Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2000-09

Flucarbazone-sodium

The active ingredient flucarbazone-sodium and the associated formulated products Everest 70DF and Everest Solupak 70DF containing flucarbazone-sodium as a post-emergence herbicide for the control of wild oats (*Avena fatua*) and green foxtail (*Setaria viridis*) in spring wheat (*Triticum aestivum*) have been granted Section 17 temporary registrations.

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

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for the technical active ingredient flucarbazone-sodium and associated end-use products EVEREST 70DF and EVEREST Solupak 70DF as a post-emergence herbicide developed by Bayer AG in Canada for the control of wild oats (*Avena fatua*) and green foxtail (*Setaria viridis*) in spring wheat (*Triticum aestivum*).

EVEREST 70DF is a Group 2 (inhibits the enzyme acetolactic synthase [ALS], also known as acetohydroxy acid synthase [AHAS]) herbicide, which allows it to be used as an effective resistance management tool against wild oats and biotypes resistant to acetyl CoA carboxylase or ACCase (Group 1) and triallate (Group 8) herbicides, and green foxtail and biotypes resistant to ACCase (Group 1) and dinitroaniline (Group 3) herbicides. EVEREST 70DF is not to be applied alone, but tank-mixed with 0.25% v/v Agral 90 or Agsurf plus a recommended broadleaf herbicide.

Flucarbazone-sodium is noteworthy in that the PMRA and the United States Environmental Protection Agency (U.S. EPA) shared the initial work of screening the submissions for completeness (PMRA) and for suitability as a reduced risk pesticide (EPA). Canada undertook the review and evaluation of the submission data package that was shared with the United States. The parallel use pattern allows for harmonized maximum residue limits (MRL) or tolerances, which are key to avoiding trade irritants.

The submission is also a pilot project to test the utility of various electronic submission review formats, which in addition to a traditional paper submission included a CADDY and web-based format. This allowed for a direct comparison of efficiency gains in any or all of the following processes associated with a regulatory petition: assembly, submission, handling, data evaluation, production of internal and public documents, and data archiving.

The registrant has changed the product names for the technical active ingredient and the formulated end-use products. A reference to the former and present product names is as follows:

Former product names	**Present product names**
MKH 6562 or MKH 6562 Technical	Flucarbazone-Sodium Technical Herbicide
MKH 6562 70DF	EVEREST 70DF
MKH 6562 Solupak 70DF	EVEREST Solupak 70DF

Methods of analysis of flucarbazone-sodium residues in various environmental media can be provided to monitoring agencies and research institutions upon request to the PMRA.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning these products. Bayer will be carrying out additional studies as a condition of this temporary registration. Following the review of this new data, the PMRA will publish a proposed regulatory decision document and request comments from interested parties before proceeding with a final regulatory decision on full registration.

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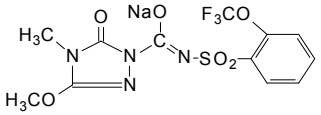
1.0 The active substance, its properties, uses, classification and labelling

1.1 Identity of the active substance and preparation containing it

Active substance:	Flucarbazone-sodium
Function:	Herbicide
Chemical name:	
International Union of Pure and Applied Chemistry:	*N*-(2-trifluoromethoxyphenyl)-4,5-dihydro-3-methoxy-4-methyl-5-oxo-1*H*-1,2,4-triazoline-1-carboxamide, sodium salt
Chemical Abstracts Service (CAS):	4,5-dihydro-3-methoxy-4-methyl-5-oxo-*N*-[[2-(trifluoromethoxy)phenyl]sulfonyl]-1*H*-1,2,4-triazole-1-carboxamide, sodium salt
CAS number:	181274-17-9
Molecular formula:	$C_{12}H_{10}F_3N_4NaO_6S$
Molecular weight:	418.29
Structural formula:	
Nominal purity of active substance:	95.6% nominal
Identity of relevant impurities of toxicological, environmental, or other significance:	Scientifically sound rationale supporting the waiver request for the absence of hydrazine contamination was accepted. The technical grade flucarbazone-sodium does not contain toxic microcontaminants identified as Toxic Substances Management Policy (TSMP) Track-1 substances.

1.2 Physical and chemical properties of active substance

Table 1.2 Technical product: MKH 6562

Property	Result	Comment
Colour and physical state	Colourless crystalline powder	
Odour	Odourless	
Melting point or range	200EC (under decomposition)	
Boiling point or range	Not applicable	
Density	1.59 g/mL at 20EC	
Vapour pressure	$<1 \times 10^{-9}$ at 20EC (extrapolated)	The active substance is considered to be non-volatile under field conditions.
Henry's Law Constant at 20EC	$<1 \times 10^{-11}$ Pa m^3 mol^{-1} ($1/H = 2.48 \times 10^{14}$)	The active ingredient is considered to be non-volatile from moist soil and water surfaces.
UV and visible spectrum	λ_{max} = 233 nm No absorption observed at λ = 310–750 nm at pH 5, 7, and 9	Photolysis will not be a principal route of dissipation of the active substance in the environment.
Solubility in water at 20EC	44 g/L in neutral, acidic, and alkaline conditions	The active substance is very soluble in water under environmentally relevant pH conditions and, therefore, has a potential to leach in soils and be transported in surface runoff water.
Solubility (g/L) in organic solvents	Solvent — Solubility (g/L) *n*-heptane <0.1 xylene <0.1 dichloromethane 0.72 2-propanol 0.27 PEG* 48.0 acetone 1.3 ethylacetate 0.14 acetonitrile 6.4 DMSO >250.0 *polyethylene glycol	

