

The potential exposure of consumers to triflusulfuron-methyl residues through dietary intake is very low. At the proposed recommended application rate of 52.5 g a.i./ha/season, residues of triflusulfuron-methyl are not expected to exceed 0.02 ppm in sugar beets (roots) and processed commodities. A proposed MRL of 0.05 ppm (harmonized with that supported by the EPA) was used for sugar beets (roots). Consumption statistics were used based on the Apparent per Capita Domestic Consumption of Food in Canada, 1996, and the U.S. Department of Agriculture Continuing Survey of Food Intakes by Individuals, 1996. Using these data, the potential daily intakes (PDI) were calculated for adults, infants and children and the PDIs were all below 1.0% of the ADI allotted to food. Ten percent of the ADI was allotted to drinking

water. The ADI was 0.04 mg/kg bw, based on a NOEL of 4.06 mg/kg bw/d in the two-year rat study with a SF of 100.

4.3 Residues relevant to worker safety

N/A

4.4 Proposed maximum residue limits and compliance with existing maximum residue limits

4.4.1 Compliance with existing residue limits

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

4.4.2 Proposed maximum residue limits

On the basis of the results of supervised trials carried out in the U.S. and Europe, when sugar beets are treated with triflusulfuron-methyl according to the proposed label directions, the residues of triflusulfuron-methyl are not expected to exceed 0.02 ppm. The EPA proposed a tolerance of 0.05 ppm in sugar beet root and top. In the spirit of harmonization, a MRL of 0.05 ppm for sugar beet (root) has been proposed for promulgation in Division 15, Table II of the Food and Drugs Regulations.

Since the anticipated residue levels in treated sugar beet commodities were under the LOQ, an animal feeding study was not required. MRLs would not be needed for meat, milk and eggs.

Codex Alimentarius has not reviewed triflusulfuron-methyl.

5.0 Fate and behaviour in the environment

5.1 Interpretation of physico-chemical properties

Triflusulfuron-methyl is soluble to very soluble in water at environmental-relevant pH. Based on the solubility and pK_a, triflusulfuron-methyl has the potential for mobility in soil and transport in surface run-off water. Triflusulfuron-methyl will not be volatile from moist soil or water surfaces, and has a low potential to bioaccumulate.

5.2 Fate and behaviour in soil

5.2.1 Phototransformation in soil

The phototransformation half-life of ^{14}C-triflusulfuron-methyl exposed to artificial light on sandy loam soil was 13 days. Similarly, the half-life on soil kept in darkness was also 13 days. Triflusulfuron-methyl was relatively unstable in soil as recovery of the parent compound from day 0 samples was 87–89% applied radioactivity (AR). As the difference between the half-lives for irradiated and dark samples was insignificant, phototransformation is not a major route of transformation of triflusulfuron-methyl. Of a total of 17 transformation products that were detected in both triazine- and ester-labelled triflusulfuron-methyl on irradiated soils, there were four that would be considered as major products: triazine amine (11.8% AR), methyl saccharin (11.7% AR), and N-desmethyl triazine urea (13.5% AR) and N-desmethyl DPX-66037 (12.2%). Triazine amine (47.5% AR) and methyl saccharin (62.4% AR) were also detected in samples kept in the dark.

5.2.2 Aerobic soil biotransformation

^{14}C-triflusulfuron-methyl transformed in a United Kingdom (U.K.) soil (Somersham sandy loam soil, pH 7.8) under aerobic conditions with an initial period required for 50% dissipation (DT_{50}) of six days. Transformation was biphasic with a second DT_{50} of 170 days. Only small amounts (<3% AR by 60 days after treatment [DAT]) of triflusulfuron-methyl may be present at the beginning of the following growing season. The total CO_2 released was 37% AR by 270 days. Based on the DT_{50} in soil, however, triflusulfuron-methyl is non-persistent in soil under aerobic conditions, and microbial transformation is a major route of dissipation. Triflusulfuron-methyl was relatively unstable as recovery of the parent compound from day 0 samples was 86–87% AR. The major transformation products were N,N-bis-desmethyl triazine amine, N-desmethyl triazine amine (23.4% AR at 368 DAT), triazine amine, and methyl saccharin (19.9% AR at 368 DAT). N,N-bis-desmethyl triazine amine was detected at 10–13% AR at 14, 120, and 270 DAT, but no pattern of accumulation was evident. Triazine amine was detected at a maximum of 55.2% AR at 21 DAT, but had decreased to 6.6% AR by 368 DAT.

The initial, rapid transformation of triflusulfuron-methyl was due to cleavage of the sulfonylurea bridge to produce triazine amine and methyl saccharin, followed by microbial transformation of these compounds to subsequent products. The half-lives of triazine amine and methyl saccharin were estimated, by the author of the study report, to be 40 days and 50 days, respectively. At the end of the 368-day study period, 26–41% and 38–65% AR was present in soil as extractable and bound residues, respectively. There may be a potential for carry-over of N-desmethyl triazine amine and methyl saccharin to the next growing season.

^{14}C-triflusulfuron-methyl was also non-persistent in a second study of aerobic biotransformation in Somersham sandy loam soil, with a DT_{50} of seven days. Approximately 3.7% AR remained as triflusulfuron-methyl by 30 days. The major transformation products detected were N-

desmethyl triazine amine (25.2% AR by 30 d) and triazine amine (28.5% AR by 30 d). At the end of the 30-day incubation period, 30–33% AR was present in soil as bound residues.

The following was referenced in a monograph, which was provided by the applicant, summarizing the environmental fate, metabolism and residues of triflusulfuron-methyl: "The rate of degradation of DPX-66037 was also determined in four more soils under aerobic conditions using the triazine ring-labelled DPX-66037 at a concentration of 0.07 ppm at 20°C. The effects of soil moisture, temperature, and application rate on the rate of degradation was studied for one of the four soils. The DT_{50} was in the range of 6 to 14 days. The DT_{50} of [triflusulfuron-methyl] was not influenced by lowering the application rate" . . . "or by reducing the soil moisture content (from 42.5% to 21% maximum water capacity). However, the DT_{50} was substantially increased (from 6 to 17 days) when the incubation temperature was reduced to 10°C."

5.2.3 Anaerobic soil biotransformation

^{14}C-triflusulfuron-methyl transformed in a U.K. soil (Somersham sandy loam soil) under anaerobic conditions with a half-life of 21 days. By day 62, 4–7% AR remained as parent compound. Triflusulfuron-methyl would be classified as slightly persistent in soil under flooded conditions. The major transformation products were triazine amine and methyl saccharin, due to cleavage of the sulfonylurea bridge. Unlike the aerobic soil transformation study, further transformation of these compounds did not occur, indicating that they are relatively stable under anaerobic conditions.

5.2.4 Field soil dissipation studies

The following information was considered as supplementary data.

The dissipation/accumulation of ^{14}C-triflusulfuron-methyl technical material was studied in a silt loam and a clay soil in stainless steel cylinders under field conditions at sites in Kimberly, Idaho, and Fargo, North Dakota, respectively, at an application rate of 95 g a.i/ha. ^{14}C-triflusulfuron-methyl was non-persistent in soil with a DT_{50} value of approximately 3 days at both sites, and was below the LOQ by 14 DAT at a soil depth of 0–15 cm. ^{14}C-triflusulfuron-methyl may have been mobile under the conditions of this field study as the parent compound was detected, but not quantifiable, in soil samples from a depth of 15–35.5 cm from 14–280 DAT. At the end of 14 days, the parent compound could not be detected at either site. Bound residues were not reported.

The major transformation products were methyl saccharin, triazine amine, N-desmethyl triazine amine, and N,N-bis-desmethyl triazine amine. The major pathway of transformation of ^{14}C-triflusulfuron-methyl was hydrolytic cleavage of the sulfonylurea bridge followed by microbial transformation of methyl saccharin and the triazine moieties. There is a possibility of carry-over of the transformation products, methyl saccharin and triazine amine, to the next growing season.

5.2.5 Mobility: Adsorption/desorption

^{14}C-triflusulfuron-methyl was weakly adsorbed on five soils, two sandy loam, a silty clay, a silt loam, and a loamy sand. Adsorption coefficients (K_D) ranging from 0.36 to 1.28 (organic carbon adsorption coefficients [$K_{oc(D)}$] of 25 to 132) indicate that triflusulfuron-methyl is highly to very highly mobile in sandy loam soils, and very highly mobile in silty clay, silt loam, and loamy sand soils. Triflusulfuron-methyl transformed rapidly during the adsorption phase. One major transformation product, methyl saccharin, was detected. The total recovery of radiolabelled material from test vessels and soil slurries ranged from 94.9 to 102.5% AR.

The soil adsorption of the major transformation products of triflusulfuron-methyl (triazine amine, N-desmethyl-triazine amine, bis-N-desmethyl-triazine amine and methyl saccharin) was determined with the same soils as the parent compound. Adsorption of methyl saccharin was weak in two of the soils, Portneuf silt loam and Speyer 2.2 loamy sand, and an adsorption coefficient could not be determined. The $K_{oc(D)}$ values were 6.9–24 for methyl saccharin, 32–213 for bis-N-desmethyl-triazine amine, 51–300 for N-desmethyl-triazine amine, and 1–10 for triazine amine. Methyl saccharin was the most mobile of the transformation products. Of the three "triazine" transformation products, bis-N-desmethyl-triazine amine was the most mobile. In general, the transformation products are slightly to very highly mobile.

5.2.6 Mobility—soil column leaching

The following was taken from a monograph, provided by the applicant, summarizing the environmental fate, metabolism and residues of triflusulfuron-methyl: "[Triflusulfuron-methyl] was most mobile on columns of Speyer 2.1 sandy soil with 38–47% applied radioactivity recovered in the leachate. This soil contained 90% sand, <1% organic matter, and very low amounts of clay. This soil type represents a worst-case scenario and is not a soil type that would be commonly used for sugar beet production. [Triflusulfuron-methyl] exhibited limited to less mobility in the other two soils studied."

"In the aged leaching study, the radioactivity from the triazine radiolabel exhibited limited mobility on Speyer 2.1 sandy soil with only about 3% applied radioactivity recovered in the leachate. None of the leachate corresponded to triazine amine. In contrast, ca. 60% of the applied radioactivity was recovered in the leachate of ester carbonyl-label treated soil columns. The major radioactive component in the leachate co-chromatographed with methyl saccharin. [Triflusulfuron-methyl] was not detected in the leachate."

5.2.7 Mobility—field leaching data

Methyl saccharin has the potential to be mobile in soil as the presence of this transformation product in soil segments from a depth of 15–35.5 cm was correlated with application of water to the sites (i.e., an irrigation event and spring rains).