Property	Result	Comment
n-Octanol–water partition coefficient (log K_{ow})	pH / log K_{ow} Unbuffered –2.85 4 –0.89 7 –1.84 9 –1.88	The active substance has a negligible potential for bioconcentration or bioaccumulation in organisms.
Dissociation constant (pK_a)	1.9 for free acid	The active substance will exist as an anion and will be mobile in soils at an environmentally relevant pH range of 5.0–9.0.
Oxidizing properties	Stable thermally at ambient temperature under air	
Storage stability	Not applicable to the technical product	

Table 1.3 End-use products: MKH 6562 70DF and MKH 6562 Solupak 70DF

Property	Result
Colour	Not provided
Odour	Not provided
Physical state	Solid
Formulation type	Wettable granule
Guarantee	70% (nominal)
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material and description	Paper, 696 g per bag *or* soluble packs, 173.5 g per polyvinyl alcohol (PVA) pouch
Bulk density	480–560 kg/m^3
pH of 5% dispersion in water	7–8 at 25EC
Oxidizing or reducing action	The product does not contain oxidizing or reducing agents.
Storage stability	The product is stable in PVA water soluble packets over-wrapped in various laminated bags after one year under warehouse conditions.
Explodability	No explosive potential

1.3 Classification and labelling

1.3.1 Classification and labelling of technical grade active ingredient

Technical MKH 6562 had low toxicity by the oral, dermal, and inhalation routes, was non-irritating to skin and minimally irritating to eyes, and was not a skin sensitizer.

The primary display panel of the label for the technical material is adequate. The following statement has been added to the secondary display panel of the label under the appropriate section: “If Inhaled — Remove from site of exposure.”

1.3.2 Classification and labelling of end-use products

The end-use products, MKH 6562 70DF Water Dispersible Granular Herbicide and MKH 6562 Solupak 70DF, had low toxicity by the oral, dermal, and inhalation routes, were non-irritating to skin and minimally irritating to eyes, and were not considered to be a skin sensitizer.

The primary display panel of the labels for the end-use products are adequate. The following statement has been added to the secondary display panel of the labels under the appropriate section: “If Inhaled — Remove from site of exposure.”

There are no known significant toxicological concerns regarding the formulant ingredients.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Two solvent programmed reversed phased high-performance liquid chromatographic (HPLC) methods were used for the determination of the active substance and three significant structurally related impurities (content $ 0.1%) in the technical product. The methods have been shown to have satisfactory specificity, linearity, precision, and accuracy.

2.2 Method for formulation analysis

An isocratic reverse phased HPLC method was used for the determination of the non-ionic compound (the corresponding acid of the active substance) in the formulation. The method has been shown to have satisfactory specificity, linearity, precision, and accuracy and is suitable for use as an enforcement method.

2.3 Methods for residue analysis

Multiresidue methods for residue analysis
Protocols from existing multiresidue methods were found to be not suitable for the determination of flucarbazone-sodium, flucarbazone sulfonamide, or *N*-desmethyl flucarbazone residues in wheat or animal commodities.

Methods for residue analysis of plants and plant products

Data gathering method
Liquid chromatography and mass spectrometry (LC/MS/MS) (limit of quantitation [LOQ] = 0.01 parts per million [ppm]; limit of detection [LOD] = 0.005 ppm)
Residue of concern (ROC) defined as flucarbazone-sodium + *N*-desmethyl flucarbazone

Flucarbazone-sodium

Matrix	Wheat forage	Wheat hay	Wheat straw	Wheat grain
Spiking levels (ppm)	0.01–0.1	0.01–0.1	0.01–0.1	0.01–0.1
Range of recoveries (%)	93–100 (*n* = 6)	77–96 (*n* = 6)	83–98 (*n* = 6)	92–97 (*n* = 6)
Recovery mean ± standard deviation (SD) (%)	96 ± 2	87 ± 7	94 ± 5	94 ± 2

***N*-desmethyl flucarbazone**

Matrix	Wheat forage	Wheat hay	Wheat straw	Wheat grain
Spiking levels (ppm)	0.01–0.1	0.01–0.1	0.01–0.1	0.01–0.1
Range of recoveries	61–89 (*n* = 6)	56–102 (*n* = 6)	85–107 (*n* = 6)	60–97 (*n* = 6)
Recovery mean ± SD (%)	79 ± 9	80 ± 20	95 ± 8	83 ± 14

Confirmatory method
LC/MS/MS acts both as a method to detect and as a confirmatory method to quantitate the analytes of interest. An additional confirmatory method was not necessary.

Enforcement method
Enforcement method equivalent to data gathering method

Interlaboratory validation (ILV)
ILV indicated good reliability and reproducibility.

Methods for residue analysis of animal matrices

Data gathering method
LC/MS/MS (LOQ = 0.02 ppm in liver, kidney, muscle, and fat, 0.005 in milk; LOD = 0.014, 0.002, 0.002, 0.009, and 0.004 ppm in liver, kidney, muscle, fat, and milk, respectively)
ROC defined as flucarbazone-sodium

Matrix	Liver	Kidney	Muscle	Fat	Milk
Spiking levels (ppm)	0.02–0.1	0.02–0.1	0.02–0.1	0.02–0.1	0.005–0.05
Range of recoveries (%)	91–104 (*n* = 8)	102–110 (*n* = 8)	91–103 (*n* = 8)	88–100 (*n* = 8)	83–104 (*n* = 12)
Recovery mean ± SD (%)	98 ± 4	107 ± 3	97 ± 4	92 ± 3	90 ± 5

Confirmatory method
LC/MS/MS acts both as a method to detect and as a confirmatory method to quantitate the analytes of interest. An additional confirmatory method was not necessary.

Enforcement method
No enforcement was proposed. The sample preparation procedure in the data gathering method is not specific to flucarbazone-sodium; therefore, it cannot be used as an enforcement method.

ILV
ILV indicated good reliability and reproducibility.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

MKH 6562 was rapidly absorbed, with maximal plasma concentration being achieved within 30 minutes. The high fecal excretion rate, low biliary excretion rate, and high levels of the unchanged parent compound in the fecal extracts suggest that absorption was low, approximately 25–30% of the administered dose for the single and repeat low-dose groups and approximately 15% for the single high-dose group. The highest tissue residues were observed in the liver. Less than 1% of the administered dose, however, remained in the carcass and tissues at sacrifice (at 72 and 96 hours post-dosing). The low mean recovery of radioactivity in the carcass and tissues at sacrifice suggests little potential for accumulation. The major route of elimination was via the feces, accounting for approximately 65–75% of the administered dose in the low-dose group and approximately 75–80% of the administered dose in the high-dose group. Urinary excretion accounted for approximately 25–30% of the administered dose in the low-dose groups and approximately 15% of the administered dose in the high-dose group. Biliary excretion accounted for approximately 2% of the administered dose. Greater than 90% of the administered dose was eliminated within 24 hours. The major component in both the urine and fecal extracts was identified as the unchanged parent compound, MKH 6562, this represented approximately 90–95% of the administered dose. Twelve other metabolites were identified. None of the other metabolites, however, comprised greater than 1% of the administered dose. The major metabolite found in the blood, fat, liver, and muscle was identified as MKH 6562 sulfonamide, although this accounted for less than 1% of the administered dose. There does not appear to be any sex-related differences in absorption, distribution, metabolism, or excretion of MKH 6562.

Technical MKH 6562 has low toxicity by the oral, dermal, and inhalation routes of exposure in rats. In rabbits, it was non-irritating when applied to the skin and minimally irritating to the eyes. It was not a dermal sensitizer in guinea pigs.

The end-use products, MKH 6562 70DF Water Dispersible Granular Herbicide and MKH 6562 Solupak 70DF containing 70% technical, have low acute toxicity by the oral, dermal, and inhalation routes of exposure in rats. In rabbits, they were non-irritating when applied to the skin and minimally irritating to the eyes. Neither induced dermal sensitization in guinea pigs.

The mutagenic potential of MKH 6562 was investigated in vitro in bacterial and mammalian cells, in an in vitro unscheduled deoxyribonucleic acid (DNA) synthesis (UDS) assay and in an in vivo mouse micronucleus assay. MKH 6562 did not cause mutations in vitro in the Ames assay, the V79-HPRT gene mutation assay, or in the chromosome aberration assay with or without metabolic activation. Results of the in vitro UDS assay and the in vivo mouse micronucleus assay were negative. The weight of evidence suggests that technical MKH 6562 is not genotoxic under the conditions of the tests performed.

The subchronic and chronic toxicity of MKH 6562 was investigated in the mouse, rat, and dog. A 28-day dermal study was also carried out in rats. In the subchronic and chronic studies, significant treatment-related findings included immunological changes in the rat and induction of microsomal liver enzymes and liver toxicity in the dog.

In the mouse, there were no adverse treatment-related findings in the 28- or 90-day dietary studies. In a two-year oncogenicity study, retarded body weight development (both sexes) and increased food consumption (males) were observed at 7000 ppm (equal to 2066 and 3212 mg/kg bw/d in males and females, respectively), the highest dose tested.

In the rat, histopathological examination revealed a reversible vacuolation of the fore-stomach squamous epithelium in both sexes at the highest dose tested (1669 and 2314 mg/kg bw/d in males and females, respectively) in the 90-day dietary study. This was considered to be due to a local irritative effect of the test substance on the fore-stomach epithelium. In the two-year dietary study, increased incidences of thickened mucosa of the glandular stomach (both sexes), inflammatory infiltrates (males), and vacuolation of the squamous epithelium in the fore-stomach (females) at 1000 mg/kg bw/d, the highest dose tested, may suggest a potential influence on the gastrointestinal tract (GIT) function. Other treatment-related findings included discoloured feces (white), decreased body-weight gain, and increased food consumption in both sexes in the high-dose groups in the 90-day and two-year dietary studies. In the 28-day dermal toxicity study in rats, there were no treatment-related systemic findings in either sex up to and including 1000 mg/kg bw/d, the highest dose tested.