5.2.8 Expected environmental concentrations in soil

According to the proposed label for UPBEET® 50 DF Herbicide, the maximum rate per application is 35–70 g/ha of product (50% triflusulfuron-methyl), which is equivalent to 17.5–35 g triflusulfuron-methyl/ha. It is proposed that UPBEET® 50 DF be applied up to two times per season, with 5–10 days between applications, to a maximum of 50 g a.i./ha per season.

Using a half-life in soil for triflusulfuron-methyl of six days, and two applications spaced five days apart (maximum application conditions), this would amount to a cumulative application rate of 42.3 g a.i./ha to soil. Assuming a soil bulk density of 1.5 g/cm^3, even mixing through a soil depth of 15 cm, and a cumulative application rate of 42.3 g a.i./ha, the expected environmental concentration (EEC) is 0.0188 mg a.i./kg soil.

5.3 Fate and behaviour in aquatic systems

5.3.1 Hydrolysis

The hydrolysis of ^{14}C-triflusulfuron-methyl was acid-catalyzed. ^{14}C-triflusulfuron-methyl hydrolysed at all pH (half-life [$t_{½}$] of 3.7 d, 32 d, and 36 d for pH 5, pH 7 and pH 9, respectively). The major hydrolysis transformation products (>10% AR) were triazine amine (N,N-dimethyl-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine-2,4-diamine, 43–98% AR) and methyl saccharin (7-methyl-1,2-benzisothiazole-3(2H)-one 1,1-dioxide, 44–99% AR). As a decrease in the concentration of the transformation products was not observed during the study period, triazine amine and methyl saccharin would be considered persistent in water (under sterile conditions). Hydrolysis is a major route of transformation of triflusulfuron-methyl at environmentally relevant pH, and triflusulfuron-methyl will not be persistent in water.

5.3.2 Phototransformation in water

The photolysis half-lives for ^{14}C-triflusulfuron-methyl in aqueous buffer solutions at pH 5, pH 7, and pH 9 were 3.5–4 days, 14–32 days, and 19–34 days, respectively. Corresponding half-lives in dark controls were 3.7 days, 32 days, and 36 days, and agreed well with higher values in the range of half-lives from irradiated solutions. Triflusulfuron-methyl phototransformation half-lives, corrected for hydrolysis and equivalent to exposure to natural sunlight, were 19 days, 127 days, and 384 days at pH 5, pH 7, and pH 9, respectively. Phototransformation in water will not be a major route of transformation of triflusulfuron-methyl in the environment at environmentally relevant pH. In total, 11 transformation products were detected in both triazine- and ester-labelled, irradiated solutions (several were unidentified). The following were the major transformation products (range, or maximum amount > 10%, present on day 15 at all pH): triazine amine (12–34% AR), methyl saccharin (18–71% AR), T9 (16–24% AR), NDM-DPX-66037 (15%), and NFM-triazine amine (20%).

5.3.3 Aerobic water biotransformation

No data were submitted.

5.3.4 Anaerobic sediment/water biotransformation

No data were submitted.

5.3.5 Expected environmental concentrations in water

According to the proposed label for UPBEET® 50 DF Herbicide, the maximum rate per application is 35–70 g/ha of product (50% triflusulfuron-methyl), which is equivalent to 17.5–35 g triflusulfuron-methyl/ha. It is proposed that UPBEET® 50 DF be applied up to two times per season, with 5–10 days between applications, to a maximum of 50 g a.i./ha per season. Under the proposed use pattern, the potential exposure of surface water is through surface runoff and spray drift.

Using a half-life in water for triflusulfuron-methyl of 32 days, and two applications spaced five days apart (maximum application conditions), this would amount to a cumulative application rate of 48.2 g a.i./ha. Assuming 100% deposition, a direct overspray of triflusulfuron-methyl at the cumulative rate of 48.2 g a.i./ha would result in a worst case $EEC_{(spray\ drift)}$ of 0.0161 mg a.i./L in a 30-cm depth of water.

Using a half-life on soil for triflusulfuron-methyl of six days, and maximum application conditions, this would amount to a cumulative application rate of 42.3 g a.i./ha. Assuming 0.5% runoff for water-soluble pesticides, a cumulative rate of 42.3 g a.i./ha under maximum application conditions, and a ratio of 100:1 of watershed area to pond area, the $EEC_{(runoff)}$ would be 0.00705 mg a.i./L for a 30 cm depth of water. Similarly, for deeper water bodies (e.g., dugouts used as sources of drinking water for humans in the Prairie regions of Canada, 0.1625 ha × 246 cm deep = 4000 m^3), the EECs are: 0.00529 mg a.i./L (100-ha watershed) and 0.106 mg a.i./L (2000-ha watershed).

6.0 Effects on non-target species

6.1 Effects on terrestrial non-target species

The toxicity endpoints for the non-target species tested are summarized in Tables 6.1 and 6.2.

Table 6.1 Toxicity of triflusulfuron-methyl to non-target terrestrial species

Group	Organism	Test	NOEC/NOEL (mg a.i./kg)	LC_{50}/LD_{50} (mg a.i./kg)	Classification
Wild Birds	bobwhite quail (*Colinus virginianus*)	14-d acute oral	1350	>2250	practically non-toxic
	bobwhite quail (*Colinus virginianus*)	8-d dietary	5620	>5620	practically non-toxic
	mallard duck (*Anas platyrhynchos*)	8-d dietary	5620	>5620	practically non-toxic
	bobwhite quail (*Colinus virginianus*)	chronic (reproduction)	250	----	no statistically significant effects
	mallard duck (*Anas platyrhynchos*)	chronic (reproduction)	250	----	no statistically significant effects
Wild mammals	rat (active ingredient)	acute oral	----	>5000	low toxicity
	rat (formulated product)	acute oral	----	>5000	low toxicity
	rat	90-d short-term dietary	100	----	regenerative hemolytic anemia and decreased body weights $ 2000 mg a.i./kg
	mouse	18-mo chronic/ oncogenicity	150	----	histopatho-logical and weight changes in the liver $ 2500 mg a.i./kg no oncogenic effects observed
	rat	22-mo chronic/ oncogenicity	100	----	weight changes (males and females) and decrease in red blood cells (RBC) (males only) $ 750 mg a.i./kg oncogenic effects include incidences of Leydig cell adenomas in males $ 750 mg a.i./kg
	rat	92-d short-term neurotoxicity	100	----	no neurotoxic effects observed
Invertebrates	earthworm	14-d acute	---	>1000	practically non-toxic
	bees	48-h acute contact	25 µg a.i./bee	>25 µg a.i./bee	relatively non-toxic
		48-h acute oral	1000 mg a.i./L	>1000 mg a.i./L	relatively non-toxic

Group	Organism	Test	NOEC/NOEL (mg a.i./kg)	LC_{50}/LD_{50} (mg a.i./kg)	Classification
Plants	onion corn wheat sorghum sugar beet soybean pea tomato canola cucumber	5-d seed germination	35.0266 g a.i./ha	IC_{25} not determined	no effect observed
	sorghum*	14-d seedling emergence plant height**	0.1366 g a.i./ha	IC_{25} not determined	phytotoxic
	sorghum*	21-d vegetative vigour shoot weight**	0.034 19 g a.i./ha	0.5792 g a.i./ha (IC_{25})	phytotoxic

* most sensitive species and ** endpoint.

6.1.1 Birds

The NOEL for the acute oral toxicity of triflusulfuron-methyl in bobwhite quail was 1350 mg a.i./kg bw, which means that a bird would have to consume a contaminated diet at that concentration for 2700 days for males and 4450 days for females before mortality would occur. Triflusulfuron-methyl is, therefore, practically non-toxic to bobwhite quail under these test conditions.

Dietary studies on both the bobwhite quail and the mallard duck resulted in no observed effect concentrations (NOEC) of 5620 mg a.i./kg feed and LC_{50}s > 5620 mg a.i./kg feed. No effects were observed with the bobwhite quails, but reductions in body weight, body-weight gain, and feed consumption (FC) were apparent in mallards at every concentration tested. The data suggests that feed aversion is responsible for the weight changes and reduction in feed consumption. No other effects were observed in mallards.

Reproduction studies, performed on both bobwhite quail and mallards, resulted in a NOEC of 250 mg a.i./kg feed for both types of birds. Observed, although not statistically significant, effects in the bobwhite quail at 1250 mg a.i./kg feed included an increase in the percentage of cracked eggs and a decrease in eggshell thickness compared with the control group. Mallards demonstrated a reduction in body weight of hens during the first eight weeks of the study, as well as a reduction in the number of laying hens during the first three weeks of egg production at 1250 mg a.i./kg feed.

6.1.2 Wild mammals

As this product is to be applied by ground equipment (maximum seasonal label rate of 50 g a.i./ha), the most likely route of exposure for wild animals to triflusulfuron-methyl would be through the consumption of contaminated prey or vegetation.

The acute oral toxicity in rats of triflusulfuron-methyl is >5000 mg a.i./kg bw, resulting in a non-toxic classification for the purposes of labelling. It is, therefore, unlikely that any group of small animal, such as rats, would be capable of eating sufficient amounts of the herbicide to induce mortality in 50% of the population. As such, it is reasonable to assume that triflusulfuron-methyl should not pose an acute hazard to mammals at the rates currently proposed for use.

The hazards to a wild mammal owing to short- and long-term dietary exposure to triflusulfuron-methyl have been estimated using a risk factor (EEC/NOEL). For the rat, the risk quotient is 0.252 (margin of safety [MOS] = 4) when using a NOEL of 100 mg/kg diet, based on the 90-day short-term oral study, the 22-month combined chronic/oncogenicity study, and the short-term neurotoxicity. It is, therefore, unlikely that there would be any significant risk to wild rats, with similar food consumption and body weight, from chronic exposure to triflusulfuron-methyl in the environment. Likewise, triflusulfuron-methyl should not be detrimental to wild voles, moles and other small herbivorous mammals.

Food consumption, body weight, and concentrations of triflusulfuron-methyl in a natural diet were also estimated for the eastern cottontail and the mountain cottontail. Both have similar feeding habits and are very similar in appearance, but the eastern cottontail is not found in the proposed area of application in Alberta, and the mountain cottontail is located in the area. For female rabbits, the lowest NOEL is derived from the non-rodent teratology studies (15 mg a.i./kg bw). This value is seven times greater than what the eastern cottontail will consume from a contaminated diet and is five times greater than the mountain cottontail's contaminated diet. It is, therefore, unlikely that primary or secondary poisoning of carnivores would occur through exposure to contaminated diet, based on data obtained for female rabbits. The NOEL for male rabbits was not obtained and the MOS not determined. The Leydig cell adenomas in male rats suggests that they may also be found in male rabbits, which may decrease the NOEL. The fact that 78–96% of the active ingredient is excreted in the urine and faeces within the first 48 hours after administration implies that insufficient quantities will remain in rabbits to affect the primary and secondary carnivores.

Triflusulfuron-methyl was not found to be genotoxic for in vivo mammalian testing and should not represent a concern for mammalian wildlife.

6.1.3 Bees

The NOEC of 25 μg a.i./bee for the acute contact toxicity study with honey bees indicates that triflusulfuron-methyl is non-toxic to this group. Studies of acute oral toxicity to the bee resulted in a NOEC of 1000 mg a.i./L. The NOEC values obtained for both contact and oral toxicity studies were equivalent to the highest concentrations tested. Based on this information, and the relatively low bioaccumulative potential of the test substance, it is unlikely that there will be adverse effects on pollinators.

6.1.4 Arthropod predators and parasites

Studies on arthropod predators and parasites were not submitted.

6.1.5 Effects on earthworms and other soil macro-organisms

The results of the studies indicate that the 14-day LC_{50} for earthworms is >1000 mg a.i./kg of soil. A statistically significant reduction in body weight ($p = 0.01$) for the earthworms at 1000 mg a.i./kg of soil suggests that the NOEC is less than this value. As there was an insufficient number of test concentrations, the NOEC could not be determined, i.e., only a control group and 1000 mg a.i./kg of soil were tested. Preliminary testing, however, indicated that the NOEC = 100 mg a.i./kg of soil, based on two replicates per test concentration.

6.1.6 Effects on soil micro-organisms

Studies of the effects on soil micro-organisms are not required by the PMRA.

6.1.7 Non-target terrestrial plants

Ten plant species were tested for seed germination, seedling emergence, and vegetative vigour. They included onion, corn, wheat, sorghum, sugar beet, soybean, pea, tomato, canola and cucumber.

The NOEC was 0.1366 g a.i./ha for seed germination, the highest concentration tested. No compound-related effects were reported.

Corn, sugar beet, soybean, tomato and cucumbers were tested for abnormal effects associated with seedling emergence at the Tier I level, but no significant effects were observed. Onion, wheat, sorghum, pea and canola were studied at the Tier II level, resulting in a NOEC of 0.1366 g a.i./ha. The most sensitive indicator was plant height in sorghum. Observed effects at the Tier II level included plant injury, chlorosis, leaf cupping, and hormonal effects. The level at which there is 25% inhibition concentration (IC_{25}) could not be determined from the data set submitted for evaluation.

With respect to vegetative vigour, sorghum was the most sensitive indicator of the 10 species tested, having a NOEC of 0.03419 g a.i./ha and an IC_{25} of 0.5792 g a.i./ha for mean shoot weight. Observable effects on the plants tested included slight to severe plant injury, chlorosis, necrosis, hormonal effects, purpling, tillering, axiliary bud stimulation, thicker leaves, stunted apical meristems, spotting, and darker green lower leaves.

6.2 Effects on non-target aquatic species

Table 6.2 Toxicity of triflusulfuron-methyl to non-target aquatic species

Group	Organism	Test	NOEC (mg a.i./L)	LC_{50} (mg a.i./L)	Classification
Invertebrates	daphnids (*Daphnia magna*)	48-h static acute	960	>960	practically non-toxic
Fish	bluegill sunfish (*Lepomis machrochirus*)	96-h static acute	120	760	practically non-toxic
	rainbow trout (*Oncorhynchus mykiss*)	21-d extended flow-through acute	210	>210	practically non-toxic
Algae	*Anabaena flos-aquae*	5-d static	71.9 µg a.i./L	---	no effect observed
	Selenastrum capricornutum	5-d static	36.0 µg a.i./L	27.7 µg a.i./L (IC_{25})	phytotoxic
	Navicula pelliculosa	5-d static	74.2 µg a.i./L	> 74.2 µg a.i./L (IC_{50})	no effect observed
	Skeletonema costatum	5-d static	67.5 µg a.i./L	> 67.5 µg a.i./L (IC_{50})	no effect observed
Plants	duckweed (*Lemna gibba*)	14-d static	1.27 µg a.i./L	2.03 µg a.i./L (IC_{25})	phytotoxic

6.2.1 Fish bioconcentration study

A study on bioconcentration in fish was not submitted. Based on the very low K_{ow} for triflusulfuron-methyl, it is not anticipated that triflusulfuron-methyl will bioconcentrate in fish.

6.2.2 Aquatic invertebrates

The 48-hour NOEC and median effective concentration (EC_{50}) for exposure of *Daphnia magna* to triflusulfuron-methyl in a static, acute toxicity study is 960 mg a.i./L and >960 mg a.i./L, respectively. As there were no signs of immobility, triflusulfuron- methyl is practically non-toxic to aquatic invertebrates.

6.2.3 Fish

Bluegill sunfish (*Lepomis machrochirus*) were exposed to triflusulfuron-methyl for 96 hours under static conditions, resulting in a NOEC of 120 mg a.i./L and an LC_{50} of 760 mg a.i./L. Treatment-related effects included dark coloration and positioning of fish at the water surface at 590 mg a.i./L and 1100 mg a.i./L. The test substance is classified as practically non-toxic to warm water fish.

No treatment-related effects were observed in a 21-day flow-through toxicity study with rainbow trout (*Oncorhynchus mykiss*) as the test organism. The NOEC and LC_{50} values are 210 mg a.i./L and >210 mg a.i./L, respectively. The test substance is classified as practically non-toxic to cold water fish.

6.2.4 Algae

Selenastrum capricornutum, a freshwater green alga, was the most sensitive of the algal species tested. A five-day static test resulted in a NOEC of 36.0 μg a.i./L and an IC_{25} of 27.7 μg a.i./L. Triflusulfuron is phytotoxic to this species of algae.

Other algal species tested include *Anabaena flos-aquae* (NOEC = 71.9 μg a.i./L), *Navicula pelliculosa* (NOEC = 74.2 μg a.i./L), and *Skeletonema costatum* (NOEC = 67.5 μg a.i./L). No treatment-related effects were observed on algal growth and/or morphology.

6.2.5 Aquatic vascular plants

The most sensitive aquatic plant species was *Lemna gibba* G3, the only aquatic vascular species tested. The NOEC and IC_{25}, both based on frond count, were 1.27 and 2.03 μg a.i./L, respectively. Morphological abnormalities included effects to the shape of the frond. Triflusulfuron is phytotoxic to this aquatic vascular plant.

6.3 Effects on biological methods of sewage treatment

These studies are not required under the Canadian regulatory system for pest control products.

6.4 Environmental risk assessment

6.4.1 Terrestrial organisms

a) Earthworms

The MOS_{LC50} for the earthworm (*Eisenia foetida*) is $53 191, based on an EEC in soil of 0.0188 mg a.i./kg soil and an LC_{50} > 1000 mg a.i./kg of soil. Triflusulfuron-methyl will not have an adverse effect on earthworms.

b) Honeybee

With NOECs of 25 µg a.i./bee and 1000 mg a.i./L for acute contact and acute oral toxicity, respectively, triflusulfuron-methyl is relatively non-toxic to honey bees. Triflusulfuron-methyl will not have adverse effects on honey bees.

c) Birds

The maximum number of days required for a bobwhite quail to consume enough triflusulfuron-methyl, equivalent to the dose administered by gavage that had no observable effect in laboratory studies, from contaminated diet, would be 4450 days in females and 2700 days in males, based on a 14-d LD_{50} and 14-d NOEC >2250 and 1350 mg a.i./kg bw, respectively. The EEC was 4.15 mg a.i./kg diet weight for both sexes.

The 8-d LC_{50} and 8-d NOEC that were derived from the results of the dietary study with the bobwhite quail were >5620 and 5620 mg a.i./kg feed, respectively. The risk quotient and the MOS of the dietary study, based on the NOEC, were calculated to be 0.000 738 and 1350, respectively. For the dietary study with the mallard duck, the 8-d LC_{50} and 8-d NOEC were >5620 and 5620 mg a.i./kg feed, respectively. The EEC for the mallard was 1.69 mg a.i./kg diet weight. The risk quotient and the MOS based on the NOEC were calculated to be 0.000 3 and 3330, respectively. The EEC for the bobwhite quail was 4.15 mg a.i./kg diet weight.

The risk quotient for reproduction in the bobwhite quail, based on the NOECs of 250 mg a.i./kg feed, was calculated to be 0.0166 MOS (60.2), assuming an EEC of 4.15 mg a.i./kg diet weight. The value for the mallard, based on the same NOEC as for a bobwhite quail, was calculated to be 0.006 76 (MOS = 148), assuming an EEC of 1.69 mg a.i./kg diet weight. Based on these values, it is anticipated that birds exposed to residues on food sources will not be adversely affected.

d) Wild mammals

Triflusulfuron-methyl is well absorbed and rapidly excreted in mammals (78–96% of the AD within 48 hours). Risk quotients, calculated from a NOEC of 100 mg a.i./kg diet weight and an EEC of 25.22 mg a.i./kg diet weight, were low for laboratory rats (0.252, resulting in a MOS = 4), as well as eastern cottontail (risk quotient = 0.143, and MOS = 7, based on a NOEL = 15 mg/kg bw/d by gavage, an EEC = 33.13 mg a.i./kg diet weight, food consumption of 60 g/d, and body weights of 900–1800 g), and mountain cottontail rabbits (0.2, and MOS = 5, based on a NOEL = 15 mg/kg bw/d by gavage, an EEC = 33.13 mg a.i./kg diet weight, food consumption of 60 g/d, and body weights of 700–1300 g). It is, therefore, unlikely that primary or secondary poisoning of carnivores would occur through exposure to contaminated diet based on data obtained for female rabbits. The test substance was not found to be genotoxic for in vivo testing of animals. Based on this data, it is reasonable to assume that wild mammals would not be harmed if exposed to a diet contaminated with triflusulfuron-methyl at concentrations estimated from the proposed application rates.

e) Non-target terrestrial plants

The risk quotient for exposure of sorghum to triflusulfuron-methyl is 1462.42 (MOS = 0.000 68), based on a NOEC of 0.034 19 g a.i./ha for mean shoot weight of the plant (vegetative vigour) and an EEC of 50 g a.i./ha. With respect to seedling emergence, the risk quotient for exposure of sorghum to the active ingredient is 309.83 (MOS = 0.003), based on the NOEC of 0.136 6 g a.i./ha and an EEC of 42.323 g a.i./ha. There is, therefore, a significant risk to non-target terrestrial plant species at the proposed rate of application.