In the rat, immunological changes were observed in both sexes in the 28- and 90-day dietary studies and in males in the two-year dietary study. In the 90-day dietary study, the immunological changes appeared to be reversible with only minimal findings being observed at the end of the five-week recovery period. In the two-year dietary study, immunological changes were observed at the interim sacrifice (at one year) but not at the terminal sacrifice (at two years). In a 90-day dietary study, decreased spleen weights were observed in males. The decreased spleen weights were reversible, however, and there were no corroborating gross pathological or histopathological findings. In addition, decreased spleen weights were not observed in the two-year dietary study in rats.

Because the toxicology database did not show evidence of immunotoxicity (increased sickness, increased oncogenic response), the significance and relevance of these

immunological findings were unclear and, according to experts in the field, the immunological components were not tested with adequate methodologies. The immunotoxicological potential of MKH 6562 in rats, therefore, was further investigated in more detail in additional antibody plaque-forming cell assays and in assays examining the cell-mediated immune response (anti-CD-3 T-cell proliferation assay), splenic T-cells, B-cells, and natural killer (NK) cells at doses up to and including 1000 mg/kg bw/d, the limit dose, according to accepted EPA guidelines (28-day dietary studies conducted in accordance with guideline requirements as indicated in OPPTS 870.7800, Immunotoxicity, 1998). Using appropriate methods, exposure to MKH 6562 did not affect immune system organ weights (spleen and thymus). There were no significant treatment-related effects on antibody-forming cell (AFC) response when expressed as either specific activity (AFC/10^6 spleen cells) or total activity (AFC/spleen). MKH 6562 did not affect splenic cell populations nor did it suppress the cell-mediated immune response (anti-CD3 T-cell proliferation) or the innate immune response (NK-cell activity). The weight of evidence does not support an immunotoxic effect for MKH 6562 on the basis of the absence of any treatment-related findings in the accepted guideline immunotoxicity studies in the rat and the transient nature of the immunological findings observed in the subchronic and chronic dietary studies in the rat.

In the dog, induction of microsomal liver enzymes (Phases I and II) was observed in both sexes in the 28- and 90-day dietary studies but not in the one-year dietary study. Decreased thyroxine (T_4) levels and increased thyroxine binding capacity (TBC) were also observed in both sexes in the 28- and 90-day dietary studies. The changes in T_4 levels and TBC were most likely associated with induction of microsomal liver enzymes, especially *p*-nitrophenol uridine 5'-diphosphatase glucuronyl transferase (UDPGT). A transient decrease in T_4 levels was observed in females in the one-year dietary study; however, in the absence of any changes in other thyroid biomarkers (tri-iodothyronine [T_3], TBC, and thyroid stimulating hormone [TSH]), this was not attributed to a primary effect on the thyroid. Other findings indicative of a treatment-related effect on the liver include changes in clinical chemistry, increased liver weights, and histopathological findings in one or both sexes. In the 90-day dietary study, gross pathological and histopathological findings in the stomach suggest that the test substance may cause local irritation in both sexes at the higher doses. Other treatment-related findings included decreased body-weight gain and decreased food consumption in both sexes in the high-dose groups.

No evidence of an oncogenicity potential of MKH 6562 was found in the oncogenicity and chronic toxicity studies performed on the mouse or rat. There was no evidence to suggest a significant increase in toxicity with increased duration of exposure in the mouse, rat, or dog. No gender sensitivity was evident in any species.

In the rat, reproductive function in males (sperm parameters) and females (estrous cycling), reproductive parameters, and litter parameters were not influenced by treatment at any dose level in the F_0 or F_1 parental animals. Sexual maturation of the external sexual organs was unaffected by treatment in the F_1 males and females. Body weights at birth were comparable between the treatment groups and the controls for both F_1 and F_2 pups,

although at lactation days 21 and 28, body weights for pups were lower in male and female F_1 pups at 12 000 ppm. Other treatment-related findings in the offspring included decreased liver weights (F_2 males), marbled liver surface (F_1 and F_2 pups), and air-filled stomach (F_1 pups) at 12 000 ppm. Uterus weights were reduced in F_0 and F_1 adult females at 12 000 ppm, although in the absence of any corroborating gross pathological or histopathological findings, the toxicological significance was uncertain. A treatment-related increased incidence of moderate to severe cecal enlargement was observed in F_1 females at 4000 ppm and higher. In the absence of any corroborating histopathological findings, this was considered to represent an adaptive response to treatment. There was no evidence from the two-generation reproduction study in the rat to indicate that neonates were more sensitive than adults to the toxic effects of MKH 6562.

In rats, there was no evidence of developmental toxicity at any dose level up to and including 1000 mg/kg bw/d. In rabbits, developmental toxicity, observed at 500 and 1000 mg/kg bw/d, was manifested as lower fetal body weights and an increased incidence of delayed fetal development (skeletal ossification). There was no evidence of any irreversible structural changes in either species; therefore, MKH 6562 was not considered to be teratogenic in rat or rabbit. On the basis of the maternal and developmental no observed adverse effect levels (NOAEL) in the rat and rabbit developmental studies, no increased susceptibility of the fetus to in utero exposure to MKH 6562 was demonstrated in either species.

There were no significant treatment-related findings in either sex in the acute or 13-week subchronic neurotoxicity screening studies up to and including dose levels at or above the limit doses for both studies (2000 and 1000 mg/kg bw in the acute and 13-week subchronic neurotoxicity studies, respectively); therefore, on the basis of the data presented, MKH 6562 was not considered to be neurotoxic under the conditions of the tests performed.