6.4.2 Aquatic organisms

a) Aquatic invertebrates

The risk quotient associated with a direct overspray in water is 0.000 016 7 (MOS = 59 627), based on a NOEC of 960 mg a.i./L for *Daphnia magna* and an EEC in water of 0.016 068 mg a.i./L. Triflusulfuron-methyl, therefore, will not pose a direct risk to aquatic invertebrates.

b) Fish

The risk quotient associated with a direct overspray in water is 0.000 076 6, where the NOEC = 210 mg a.i./L and the EEC = 0.016 068 mg a.i./L (MOS = 13 055) for the 21-day rainbow trout study, and 0.000 134, where the 96-hour NOEC = 120 mg a.i./L and the EEC = 0.016 068 mg a.i./L (MOS_{LC50} = 7453) for the bluegill sunfish study. Triflusulfuron-methyl will not pose a direct risk to freshwater fish species.

c) Algae

The risk quotient for exposure of *Selenastrum capricornutum* to triflusulfuron-methyl is 0.447 (MOS = 2), based on the NOEC of 36.0 μg a.i./L and an EEC of 16.068 μg a.i./L. The freshwater algae are, therefore, not at risk from triflusulfuron-methyl.

d) Non-target aquatic plants

The risk quotient for *Lemna gibba* G3, based on the NOEC of 1.27 μg a.i./L and an EEC of 16.068 μg a.i./L, is 12.68 (MOS = 0.08). Triflusulfuron-methyl represents a significant risk to aquatic vascular plants particularly if exposure is a result of a direct overspray.

6.5 Environmental risk mitigation

Aquatic buffer zones

Using the 14-day NOEC (1.27 μg a.i./L) for the most sensitive species, *Lemna gibba*, a buffer zone of 10 metres is required to protect aquatic organisms.

Terrestrial buffer zones

Based on the IC_{25} (0.5792 g a.i./ha) for mean shoot weight in sorghum, a buffer zone of 23 metres is required for the protection of sensitive terrestrial habitats (e.g., shelter-belts).

7.0 Efficacy, crop tolerance and sustainability

7.1 Sources of data/information

Field trial data: The data package submitted by the URMUR sponsors, Ontario Sugarbeet Growers Association and Rogers Sugar Ltd., consisted of six trials from Michigan and five trials each from Manitoba and Alberta.

The trials conducted in Manitoba were all from 1996, whereas those conducted in Alberta were from 1994 and 1997. One of the three trials conducted in Alberta in 1994 was irrelevant as there was no triflusulfuron treatment. The Michigan trials were conducted over a five-year period from 1991 to 1995.

In Ontario, two trials were conducted in 1998, one at Harrow and the other at Ridgetown.

Literature search, OECD data/labelling information: A search of the scientific journals in North America revealed two published papers in Weed Technology and one in Weed Science. A literature search beyond North America retrieved six articles from Europe, but these were of limited use.

In response to the PMRA's request for additional information from other regulatory agencies, some data/label information were received from Sweden, Germany, Finland, the U.K. and the U.S., which were helpful in gaining a better understanding of the selectivity of triflusulfuron-methyl, but of limited use with respect to efficacy and residual activity as the weed flora and edaphic/climatic conditions in the two sugar beet-producing regions of Canada vary greatly from those of Europe.

7.1.1 Intended use

Triflusulfuron is a sulfonylurea herbicide, which is classified as a Group 2 family of herbicides. Triflusulfuron will be marketed as a 50% dry flowable product under the name UPBEET® 50 DF.

Triflusulfuron-methyl was first registered in 1993 in Belgium and France, and subsequently in Germany, the Netherlands, Finland and Italy. In Europe, the end-use product is known as SAFARI and DEBUT. In the U.S., the product was registered in 1996.

UPBEET® 50 DF may be used in combination with 0.25% v/v of a non-ionic adjuvant as a post-emergence application in sugar beets for control of velvetleaf. UPBEET® 50 DF may also be used as a sequential tank-mix application with BETAMIX at 1.75–3.5 L/ha (262-525 g a.i./ha) for control of additional weeds such as redroot pigweed, lamb's quarters, kochia and suppression of green foxtail.

UPBEET® 50 DF is to be applied at 35–70 g/ha (17.5–35.0 g a.i./ha) alone or in combination with BETAMIX. More than one application of UPBEET® 50 DF may be made to the same crop provided the total amount applied does not exceed 100.0 g/ha (50.0 g a.i./ha).

7.1.2 Mode of action

Based on available published information, triflusulfuron-methyl, similar to other sulfonylurea herbicides, inhibits acetolactate synthase (ALS), also called acetolhydroxyacid synthase, a key enzyme in the biosynthesis of the branched-chain amino acids (Weed Science Society of America Handbook [WSSA], 7th edition, 1994). Susceptible plants succumb to herbicidal action due to ALS inhibition. The actual sequence of phytotoxic processes, however, is not clear.

In sugar beet plants, <10% of the applied herbicide is absorbed 20 hours after application. There is very little translocation from the treated leaf after a post-emergence application. Selectivity in sugar beet appears to be due to differential metabolism. The half-life of triflusulfuron is one hour in tolerant sugar beets, six to seven hours in moderately tolerant weeds such as lamb's quarters (*Chenopodium album* L.) and greater than 35 hours in susceptible weeds.

7.1.3 Crop

The proposed URMUR is intended for post-emergence control of broadleaf weeds in sugar beets (*Beta vulgaris* L.), which is considered a minor crop in Canada due to its limited hectarage. Until 1995, sugar beet production in Canada was confined to southern Manitoba and southeastern Alberta. Production stopped in Manitoba in 1997 because Rogers Sugar Ltd. closed its operation in Manitoba. The total area under sugar beet production and the number of growers involved over the last three years are as follows:

	Area (ha)			Growers		
	1996	**1997**	**1998**	**1996**	**1997**	**1998**
Alberta	13777	13544	16 893	498	500	452
Manitoba	11000	0	0	233	0	0
Ontario	100	1200	2600	5	65	103
Total	24 877	14 744	19 493	731	565	555

In southwestern Ontario (Kent and Lambton Counties), which was a major sugar beet-producing area in the 1960s, production of sugar beet was re-introduced to the area in 1995. Production is expected to exceed 5000 ha in a few years according to the Ontario Sugarbeet Growers Association.

7.1.4 Effectiveness against pests

7.1.4.1 Description of pest problem

Velvetleaf (*Abutilon theophrasti* L.)

In southwestern Ontario, velvetleaf is a major problem for most of the potential sugar beet growers. Velvetleaf is an annual herb belonging to the Malvaceae family and reaching 60–120 cm in height. Velvetleaf reproduces by seed and is found in waste places, vacant lots, gardens, and cultivated fields, especially corn and soybean fields, and along fence rows.

Velvetleaf is a serious competitor with sugar beets because of high seedling vigour, rapid growth habit, tolerance to many herbicides, and ability to produce large amounts of seeds. A 30% reduction in sugar beet yield has been observed by one velvetleaf plant per metre of row.

Kochia (*Kochia scoparia* L.)

In southern Alberta, kochia is a major weed. Kochia is an annual herb belonging to the Goosefoot family (Chenopodiaceae) and reproduces by seed. It is found in waste places, roadsides and cultivated fields, especially on saline soils.

In Alberta and Saskatchewan, kochia is no longer considered a weed, since it has nutritive value as a forage crop and has been found useful for growing on saline soils to reduce salinity. However, if kochia is found in field crops, it can be a serious problem as it is a prolific seed producer that spreads rapidly by seed and competes vigorously with sugar beets.

UPBEET® 50 DF, in combination with BETAMIX, provides improved control of other problem weeds such as lamb's quarters (*Chenopodium album* L.) and redroot pigweed (*Amaranthus retroflexus* L.), which compete aggressively with sugar beets.

The draft label submitted by URMUR sponsors recommends a broadcast rate of 17.5–35 g a.i./ha with a maximum of 50 g a.i./ha per growing season. Two sequential applications are proposed with a tank-mix of UPBEET® 50 DF and BETAMIX (Registration Number 19652). The draft label claims control of 24 broadleaf species and suppression of two annual grasses and an additional two broadleaf weed species with the tank-mix of UPBEET® 50 DF + BETAMIX.

The draft label has a claim for control of 10 broadleaf weed species with UPBEET® 50 DF + surfactant.

The Canadian draft label claims have been copied from the U.S. label, which are not supported by data as the EPA does not review value data. Efficacy data for weed species that occurred in at least one trial are summarized as follows.

7.1.4.2 Pigweed (*Amaranthus spp.*)

In Manitoba, this species was found in four of the five trials conducted. Average control at 35 (1×) and 70 (2×) g a.i./ha of triflusulfuron were, respectively, 76 and 78%. When tank-mixed with desmedipham, the average control increased to 84 and 87%, respectively, with the 1× and 2× rate of triflusulfuron. In two trials where a tank-mix of triflusulfuron and (desmedipham + phenmedipham) was tested, the average control achieved were 81 and 85%, respectively, with the 1× and 2× rate of triflusulfuron.

In Alberta, redroot pigweed occurred in only one of the four trials and the control ratings recorded for triflusulfuron and triflusulfuron + (desmedipham + phenmedipham) were, respectively, 2.0 and 8.0.

In Michigan, redroot pigweed occurred in four of the five trials conducted. Average control with a sequential treatment of (phenmedipham + desmedipham) + triflusulfuron + (phenmedipham + desmedipham) + triflusulfuron was 99%. Triflusulfuron was tested at the 0.5× rate of 17.5 g a.i./ha and there were no ratings for triflusulfuron alone.

At Ridgetown, Ontario, control with three applications of triflusulfuron at 17.5 g was 51%, but improved to 89% later in the season. Tank-mix applications with desmedipham + phenmedipham provided 59% control at second evaluation, which indicates antagonism. At Harrow, Ontario, control of redroot pigweed was 70 and 94%, respectively, with three applications of triflusulfuron alone and in combination with BETAMIX.

Foreign data/labels: The EPA-approved label lists control of both redroot pigweed as well as prostate pigweed (*Amaranthus bilitoies* S. Wats) with a minimum of two sequential applications of triflusulfuron + (desmedipham + phenmedipham). The U.K. label (DEBUT Herbicide) does not make any reference to *Amaranthus spp.* The German label lists spiny amaranth (*Amaranthus spinosus* L.).

Data available are not adequate to support a claim for control of redroot pigweed with triflusulfuron alone. However, since the BETAMIX label refers to a claim for control of *Amaranthus spp.*, the proposed claim for control of redroot pigweed with sequential application of tank-mix of UPBEET® 50 DF + BETAMIX is acceptable.