On the basis of the data presented, there are no significant toxicological concerns regarding the plant, animal, or soil metabolites of MKH 6562.

3.2 Determination of acceptable daily intake

The recommended acceptable daily intake (ADI) is 0.36 mg/kg bw/d on the basis of the most appropriate NOAEL, 35.9 mg/kg bw/d in the one-year dietary study in dogs, and a safety factor of 100. In the one-year dietary study in dogs, treatment-related findings at the lowest observed effect level (183 and 187 mg/kg bw/d in males and females, respectively), the highest dose tested, included impaired body weight development (males and females), decreased T_4 levels (females), increased D-methylase levels (males and females), and marginally increased liver weights (females). A safety factor of 100 to account for intra- and inter-species variations was applied to this NOAEL to determine the ADI.

ADI calculation:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{Safety factor}} = \frac{35.9 \text{ mg/kg bw/d}}{100} = 0.36 \text{ mg/kg bw/d}$$

Margin of exposure (MOE) for other critical end points (calculated as NOAEL/ADI):

Developmental toxicity: NOAEL = 300 mg/kg bw/d
MOE = 833

Reproductive toxicity: NOAEL = 800 mg/kg bw/d
MOE =2222

3.3 Acute reference dose

An acute reference dose was not established, since MKH 6562 (flucarbazone-sodium) was considered unlikely to present an acute hazard. There were no significant treatment-related findings in the acute, short-term, or developmental toxicity studies or in the acute or subchronic neurotoxicity studies to indicate a concern in acute dietary risk assessment.

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

Technical MKH 6562 has low toxicity by the oral, dermal, and inhalation routes of exposure in rats. In rabbits, it was non-irritating when applied to the skin and minimally irritating to the eyes. It was not a dermal sensitizer in guinea pigs.

The end-use products, MKH 6562 70DF Water Dispersible Granular Herbicide and MKH 6562 Solupak 70DF containing 70% technical, have low acute toxicity by the oral, dermal, and inhalation routes of exposure in rats. In rabbits, they were non-irritating when applied to the skin and minimally irritating to the eyes. Neither induced dermal sensitization in guinea pigs.

MKH 6562 was poorly absorbed (25–30 and 15% of the administered dose at the low and high dose, respectively), rapidly excreted (>90% of the administered dose excreted within 24 hours), and not extensively metabolized (>90% of the administered dose was excreted as the parent compound, MKH 6562). Less than 1% of the administered dose remained in the carcass and tissues at sacrifice (72 and 96 hours, post-dosing) indicating little potential for accumulation.

In the rat, immunological changes were observed in both sexes in the 28- and 90-day dietary studies and in males in the two-year dietary study. The immunological changes appeared to be reversible, however, and additional immunotoxicity studies in the rat indicate that MKH 6562 did not affect immune system organ weights (spleen or thymus), AFC response, or splenic cell populations, nor did it suppress the cell-mediated immune response (anti-CD3 T-cell proliferation) or the innate immune response (NK-cell activity)

at dose levels up to and including 1000 mg/kg bw/d. The weight of evidence suggests that MKH 6562 was not immunotoxic under the conditions of the tests performed.

In the dog, induction of microsomal liver enzymes (Phases I and II) was observed in both sexes in the 28- and 90-day dietary but not in the one-year dietary study. Decreased T_4 levels and increased TBC were also observed in both sexes in the 28- and 90-day dietary studies. The changes in T_4 levels and TBC in the 28- and 90-day dietary studies were most likely associated with induction of microsomal liver enzymes, especially *p*-nitrophenol UDPGT. A transient decrease in T_4 levels was observed in females in the one-year dietary study. In the absence of any effects on other thyroid biomarkers (T_3, TBC, and TSH), however, the transient decrease in T_4 levels was not attributed to a primary effect on the thyroid.

In the rat and the dog, gross pathological and histopathological findings in the GIT suggest that MKH 6562 may cause local irritation in the GIT at higher dose levels.

No evidence of an oncogenicity potential of MKH 6562 was found in the oncogenicity and chronic toxicity studies performed on the mouse or the rat. MKH 6562 was not mutagenic. There was no evidence to suggest a significant increase in toxicity with increased duration of exposure in the mouse, the rat, or the dog. No gender sensitivity was evident in any species. MKH 6562 was not considered to be neurotoxic.

MKH 6562 was not teratogenic in rats or rabbits. On the basis of the maternal and developmental NOAELs in the rat and rabbit developmental studies, no increased susceptibility of the fetus to in utero exposure to MKH 6562 was demonstrated in either species. MKH 6562 was not a reproductive toxicant. On the basis of the parental and offspring NOAELs in the rat two-generation reproductive toxicity study (one litter per generation), there was no indication that neonates were more sensitive than adults to the toxic effects of MKH 6562.

On the basis of the data presented, there are no significant toxicological concerns regarding the plant, animal, or soil metabolites of MKH 6562.

Given the single exposure for farmers, the short-term nature of the exposure period for custom applicators, and the predominantly dermal exposure route, a dermal toxicity study is considered to be the most relevant to use in the risk assessment. In a four-week dermal toxicity study in the rat, there were no treatment-related systemic findings in either sex. Local irritation findings included increased skinfold thickness in both sexes and minimal to slight acanthosis in males. The lowest observed adverse effect level (LOAEL) for systemic toxicity was not determined. The NOAEL for systemic toxicity was 1000 mg/kg bw/d, the highest dose tested.

A safety factor of 100 to account for intra- and inter-species variations is considered to be adequate for all end points in male and female workers.

3.5 Impact on human health arising from exposure to flucarbazone-sodium

3.5.1 Operator exposure assessment

MKH 6562 is a water dispersible granule containing 70% flucarbazone-sodium and is to be applied to wheat fields in Manitoba, Saskatchewan, and Alberta and the Peace River region of British Columbia. The product will be available in two different packaging types: water soluble packets (MKH Solupak 70DF) and loose pack paper packages (MKH 6562 70DF). The total size of the wheat crop in this region of western Canada is 14 million hectares (ha) (1991 Census, Statistics Canada). The average wheat field size ranges from approximately 130 ha (Manitoba and Alberta) to 170 ha (Saskatchewan) (1991 Census, Statistics Canada). Typically, 140 and 300 ha of wheat can be treated in a day by a farmer and a custom applicator, respectively (OEAS Agricultural Database, 1997).

The product will be applied at a maximum rate of 30 g/ha active ingredient [a.i.] normally in late May or June. It is to be a foliar application after wheat has emerged and is 8–15 cm in height (one to four leaves on main stem plus two tillers). It is not to be applied before the crop has fully emerged and not after the four-leaf stage (plus two tillers). Generally, the application window when a farmer could apply this product would be 7–10 days. The application window when a custom applicator could apply this product would be 14–17 days. There is a 60-day preharvest interval (PHI) indicated on the label.

A Pesticide handlers Exposure Database (PHED) 1.1 assessment was submitted to quantify exposure to flucarbazone-sodium when using MKH 6562. The PHED is a database of generic mixer, loader, and applicator passive dosimetry data that facilitates the generation of scenario specific exposure estimates. This PHED assessment conforms to the North American Free Trade Agreement Guidelines for using and reporting PHED data. The PHED subsets compare well with the proposed formulation and use pattern and are therefore acceptable as surrogate data for estimating exposure to flucarbazone-sodium. The PHED estimate is based on a worker wearing one layer of clothes (e.g., long-sleeved shirt, pants) and gloves while mixing and loading and one layer of clothing and no gloves during application. The personal protective equipment recommended on the label is coveralls and gloves for workers mixing or loading MKH 6562. On the basis of this data, a potential exposure of 12.01 and 25.73 Fg a.i./kg bw/d was estimated for farmers and custom applicators, respectively. The estimate is based on a 70-kg person, assuming that farmers and custom applicators would handle 4.2 kg a.i./d and 9.0 kg a.i./d, respectively. The primary route of exposure was dermal, accounting for approximately 98% of exposure.

The flucarbazone-sodium exposure values and MOEs for farmers and custom applicators are presented in Table 3.1. All exposure estimates are based on wearing one layer of clothing at all times and wearing gloves during mixing and loading. The MOEs for farmers and custom applicators are greater than 38 000 and are considered adequate. The 28-day dermal rat study with a no observed effect level (NOEL) of 1000 mg/kg bw was used for

the risk assessment for these exposure scenarios because it had a relevant duration and route of exposure.

3.5.2 Bystanders

Given the proposed commercial and agricultural use scenarios, exposure and risk to bystanders should be minimal.

3.5.3 Post-application exposure

Data are not available to make a quantitative estimate of re-entry exposure. The proposed use pattern is such, however, that re-entry exposure should be minimal. Application is recommended at the one- to four-leaf crop stage and the label specifies a PHI of 60 days. Minimal foliar contact is expected after application and wheat is harvested mechanically.

Table 3.1 Exposure estimates and resulting MOEs

Exposure scenario	NOAEL (mg/kg bw/d)	Exposure (mg/kg bw/d)	MOE
Farmer	1000	0.012	83 000
Custom applicator	1000	0.026	38 000

4.0 Residues

4.1 Residue summary

The wheat metabolism study demonstrated that flucarbazone-sodium is readily metabolized in wheat. Sixty percent of the total radioactive residues (TRR) in grain were composed of sulfonamide and sulfonamide conjugates (lactate, acetate, and glucosides). A similar metabolic profile was observed for forage, hay, and straw, with the *N*-desmethyl (and glucoside conjugates) and sulfonic acid comprising an additional 18–25% of the TRRs.

The metabolism of flucarbazone-sodium in wheat proceeded via hydrolysis of the parent compound to the *N*,*O*-dimethyl triazolinone (NODT), sulfonamide, sulfonamide conjugates, and sulfonic acid. The sulfonamide metabolites were further conjugated to acetate, lactate, and their glucosides. An additional pathway was the demethylation of the parent compound to the *N*-desmethyl metabolite.

On the basis of the wheat metabolic profile, the ROC may be defined as flucarbazone-sodium and *N*-desmethyl flucarbazone.

The rat, goat, and hen metabolism studies indicated that the major route of metabolism of flucarbazone-sodium was via hydrolysis to NODT and to the flucarbazone sulfonamide metabolite, which appeared to conjugate to proteins in the liver. Products found in the muscle and the liver were indicative of a minor route of metabolism that appeared to proceed via the *N*-dealkylation of the parent compound to the *N*-desmethyl flucarbazone. Methylurethane may have been formed via hydrolysis of *N*-desmethyl fulcarbazone or through an *N*-demethylation of NODT to produce *O*-methyl triazolinone (OMT). This may have been further hydrolysed to yield methyl urethane. Bayer indicated that the NODT was likely dealkylated to OMT, followed by hydrolysis.