7.1.4.3 Green smartweed (*Polygonum scabrum* L.)

In Manitoba, this species was found at all five sites. Average control at 35 and 70 g a.i./ha of triflusulfuron were, respectively, 69 and 74%. When tank-mixed with desmedipham, the average control recorded for the 1× and 2× rate of triflusulfuron were, respectively, 70 and 68%. Average control across two trials with a tank-mix of triflusulfuron + (desmedipham + phenmedipham) at 1× and 2× rate of triflusulfuron were, respectively, 75 and 80%.

Smartweed did not appear in any of the Alberta trials. In one Michigan trial, 97% control of this species was achieved with two sequential applications of triflusulfuron + (desmedipham + phenmedipham).

At Harrow, three applications of triflusulfuron alone and as tank-mix with BETAMIX provided, respectively, 97 and 95% control, but since pyrazon had also been included in all treatments except the check and since pyrazon has a claim for control of smartweed, it was not possible to ascertain that triflusulfuron contributed anything to the control of smartweed.

Foreign data/labels: The EPA label for UPBEET® 50 DF lists control of *Polygonum pensylvanicum* L. with the tank-mix of UPBEET® 50 DF + BETAMIX. The U.K. label does not make any reference to this species. The German label lists *Polygonum persicaria* L. and *Polygonum lapatifolium* L.

Data received from Sweden indicates 90% control of *Polygonum spp*. with tank-mix of triflusulfuron + phenmedipham.

Data received from Finland indicates that tank-mix of SAFARI (triflusulfuron) + phenmedipham + ethofumesate controls *Polygonum aviculare* L.

In consideration of the available data from the U.S. and Canada, a claim for control or suppression of green smartweed is not acceptable with triflusulfuron alone or two sequential applications of triflusulfuron + (desmedipham + phenmedipham).

7.1.4.4 Lamb's quarters (*Chenopodium album* L.)

Lamb's quarters appeared in two of the four Alberta trials. In one trial, control was 60% when triflusulfuron was tested alone at 17.5 g a.i./ha but increased to 100% when tank-mixed with desmedipham + phenmedipham. In the second trial, a rating of 1.3 was recorded for triflusulfuron alone, but 8.2 for the tank-mix treatment.

In Michigan, this species was found in three trials where average control was 98% with two sequential applications of UPBEET® 50 DF at 0.5× rate and BETAMIX at 369 g a.i./ha.

At Harrow, three applications of triflusulfuron alone and in combination with BETAMIX provided 22 and 86% control.

Foreign data/labels: The EPA-approved label lists control of this species with a tank-mix of UPBEET® 50 DF + BETAMIX. There is no reference in the U.K. label.

Data received from Sweden indicate 85% control of lamb's quarters with tank-mix of triflusulfuron + phenmedipham. Data from Finland indicates control of this species with three applications of triflusulfuron + phenmedipham + metamitron.

The proposed claim for control of lamb's quarters with a tank-mix of triflusulfuron + (desmedipham + phenmedipham) is acceptable.

7.1.4.5 Velvetleaf (*Abutilon theophrasti* L.)

Velvetleaf did not appear in the Alberta and Manitoba trials, as expected, but were found in three Michigan trials. Average control across the three sites was 93% with two sequential applications of UPBEET® 50 DF (0.5×) and BETAMIX (1×).

At Ridgetown, Ontario, 92 and 50% control of velvetleaf was achieved, respectively, with three applications of triflusulfuron (0.5×) alone and in combination with BETAMIX at first evaluation, suggesting antagonism. Agral 90 was used at 0.25% v/v where triflusulfuron was used alone. At

second evaluation, the trend reversed as control was 71 and 82%, respectively, with triflusulfuron alone and as tank-mix.

Starke and Renner (1996), who investigated the effect of triflusulfuron alone and in combination with desmedipham + phenmedipham and non-ionic surfactant under greenhouse and field conditions in Michigan, reported that triflusulfuron (0.25×, 0.5×) controlled velvetleaf only when non-ionic surfactant was added to the spray solution. Addition of desmedipham + phenmedipham decreased velvetleaf control under greenhouse conditions.

In another study in Michigan, Starke (1996) reported that velvetleaf control by triflusulfuron increased from 0 (no adjuvant) to 80% by addition of Sylgard 309 plus urea. Desmedipham + phenmedipham decreased velvetleaf control by triflusulfuron plus X-77 adjuvant compared to triflusulfuron plus adjuvant alone.

Velvetleaf is not listed on the BETAMIX label. The EPA-approved label has a claim for control of velvetleaf with UPBEET® 50 DF alone as well as UPBEET® 50 DF + BETAMIX. There is no claim for control of this species on the German label, DEBUT.

Based on the limited but consistent results of the Michigan trials, a claim for control of velvetleaf is acceptable with two applications of triflusulfuron + surfactant as well as sequential applications of triflusulfuron + (desmedipham + phenmedipham) without an adjuvant. If velvetleaf is the predominant weed in a sugar beet field, two applications of triflusulfuron plus a non-ionic adjuvant is preferable to a tank-mix because of possibility of antagonism.

7.1.4.6 Ragweed (*Ambrosia artemisiifolia)*

Ragweed does not occur in the Prairies, therefore, the available data is limited to one trial from Michigan, where 99% control was observed with two sequential applications of UPBEET® 50 DF (17.5 g a.i./ha) + BETAMIX (365 g a.i./ha).

The BETAMIX label refers to control of ragweed prior to the 2-leaf stage and when BETAMIX is preceded by a preplant or pre-emergence herbicide treatment. The U.S. label refers to control of this species with a tank-mix of UPBEET® 50 DF + BETAMIX.

Since there is no data on efficacy of triflusulfuron alone and only one trial for sequential applications of the tank-mix, a claim for control of ragweed is not accepted.

7.1.4.7 Round-leaved mallow (*Malva rotundifolia* L.)

Mallow appeared in three trials conducted in Alberta. In one trial, triflusulfuron tested alone at 17.5 and 35 g a.i./ha provided, respectively, 80 and 84% control of mallow. Tank-mixing with desmedipham + phenmedipham improved the level of control slightly. In the second trial,

control ratings for mallow were 2.3 and 4.3 for triflusulfuron and triflusulfuron + (desmedipham + phenmedipham), respectively.

Tank-mix of triflusulfuron + ethofumesate + (desmedipham + phenmedipham) at 0.5× and 1× rates provided 84 and 91% control, respectively, in the third trial. This trial can not be considered because of inclusion of ethofumesate.

The U.S. label refers to control of common mallow (*Malva neglecta*) and small-flowered mallow (*Malva parviflora*) on the UPBEET® 50 DF label. The BETAMIX label does not have a claim for control of *Malva spp*.

Because of inadequate data, claims for control of little mallow or round-leaved mallow are not acceptable with triflusulfuron alone or with two sequential applications of triflusulfuron + (desmedipham + phenmedipham).

7.1.4.8 Kochia (*Kochia scoperia* L.)

Kochia was found in one Alberta trial and one of the Manitoba trials. At the Alberta site, the control ratings recorded were 2.0 and 4.0, respectively, for triflusulfuron alone and the tank-mix treatment. In Manitoba, control achieved with triflusulfuron at 35 g a.i./ha was 71%. The control for the tank-mix of triflusulfuron + desmedipham was 90%. Tank-mix of triflusulfuron (2×) + (desmedipham + phenmedipham) provided 95% control. In Nebraska, Wilson (1994) reported improved control of kochia with combination of triflusulfuron + (desmedipham + phenmedipham).

The BETAMIX label in Canada refers to control of kochia while in the rosette stage (less than 2.5 cm in diameter) and when preceded by a preplant/pre-emergence treatment. The U.S. label for UPBEET® 50 DF does not restrict the control of kochia to the seedling stage.

The proposed claim for control of kochia while in the rosette stage (less than 2.5 cm in diameter) is acceptable as stated on the BETAMIX label with two sequential applications of triflusulfuron + (desmedipham + phenmedipham).

7.1.4.9 Green foxtail (*Setaria virides* L.)

Green foxtail occurred at two sites in Manitoba. The average control with 1× and 2× of triflusulfuron were 72 and 74%. Tank-mixing with desmedipham improved the level of control to 80%.

The U.S. label lists partial control with a tank-mix of UPBEET® 50 DF and BETAMIX. The U.K. and German labels do not list any Setaria species.

Since the BETAMIX label has a claim for control of green foxtail (before the 4-leaf stage) and suppression was observed in two Manitoba trials, the proposed claim on the Canadian label for suppression of green foxtail is acceptable for sequential application of triflusulfuron plus BETAMIX.

7.1.4.10 Nightshade species (*Solanum spp.*)

Nightshade species did not occur in any of the trial sites in Alberta, Manitoba or Michigan. At Harrow, control of hairy nightshade was 97 and 95%, respectively, with triflusulfuron alone and as tank-mix. The BETAMIX label has a claim for control of *Solanum spp*. when preceded by another treatment. The U.S. label refers to control of black nightshade (*Solanum nigrum*) and seedlings of hairy nightshade (*Solanum sarrachoides*). The German label has a claim for control of black nightshade. Data from Sweden indicates 85% control of black nightshade.

Because of inadequate data, claims for control of black nightshade or hairy nightshade are not acceptable for triflusulfuron alone or with a tank-mix of desmedipham + phenmedipham.

7.1.4.11 Shepherd's purse (*Capsella bursa-pastoris*)

Data were not recorded for this species in any of the 17 trials. This species is not listed on the BETAMIX label, but appears on the U.S. and German labels for triflusulfuron. Data obtained from Sweden indicates greater than 90% control when triflusulfuron was tested with phenmedipham. Data from Finland also indicates control with three sequential applications of triflusulfuron + phenmedipham + metametron.

Since no data is available from Canada or the U.S., a claim for shepherd's purse is not acceptable.

7.1.4.12 Yellow foxtail (*Setaria glauca* (L.) Beauv.)

No data were submitted.

The BETAMIX label in Canada carries a claim for control of this species and the U.S. UPBEET® 50 DF label refers to partial control with a tank-mix of UPBEET® 50 DF and BETAMIX.

The proposed claim for suppression of yellow foxtail with a tank-mix of UPBEET® 50 DF + BETAMIX is not acceptable because of lack of data from the U.S. or Canada.

7.1.4.13 Wild buckwheat (*Polygonum convolvulus* L.)

This species did not occur in any of the 17 experimental sites. A claim for control of this weed appears on the U.S. label whereas the German label contraindicates control. Data from Sweden indicated less than 75% control with a tank-mix of triflusulfuron + phenmedipham.

The proposed claim for control of wild buckwheat is not acceptable.

7.1.4.14 Wild mustard (*Brassica kaber*)

This species did not occur in any field trials. The BETAMIX label refers to a claim for control when sprayed prior to 4-leaf stage. The U.K. label indicates that *Brassica* species are susceptible to triflusulfuron alone as well as to tank-mix. The German label also indicates control. Data from Sweden indicates that tank-mix of triflusulfuron + phenmedipham provides greater than 90% control.

Because of lack of data from the U.S. or Canada, a claim for control of wild mustard or black mustard (*Brassica niger*) is not acceptable for triflusulfuron used alone or as tank-mix of desmedipham + phenmedipham.

7.1.4.15 The following weeds were deleted from the draft label as no data were submitted in support of these species:

California burclover	*Medicago polymorpha* L.
Common chickweed	*Stellaria media* (L.) Vill
Curly dock	*Rumex crispus* L.
Common purslane	*Portolaca oleracea* L.
Goosefoot	*Chenopodium murale* L.
Groundcherry	*Physalis wrightii*
Knotweed	*Polygonum argyrocolen*
London rocket	*Sisimbrium irio*
Wild radish	*Raphanus sativus*
Sow thistle	*Sonchus oleraceus*

7.1.5 Tank-mixes with other herbicides

Reference to tank-mixes of UPBEET® 50 DF with BETANEX, LONTREL and graminicides is not acceptable because of lack of data. Data must be provided to show that there is no antagonism.

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

There are 17 ALS-inhibitor-resistant weed species found in the U.S. and five in Canada. ALS-inhibitor weeds have appeared in cereal crops, corn/soybean rotations, forestry and industrial sites. ALS-inhibitor-resistant *Kochia scoparia* and *Salsola iberica* have become widespread problems in cereal producing regions of the Canadian Prairies and the U.S. Great Plains. Recently, tolerance of *Galium spurium* was documented in Alberta and evidence of *Stellaria media* resistance was found in Nova Scotia.

Since triflusulfuron was only registered three years ago in the U.S., specific broadleaf weed tolerance to this sulfonylurea has not yet been documented.

The two trials conducted at Harrow and Ridgetown, Ontario, had identical lists of treatments. Three sequential applications of triflusulfuron (0.5×) plus BETAMIX caused no phytotoxicity to sugar beet at any of the sites.

In addition to the 17 trials, three articles published in Weed Science/Weed Technology were also consulted.

Wilson (1994) reported that combining triflusulfuron (0.5×) with desmedipham (18–37 g a.i./ha) + phenmedipham (18–37 g a.i./ha) did not affect sugar beet vigour, root yield or percent sucrose compared with desmedipham + phenmedipham in Nebraska.

Starke and Renner (1996) investigated the response of sugar beet to post-emergence applications of triflusulfuron applied alone and in combination with desmedipham + phenmedipham, non-ionic surfactant and urea under greenhouse and field conditions in Michigan. The authors reported that adding a non-ionic surfactant to the mixture of triflusulfuron plus desmedipham + phenmedipham increased injury compared to triflusulfuron + non-ionic surfactant or the three herbicides without the surfactant.

In another study in Michigan, Starke et al. (1996) reported sugar beet was not injured when 11 different adjuvants were tested with triflusulfuron. However, the addition of any adjuvant to desmedipham + phenmedipham increased injury compared to desmedipham + phenmedipham alone.

Based on crop injury/vigour ratings reported for Canadian trials, the label recommendation for a broadcast rate of sequential applications of 17.5–35.0 g a.i./ha of triflusulfuron + (desmedipham + phenmedipham) at 262–525 g a.i./ha is acceptable. Use of an adjuvant in combination with a tank-mix of triflusulfuron + BETAMIX will be contradicted on the approved draft label.

7.3 Phytotoxicity to target crop and effects on yield

A total of 17 trials conducted in Alberta, Manitoba, Michigan and Ontario reported crop injury, crop yield or crop quality parameters. The 17 trials were conducted over a span of seven years from 1991 to 1998.

In Manitoba, average injury rating across five sites was 1% at 35 and 70 g a.i./ha of triflusulfuron. Tank-mixes of triflusulfuron + desmedipham, or phenmedipham + desmedipham at 1× or 2× rates (70 + 800) caused only 2.5% injury. Yield increases in response to application of triflusulfuron alone or in combination with various desmedipham + phenmedipham treatments ranged from 587–658% of the untreated control at one site for which yield data were reported.

In Alberta, crop vigour ratings for triflusulfuron + surfactant and triflusulfuron + (desmedipham + phenmedipham) combinations averaged 8.3, on a scale of 0–9, at three sites. Average yield for these treatments was 111% of the untreated check across three sites.

In Michigan, where two sequential applications of triflusulfuron + (desmedipham + phenmedipham) were tested at the cotyledon stage at 17.5 + 365 g a.i./ha, early crop injury was 30% but declined to 15% later in the season. In another site, the same treatment caused only 4% injury.

Early post-emergence applications of above treatments caused an initial injury of 6–24% at three Michigan sites. The crop recovered later in the season as only 0–6% injury was observed and sugar beet yields increased 286–416% of the untreated check.

7.4 Impact on succeeding crops

No crop rotation data were submitted.

Based on information supplied by Dupont, triflusulfuron-methyl breaks down very rapidly in soil, and rotational crops can be replanted 14 days after application (WSSA Handbook, 7th Edition, 1994). The half-lives were two to four days in an Idaho soil (pH 8.2), and North Dakota soil (pH 7.6). Triflusulfuron is weakly adsorbed to soil and adsorption decreases as pH increases. In laboratory studies, more than 90% of triflusulfuron was degraded within 30 days.

Due to the short residual life of this sulfonylurea herbicide, carry-over effects may not be considered to be of concern to rotational crops such as winter wheat or spring wheat in southwestern Ontario. However, there may be risk of injury to soybeans, which is a common and major rotational crop after sugar beets in Ontario; and to tomatoes, which are highly sensitive to ALS-inhibiting herbicides in general.

Based on consultations with Rogers Sugar, the main rotational crops after sugar beets in the irrigated areas of southern Alberta would be cereal crops for two years (60–70% of the fields). Other possible rotational crops would be beans, potatoes, sweet corn and alfalfa. Potatoes, which are highly sensitive to sulfonylurea herbicides in general, are not planted immediately after a sugar beet crop.

7.4.1 Consideration of Organisation for Economic Co-operation and Development label restrictions

There are no recropping restrictions on the EPA-approved label for UPBEET® 50 DF. The U.K. label, DEBUT, carries the following statements:

> Following Crops—After applying DEBUT to a sugar beet crop, only winter cereals should be sown in the same calendar year. Any crop may be sown or planted in the following spring (next calendar year) after a sugar beet crop treated with DEBUT.
>
> Crop Failure—In the event of crop failure for any reason, sow only spring barley, linseed or sugar beet within four months of application of DEBUT, provided this agrees with the recommendations of any partner product. After four months from application, refer to "Following Crops" section.

Information obtained from Germany indicates that triflusulfuron residues may cause phytotoxicity to table beets.

In Finland, there are no recropping restrictions; however, there may be problems with potatoes at a certain soil pH.

7.4.2 Conclusions

Based on a summary of the environmental chemistry/environmental fate profile of this sulfonylurea herbicide and consideration of foreign labels, it is concluded that cereal crops (spring wheat, durum wheat, winter wheat, barley) may not sustain injury the following year on the assumption that:

- cereal crops are tolerant to sulfonylurea herbicides in general; and
- triflusulfuron is considered non-persistent in soil (laboratory half-life = six days, DT_{50} = three days in a silt loam and clay loam in Idaho and North Dakota).

The following crop rotation restrictions should appear on the UPBEET® 50 DF label:

- **In case of crop failure, only sugar beets may be replanted within 30 days of application of UPBEET® 50 DF. However, no more UPBEET® 50 DF may be applied if a maximum of 100 g/ha has already been applied.**

- **Cereal crops (spring wheat, durum wheat, winter wheat, barley) may be planted the following year.**

- **For all other crops, conduct a field bioassay.**

The proposed section on “Field Bioassay” is acceptable.

The sponsors of this URMUR are encouraged to generate crop rotation data in southwestern Ontario and southern Alberta to address this label restriction under a new submission.

7.5 Impact on beneficial and other non-target organisms

Because of low acute toxicity (oral, dermal, inhalation), UPBEET® 50 DF is considered practically non-toxic to aquatic, avian and non-target species.

7.6 Weed resistance management

Based on consultations with sugar beet growers, sugar beets are grown after a strictly-adhered four-year rotation because of risk of nematodes. Application of an ALS-inhibitor herbicide after every four years in the same field is not expected to lead to development of weed resistance. The proposed paragraph on “Resistance Management” is acceptable.

7.7 Contribution to sustainability

- Herbicides currently available for post-emergence control of broadleaf weeds are BETANEX, BETAMIX, and LONTREL. According to the sponsors, these products do not provide effective control of velvetleaf, which is the main problem weed in southwestern Ontario. In Western Canada, registration of UPBEET® 50 DF will supplement the activity of BETAMIX on kochia, which is a problem weed, and offer an alternative tool for management of green foxtail, which has developed resistance to dinitroaniline and acetyl-Coenzyme A carboxylase herbicides.

- Registration of UPBEET® 50 DF would enable Canadian sugar beet growers to have access to "Group 2" chemistry, which will support weed resistance management objective by offering alternative mode of action.

- Sugar beet growers across the border in Michigan, where the Canadian sugarbeet is shipped, currently have access to Group 2 chemistry. The producer groups in Alberta and Ontario are vulnerable to competition in absence of this product.

- Having access to another weed management tool will support the viability of the crop, and hence promote crop diversification.

- A reduction in the current rate of BETAMIX will be achieved. UPBEET® 50 DF has a safer toxicological profile compared to BETAMIX, which has 55.7% isphorone.

8.0 Conclusions

Triflusulfuron-methyl is a sulfonylurea herbicide (Group 2) that inhibits acetolactase synthase. Triflusulfuron-methyl will be marketed as a 50% dry flowable product under the name UPBEET® 50 DF. UPBEET® 50 DF may be used in combination with a non-ionic adjuvant as a post-emergence application in sugar beet for control of velvetleaf, which is a serious competitor in this crop in southwestern Ontario. UPBEET® 50 DF may also be tank-mixed with BETAMIX (desmedipham + phenmedipham) for control of additional weeds such as redroot pigweed, lamb's quarters, kochia and green foxtail. UPBEET® 50 DF is to be applied at 35–75 g/ha (17.5–35.0 g a.i./ha) alone or in combination with BETAMIX. More than one application of UPBEET® 50 DF may be made to the same crop provided the total amount applied does not exceed 100.0 g/ha (50g a.i./ha). UPBEET® 50 DF is to applied by ground equipment only.

Occupational exposure assessment

The short-term dermal toxicity study was deemed most appropriate for use in the occupational risk assessment. Calculated MOEs were adequate for the proposed use. From the perspective of occupational exposure, the product may be supported.