The minor metabolic routes differ slightly between the animals (rat, poultry, and goat); however, all metabolites that were observed in the goat and poultry have been identified or accounted for in the rat metabolism and, therefore, the biological effects were covered by the toxicological studies.

On the basis of the animal metabolic profiles, the ROC may be defined as flucarbazone-sodium.

The confined crop rotation study indicated that residues of flucarbazone-sodium were 12 parts per billion (ppb) or less in the edible fractions of the rotational crops (wheat, kale, and turnips) and 37 ppb or less in the livestock feed portions of the rotational crops planted in soil that had been treated with flucarbazone-sodium at the rate of 45 g a.i./ha (1.5 × Canadian good agricultural practices [GAP]) and aged for 368 days. The metabolites, identified as sulfonamide acetate, sulfonamide alanine, and sulfonamide lactate, were determined to be adequately tested in the rat and not to be of toxicological concern. It appears unlikely that residues of flucarbazone-sodium and its related metabolites in soil will translocate and accumulate in the rotational crops at a plantback restriction of 11 months. Flucarbazone-sodium residues in wheat and in turnip roots were determined to be stable over the course of freezer storage; however, storage stability data is required to confirm the stability of flucarbazone-sodium residues in kale and in turnip tops.

An accelerated solvent extraction, clean-up using both C-18 and ethylene diamine-*N*-propyl solid phase extraction columns followed by detection and quantitiation by LC/MS/MS was used to quantitate residues of flucarbazone-sodium and *N*-desmethyl flucarbazone in wheat. The method's LOQ was 0.005 ppm for both flucarbazone-sodium and *N*-desmethyl flucarbzone individually, for a combined LOQ of 0.01 ppm. Good linearity (correlation coefficient $r > 0.999$) for both flucarbazone-sodium and *N*-desmethyl flucarbazone was observed in the range of 0.005–0.100 ppm in hay, straw, and grain and 0.005–0.250 ppm in forage extracts. The ILV supported the reliability and reproducibility of the proposed Bayer method for the determination of flucarbazone-sodium and *N*-desmethyl flucarbazone residues in wheat commodities. The small relative standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having good repeatability. Representative chromatograms of control samples showed no interferences from matrix components or from reagents,

solvents, and glassware. This method was also deemed acceptable for enforcement purposes.

A common moiety method which extracted and hydrolysed flucarbazone-sodium and flucarbazone-related residue to flucarbazone sulfonamide followed by detection and quantitation by LC/MS/MS method was used to quantitate residues in animal matrices. The method's LOQ was 0.020 ppm in animal tissues (liver, kidney, muscle, and fat) and 0.005 ppm in milk. Good linearity was observed ($r > 0.99$) for tissue standards (0.005–0.300 ppm) and for milk standards (0.001–0.300 ppm). The ILV supported the reliability and reproducibility of the proposed Bayer method for the determination of flucarbazone-sodium and flucarbazone-related residues in animal tissues. The small relative standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having good repeatability. Representative chromatograms of control samples showed no interferences from matrix components or from reagents, solvents, and glassware. The common moiety analytical method for animal commodities was found to be valid for data gathering but was not suitable for enforcement or compliance purposes. The method was deemed not to be sufficiently specific to measure and identify the ROC in the presence of other chemicals that could reasonably be expected to be present on the same commodity. Bayer is required to submit an analytical method specific to the parent compound, flucarbazone-sodium.

The freezer storage stability study indicated that residues of flucarbazone-sodium and *N*-desmethyl flucarbazone were stable in wheat forage, wheat hay, and wheat straw for 25 months when stored at –20EC. In wheat grain, *N*-desmethyl flucarbazone was also shown to be stable over the 25-month storage period; however, no data was submitted to support the stability of the parent compound, flucarbazone-sodium. Bayer is required to submit additional freezer storage stability data to confirm the stability of flucarbazone-sodium in wheat grain over the storage periods in the wheat metabolism and supervised residue trial studies.

The results from the 25 North American supervised field trials treated with flucarbazone-sodium (70% water dispersible granular formulation) at a rate of 30 g a.i./ha (1 × GAP) demonstrated that maximum residues in wheat grain (harvested at a PHI of 60–127 days) did not exceed the LOQ (0.01 ppm), residues in forage (harvested at a PHI of 11–66 days) did not exceed 0.27 ppm, residues in hay (harvested at a PHI of 31–86 days) did not exceed 0.08 ppm, and residues in straw (harvested at a PHI of 60–127 days) did not exceed 0.04 ppm.

An MRL of 0.01 ppm, therefore, is recommended to cover residues of flucarbazone-sodium and *N*-desmethyl flucarbazone on wheat grain. Since only one residue trial was conducted, however, at the proposed PHI of 60 days for wheat grain and the majority were conducted at PHIs between 70–110 days, a PHI of 80 days is recommended.

In the residue decline experiments, wheat was treated at a rate of 30 g a.i./ha and forage, hay, and straw and grain were harvested at PHIs of 15–71, 33–91, and

60–117 days, respectively. On the basis of the magnitude of residues observed in grain, a PHI of 80 days is considered to be adequate.