Based on the evaluation of the acute toxicity data package on the UPBEET® 50 DF Herbicide, the signal words **WARNING - EYE IRRITANT** are required on the primary display panel.

The precautionary label statement should be changed from:

> "Do not handle pesticides with bare hands. Chemical-resistant gloves significantly reduce hand exposure. Wear waterproof gloves, long-sleeved shirt and pants, shoes and socks for mixing/loading/cleanup operations and when making sprayer and nozzle repairs and adjustments. Do not use leather or cloth gloves."

to:

> "When mixing, loading or applying, wear a long-sleeved shirt, long pants, shoes and socks. In addition, wear chemical-resistant gloves and face shield or safety glasses for mixing and loading."

Food residue exposure assessment

The plant metabolism studies demonstrated that triflusulfuron-methyl degraded rapidly. No parent or metabolites were detected in sugar beet (roots) by 56 days (PHI 60 d). Since all processed commodities (sugar, molasses) are derived from sugar beet root, the ROC for sugar beets was defined as parent only.

The results of the supervised trials conducted in the U.S. (from zones common to the U.S. and Canada) and Europe indicated that when sugar beets were treated with triflusulfuron-methyl according to the proposed label directions, no residues (<0.02 ppm) were detected at harvest in sugar beet roots and foliage. In a processing study, there was no concentration of triflusulfuron-methyl residues in sugar, molasses or dried pulp at an application rate equivalent to 8× the proposed rate.

A specific method was developed for the analysis of triflusulfuron-methyl residues in sugar beets (roots and tops). Quantification was performed by HPLC with UV detection. The LOQ and LOD are 0.02 ppm, 0.005 ppm, respectively. Recoveries and independent laboratory validation supported the method for the analysis of triflusulfuron-methyl residues in sugar beets.

The EPA proposed a tolerance of 0.05 ppm in sugar beet roots and tops. To harmonize with the U.S. tolerance, the PMRA proposes a MRL of 0.05 ppm for sugar beet (roots).

The livestock metabolism study showed that a majority of the total radioactive dose (75–95%) was excreted in the urine and faeces. The anticipated residue levels in treated sugar beet are expected to be under the LOQ. Total radioactive residues in all edible livestock commodities were <0.005 ppm when extrapolated from the 500× feeding level (10 ppm) to the anticipated

1× feeding level (0.02 ppm); therefore, an animal feeding study was not required. MRLs would not be required for meat, milk and eggs.

Metabolism studies indicated that there were no significant novel plant metabolites when compared to goat, or rat metabolic profiles.

In the confined crop rotation study, measurable residues of several metabolites were detected in livestock feeds at the 30-day plantback interval. In order to ensure that potential residues in meat, milk and eggs would not be detectable if wheat forage, straw and beet root foliage were fed to livestock, it was concluded that a 120-day plantback interval should be placed on the label for all rotation crops.

Potential exposure to triflusulfuron-methyl in the diet is very low. If a proposed MRL of 0.05 ppm is used for sugar beet (root), the PDI for adults, infants and children will all be below 1% of the ADI allotted to food. Ten percent of the ADI is allotted to drinking water.

Environmental risk assessment

Hydrolysis of triflusulfuron-methyl is the major route of transformation in aerobic and anaerobic soils. Two major transformation products, triazine amine and methyl saccharin, are produced from the acid-catalyzed hydrolytic cleavage of the sulfonylurea bridge. Both have a significant potential for carry-over to the next growing season.

Triflusulfuron-methyl is non-persistent in soil studies performed in the laboratory ($t_{1/2}$ = six days), non-persistent in soil used for field testing (DT_{50} = three days), and slightly persistent under anaerobic (flooded) soil conditions (DT_{50} = 21 days).

Microbial transformation in soils under aerobic conditions is a major route of dissipation, resulting in N,N-bis-desmethyl triazine amine, N-desmethyl triazine amine, triazine amine, and methyl saccharin as the major transformation products. Under anaerobic conditions, the major transformation products are triazine amine and methyl saccharin. Further transformation of these products did not occur.

Although triflusulfuron-methyl is highly mobile, its short half-life of six days in soil suggests that it is unlikely to leach into groundwater.

In aqueous solution, hydrolysis is the major route of transformation, with half-lives of 3.7, 32, and 36 days at pH 5, pH 7, and pH 9, respectively. Hydrolysis in water is by an acid-catalyzed hydrolytic cleavage of the sulfonylurea bridge, resulting in two major transformation products, triazine amine and methyl saccharin, which appear to be persistent.

The use of UPBEET® 50 DF will not pose a threat to mammalian wildlife, fish, terrestrial and aquatic invertebrates, pollinators, birds, or algae at expected environmental concentrations. This

herbicide does, however, represent a serious threat to non-target terrestrial and aquatic vascular plant species. The MOS, based on the mean shoot weight for sorghum, was calculated to be 0.000 68 and the MOS for *Lemna gibba*, based on frond count, was 0.08.

In order to protect both non-target aquatic and terrestrial plant species, an aquatic buffer zone of 10 metres and a terrestrial buffer zone of 23 metres was established.

The following mitigative label statements should be incorporated into the final label:

> "For the protection of non-target habitats, overspray or drift to sensitive habitats must be avoided. A buffer zone of 23 metres is required between the downwind edge of the boom and sensitive terrestrial habitats including grasslands, forested areas, shelter belts, woodlots, hedgerows, dry slough beds, and shrublands. A buffer zone of 10 metres is required between the downwind edge of the boom and sensitive aquatic habitats such as sloughs, ponds, Prairie potholes, lakes, rivers, streams and irrigation ditches, and the vegetation in and surrounding wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers."

Under "Use Precautions":

> "Do not apply during periods of dead calm, when winds are gusty or when wind speed is greater than 15 km/h at two metres high above ground at the site of application."
>
> "When a tank mixture is used, consult the label of each of the tank-mix partners for additional use precautions, and observe the largest (most restrictive) buffer zone, of the products used, for application of the tank mixture."
>
> "To reduce the risk of leaching, do not apply more than ¾ inches of irrigation water to treated areas within seven (7) days after an application of UPBEET® 50 DF Herbicide."

List of Abbreviations

a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ALS	acetolactate synthase
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
bwg	body-weight gain
d	days
DAT	days after treatment
DF	dry flowable
DT_{50}	period required for 50% dissipation
EC_{50}	median effective concentration
EEC	expected environmental concentration
EPA	United States Environmental Protection Agency
FC	feed consumption
FOB	functional observational battery
FSH	follicle-stimulating hormone
h	hours
ha	hectare
hcg	human chorionic gonadotropin
HPLC	high performance liquid chromatography
HPT	hypothalmic-pituitary-testicular
IC_{25}	25% inhibition concentration
K_D	adsorption coefficients
$K_{oc(D)}$	organic carbon adsorption coefficients
K_{ow}	octanol/water partition coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LH	luteinizing hormone
LOD	limit of detection
LOEL	lowest observable effect level
LOQ	limit of quantification
mo	months
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NZW	New Zealand White

OECD	Organisation for Economic Co-operation and Development
PC	position control
PDI	potential daily intake
PHED	Pesticide Handler Exposure Database
PHI	pre-harvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodities
RBC	red blood cell
ROC	residue of concern
SF	safety factor
$t_{1/2}$	half-life
TGAI	technical grade active ingredient
TRR	total radioactive residue
U.K.	United Kingdom
U.S.	United States
UDS	unscheduled deoxyribonucleic acid synthesis
URMUR	User Requested Minor Use Registration
UV	ultra-violet
v/v	volume ratio
vs	versus
wk	week
WSSA	Weed Science Society of America
yr	year
Fg	micrograms
FM	micromolars

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Appendix I Summary Table of Toxicology Studies for Triflusulfuron-Methyl

METABOLISM
Four groups of 5–6 rats/sex were treated by gavage with the following single doses of radiolabelled DPX-66037: group 1, 25 mg/kg bw [triazine(U-14C)]; group 2, 25 mg/kg bw unlabelled DPX-66037 for 14 days, then a single dose, 25 mg/kg bw [triazine(U-14C)]; group 3250 mg/kg bw [triazine(U-14C)]; and group 4250 mg/kg bw [ester carbonyl-14C]. DPX-66037 is well absorbed by the gastrointestinal tract when administered orally, and is rapidly excreted (78–96% of the AD within 48 h) in the urine and faeces. Female rats excreted more radioactivity in the urine than male rats, regardless of dose or preconditioning. Urinary excretion of radioactivity in females was lower after repeat low-dose administration than after a single low-dose administration. Faecal excretion was higher in the 250 mg/kg bw groups than in the 25 mg/kg bw groups. Parent compound was a major component of the radioactivity in the faeces of male and female rats treated at 250 mg/kg bw. Since no detectable parent compound was found in the 25 mg/kg bw groups, it appears that 250 mg/kg bw overwhelmed the absorptive capacity of the rats. DPX-66037 was extensively metabolized (see proposed pathway, Figure 3.1) and similar metabolites were found in the faeces, urine and liver in different proportions. The metabolites identified were N-desmethyl DPX-66037 (in urine), N-hydroxymethyl DPX-66037 (in urine), triazine metabolites (triazine amine, N-desmethyl triazine amine, N,N-bis-desmethyl triazine amine) (in urine and liver), methyl saccharin (in liver), and the unchanged parent compound (in faeces and liver).

STUDY	**SPECIES/STRAIN AND DOSES**	**NOEL/NOAEL and LOEL mg/kg bw/d**	**TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS**
ACUTE STUDIES			
Oral	Rat, SD, 5/sex, 0, 800, 1600, 3200 and 6200 mg/kg	LD_{50} = 4149 mg/kg [bw] in males and 5971 mg/kg [bw] in females	Clinical observations consisted of reduced activity, reduced muscle tone, prostration, body soiling, urogenital soiling, ataxia and hunched posture. LOW TOXICITY
Oral	Mouse, CD-1 5/sex, 0, 1250, 2500 or 5000 mg/kg bw.	LD_{50} = 4665 (3322–6552) mg/kg bw in males and 5359 (3816–7526) mg/kg bw in females	Mortality was reported in 4/5 males and 2/5 females at 5000 mg/kg bw. Clinical observations: reduced activity, reduced muscle tone, prostration, body and urogenital soiling, coolness to touch and pale extremities. LOW TOXICITY
Dermal	Rat, SD, 5/sex @ 5000 mg/kg	LD_{50} > 5000 mg/kg bw	Slight focal erythema noted in 2/5 males and sloughing of superficial dermis in 3/5 females—recovery by Day 2–7 LOW TOXICITY
Inhalation (4 h)	Rat, SD (CD), 5/sex, 1.98 mg/L	LC_{50} > 1.98 mg/L	Mass median aerodynamic diameter = 8.3 Fm, F_g = 3.0 Fm 35% < 6 Fm LOW ACUTE TOXICITY

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL and LOEL mg/kg bw/d	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Skin irritation	Rabbit, NZW, 3 females, 0.5 g dose	Primary irritation score (24 and 48 h) = 0.3/8	NON-IRRITATING
Eye irritation	Rabbit, NZW, 3 females, 0.05 g dose	Maximum average score = 8.67/110	conjunctival redness in one rabbit only at 1 h; no effects at 24 h NON-IRRITATING
Skin sensitization (Maximization test)	Guinea pig, Pirbright, test material, intra-dermal injection 20% followed by a topical application of 50% PC reference data: with DNCB	Test material not sensitizing but P.C. was sensitizing—demonstrating responsiveness of assay	NOT A SENSITIZER
SHORT TERM			
21-d dermal	NZW rabbits, 5/sex/group, 0, 50, 300, or 1000 mg/kg bw	NOEL = 1000 mg/kg bw no LOEL	No systemic toxicity observed
90-d dietary	Rat, 10/sex/group, 0, 100, 2000, 10 000 or 15 000 ppm (equal to 6.2, 127, 646 or 965 mg/kg bw/d for males and 7.54, 150, 774 or 1070 mg/kg bw/d for females)	NOEL = 100 ppm (6.2 mg/kg bw/d) based on regenerative hemolytic anemia and body weights LOEL = 2000 ppm (127 mg/kg bw/d)	At 2000 ppm: lower bw, bwg, food consumption, feed efficiency, and regenerative hemolytic anemia At 10 000 ppm: serum glucose and phosphate were statistically significantly lower than controls; control terminal bw: males, 534.3 g, females, 305.3 g; control terminal FC: (days 84–91) males, 26.6 g/rat, females, 23.2 g/rat

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL and LOEL mg/kg bw/d	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
90-d dietary	Rat, 10/sex/group 0, 100, 2000, 10 000 or 15 000 ppm (equal to 6.56, 133, 658 or 1036 mg/kg bw/d for males and 7.71, 153, 783 or 1124 mg/kg bw/d for females)	NOEL = 100 ppm (6.56 mg/kg bw/d) LOEL = 2000 ppm (133 mg/kg bw/d)	At 2000 ppm: bw, bwg, food consumption, feed efficiency, and regenerative hemolytic anaemia decreased At 10 000 ppm: relative liver weights were increased in males and females. Splenic extramedullary hematopoiesis was observed in males at $10 000 ppm and in females at $ 2000 ppm. Renal hemosiderosis in males and females at $10 000 ppm; control terminal bw: females, 565.0 g, males, 309.3 g; control terminal FC: (days 84–91) males, 28.0 g/rat, females, 20.6 g/rat
12-mo dietary/capsule	Dog, beagle; 5/sex/dose; 0 35, 875, or 3500 ppm (equal to 1.0, 26.9 or 95.5 mg/kg bw/d for males, and 1.2, 27.7 or 95.5 mg/kg bw/d for females)	NOEL = 875 ppm (26.9 mg/kg bw/d) LOEL = 3500 ppm (95.5 mg/kg bw/d	At 3500 ppm: lower bw, bwg and slight decrease in hematology parameters (RBCs, Hg, hct), increase in liver weights, minimum centrilobular hepatocellular hypertrophy
CHRONIC TOXICITY/ONCOGENICITY			
18-mo dietary	Mouse, Crl:CD-1(ICR)BR, 80/sex/dose 0, 10, 150, 2500 or 7000 ppm (equal to 1.37, 20.9, 349 or 1024 mg/kg bw/d for males, and 1.86, 27.7, 488 or 1360 mg/kg bw/d for females)	Chronic Effects NOEL = 150 ppm (20.9 mg/kg bw/d) LOEL = 2500 ppm (349 mg/kg bw/d) Oncogenicity No oncogenic effects in either sex	Absolute and relative liver weights were increased at $2500 ppm. Histopathological changes in the liver were at $2500 ppm (foci of cellular alteration, intrahepatocellular hematopoesis, individual necrosis)

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL and LOEL mg/kg bw/d	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
22-mo dietary	Rat, SD (CD), 62/sex/group 0,10, 100, 750 or 1500 ppm (equal to 0.406, 4.06, 30.6 or 64.5 mg/kg bw/d for males and 0.546, 5.47, 41.5 and 87.7 mg/kg bw/d for females)	Chronic Effects NOEL = 100 ppm (4.06 mg/kg bw/d) LOEL = 750 ppm (30.6 mg/kg bw/d) Oncogenicity NOEL = 100 ppm (4.06 mg/kg bw/d) for males and 1500 ppm for females LOEL = 750 ppm (30.6 mg/kg bw/d) for males	At $750 ppm: bw and bwg were decreased, and females had decreased RBCs and an increased incidence of Leydig cell hyperplasia, increased incidence of myelin/axonal degeneration of the sciatic nerve in the 1500-ppm group of females (25/48 vs 42/49). Oncogenic in male rats, increased incidence of Leydig cell adenomas in the 750 and 1500 ppm groups
REPRODUCTION / DEVELOPMENTAL TOXICITY			
Multi-generation	Rat, CRL:COBS (SD), 30/sex/dose, F0; 0, 10, 100, 750 or 1500 ppm (equal to 0.588, 5.81, 44.0 or 89.5 mg/kg bw/d for males and 0.764, 7.75, 58.0 or 115 mg/kg bw/d for females)	Systemic NOEL = 100 ppm (5.81 mg/kg bw/d) Reproductive NOAEL = 750 ppm (44 mg/kg bw/d)	At $750 ppm: bw and bwg were decreased during the premating periods of both generations. Decreased bw at $750 ppm during gestation and lactation. At $750 ppm: decreased F1 male pup bw on day 14 At 1500 ppm: bw both sexes on days 14 and 21 No effects on reproductive parameters
Teratogenicity	Rat, CRL:COBS (SD) BR, 25/dose 0 30, 120, 350 or 1000 mg/kg bw	Maternal NOEL = 120 mg/kg bw/d Developmental NOEL = 120 mg/kg bw/d No teratogenic effects up to highest dose tested	Maternal: at $350 ppm: decreased bw and bwg. Decreased food consumption in the 350 and 1000 mg/kg bw/d groups Developmental: delayed ossification at $350 mg/kg bw/d No teratogenic effects
Teratogenicity	Rabbit/NZW, 20/dose 0, 15, 90, 270 or 800 mg/kg bw	Maternal NOEL = 15 mg/kg bw/d Developmental NOEL = 90 mg/kg bw/d No teratogenic effects up to highest dose tested	Maternal: at 90 mg/kg: significant decreased bw and bwg at the onset of dosing at $270 mg/kg: clinical signs (gastrointestinal tract), decreased FC Developmental: at $270 mg/kg abortions No teratogenic effects

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL and LOEL mg/kg bw/d	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
MUTAGENICITY			
Salmonella/Ames Test	*S. typhimurium* - TA98, 100, 1535, 1537	0, 62.5, 125, 250, 500 or 1000 Fg/plate, ± S9	Negative
Mammalian cytogenetics (in vitro)	CHO/HGPRT forward mutation assay	0, 100, 500, 1000, 1500 or 2000 Fg/plate ± S9	Negative
Mammalian chromosomal aberration (in vitro)	Human lymphocyte cytogenetic assay	0, 50, 100, or 200 Fg/mL -S9 0, 100, 200 or 400 Fg/mL +S9	Unacceptable
Mammalian chromosomal aberration (in vitro)	Human lymphocyte cytogenetic assay	0, 0.5, 1.5, 1.7, 1.85, or 2.0 mg/mL ± S9	Positive (+S9) clastogenic at 2.0 mg/mL Cytotoxic at $1.85 mg/mL
Mammalian chromosomal aberration (in vitro)	Human lymphocyte cytogenetic assay	0.1 to 2.0 mg/mL ± S9	Positive (+S9) $1.7 mg/mL
Micronucleus assay (in vivo)	Mouse, Swiss OF1	5000 mg/kg bw with cells harvested at 24- and 48-h post-treatment	Unacceptable
Micronucleus assay (in vivo)	Mouse, Crl:CD-1(ICR)BR	1250, 2500 or 5000 mg/kg bw harvested at 24- and 48-h post-treatment	Negative
UDS in vitro	Rat hepatocytes	0, 0.05 to 2.0 mg/mL	Negative

STUDY	SPECIES/STRAIN AND DOSES	NOEL/NOAEL and LOEL mg/kg bw/d	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Possible mechanisms of Leydig cell tumour development	1) Ten Crl:CD®BR male rats/group were treated by gavage for 15 d 2) Rat liver for aromatase and P450 activity 3) Blood samples from the 1-yr sampling in the chronic study 4) Leydig cells from 11-wk old male rats	1) 0, 1000, 1500 or 2000 mg/kg bw 2) 0.01 to 0.5 FM 3) 0,10, 100, 750 or 1500 ppm 4) 0, 0.1, 0.5, 1.0, 10, 100 or 1000 FM	1) slight increase in LH, FSH and prolactin In the rats treated with hCG, the 2000 mg/kg bw/d group had increased testosterone and lower estradiol than the controls 2) dose-dependent decrease in aromatase activity. P450 showed a type II binding spectra 3) trends at $750 ppm toward increased testosterone and FSH and decreased estradiol 4) testosterone increased (198%) and estradiol decreased
Acute neurotoxicity	Rat, Crl:CD®BR, 10/sex/group 0, 500, 1000 or 2000 mg/kg bw	NOAEL: 2000 mg/kg bw No evidence of neurotoxicity was observed at any dose.	bw, bwg and FC in the 2000 mg/kg bw males was lower than controls on days 1 and 2
Sub-chronic neurotoxicity (92 d)	Rat, Crl:CD®BR, 11/sex/group 0, 100, 750, 1500 or 3000 ppm (equal to 6.1, 46.1, 92.7 or 186.2 mg/kg bw/d)	NOEL: 100 ppm (6.1 mg/kg bw/d) No evidence of neurotoxicity was observed at any dose.	At $750 ppm: bw, bwg and FC decreased in females Similar effects were observed in males at 3000 ppm.
Compound-induced mortality: In the rabbit teratology study there was increased mortality (9/20) at 800 mg/kg bw/d.			
Recommendation for ADI: 0.04 mg/kg bw MOE for Leydig cell tumours: The MOE for Leydig cell tumours in male rats is 765 compared to the ADI. A threshold for this effect is postulated by its non-genotoxic mechanism.			