Because residues of flucarbazone-sodium and *N*-desmethyl flucarbazone were below the LOQ (<0.01 ppm) of wheat grain treated at 5–5.9× the proposed North American application rate, a wheat processing study was not required. As a result, residues of flucarbazone-sodium and *N*-desmethyl in wheat processed fractions will be covered under the raw agricultural commodity MRL of 0.01 ppm.

All tissue samples analysed in the animal metabolism and animal feeding studies were analysed within 47 and 24 days, respectively, of collection. Sufficient evidence was presented to limit degradation of flucarbazone-sodium and its metabolites, with storage of samples and extracts at less than –10EC and less than –20EC, respectively. The residues of flucarbazone-sodium and its metabolites in the studies, therefore, are deemed to be stable on the basis of the physical and chemical characteristics of flucarbazone-sodium. No freezer storage stability study for flucarbazone-sodium in meat tissues was required.

According to the supervised residue trials, conducted at 25 representative growing locations in North America, residues of flucarbazone-sodium and *N*-desmethyl flucarbazone are unlikely to exceed 0.27, 0.08, and 0.04 ppm, respectively, in the livestock feed items, forage, hay, and straw when treated according to the Canadian use pattern. On the basis of the maximum anticipated theoretical dietary burdens of flucarbazone-sodium and *N*-desmethyl flucarbazone to dairy cattle, residues in meat (including meat by-products, excluding liver), liver, and milk are expected to be 0.02 ppm or less, 0.05 ppm or less, and 0.005 ppm or less, respectively, when flucarbazone-sodium is used in accordance with the label directions.

On the basis of the maximum anticipated theoretical dietary burdens of flucarbazone-sodium and *N*-desmethyl flucarbazone and the metabolic profile in poultry, no quantifiable residues of flucarbazone-sodium or any compound of toxicological interest in poultry meat and eggs are expected.

Since the common moiety analytical method for animal commodities cannot be used to enforce MRLs on meat, meat by-products, milk, or eggs, MRLs on these commodities cannot be proposed.

For the chronic dietary risk assessment, the potential daily intake (PDI) was determined using the proposed MRL on wheat grain, the expected residues in animal commodities, the expected environmental concentration (EEC) in drinking water (7.1 Fg a.i./L), and the Dietary Exposure Evaluation Model™ (DEEM™) software. The assessment was conducted using the 1994–1996 Continuing Survey of Food Intake for Individuals. The PDI accounted for less than 1% of the ADI (0.36 mg/kg bw/d) for every subgroup population including infants, children, adults, and seniors.

An additional chronic dietary risk assessment was performed to assess a worst case scenario using the criteria stated above and assuming residues on animal commodities may reach 0.1 ppm of the general Food and Drug Regulations (B.15.002). The results indicated that the PDI accounted for less than 1% of the ADI for every subgroup population including infants, children, adults, and seniors.

Consequently, the commercial use of flucarbazone-sodium on wheat does not pose an unacceptable dietary (both food and water) risk to any segment of the population, including infants, children, adults, and seniors.

5.0 Fate and behaviour in the environment

5.1 Fate and behaviour in soil

5.1.1 Transformation

MKH 6562 is stable to hydrolysis. Hydrolysis is, therefore, not a principal route of transformation in soil at environmentally relevant conditions. Phototransformation of MKH 6562 on soil will not be a principal route of transformation in the environment. No major transformation products were detected in the hydrolysis and phototransformation of MKH 6562 (Tables 1 and 2 of Appendix III). Aerobic biotransformation of MKH 6562 in soil is a principal route of transformation in the environment. The major transformation products detected under laboratory conditions were MKH 6562 sulfonamide, MKH 6562 sulfonic acid, *O*-desmethyl MKH 6562, and *N*-methyl triazolinone (NMT).

MKH 6562 is non-persistent to slightly persistent in loam, clay loam, and loamy sandy soils under Canadian and northern U.S. field conditions. These results are not in agreement with those of laboratory studies of soil aerobic biotransformation, which indicate that MKH 6562 is slightly to moderately persistent. The major transformation products detected in soils under field conditions were MKH 6562 sulfonamide and *O*-desmethyl MKH 6562. Field data indicated that MKH 6562 has a low potential for carryover into the following season. At the end of a one-year study period, the concentrations of MKH 6562 sulfonamide that accumulated in all the soils ranged from 5 to 20% of the applied amount, except in Washington soil where none was detected. On the basis of a dissipation time 50% (DT_{50}) value (>400 days) calculated from the day of maximum concentration to the end of the study period, MKH 6562 sulfonamide is considered as persistent in soils. Although mass accounting was not reported, the principal route of dissipation of MKH 6562 under terrestrial field conditions appears to be transformation to MKH 6562 sulfonamide and *O*-desmethyl MKH 6562.

5.1.2 Mobility

The adsorption values, K_d and K_{oc}, and the aged soil column leaching studies (Table 1, Appendix III) indicate that MKH 6562 and its transformation products will be highly mobile in soils and have the potential to leach and contaminate groundwater. Less than

20% of the added MKH 6562 was adsorbed by the five soils. Under field conditions, however, the parent compound and its transformation products did not leach below the 30 cm soil depth.

5.2 Expected environmental concentration in soil

The EEC for MKH 6562 in soil is 0.013 mg/kg dry soil, immediately following the application of 30 g/ha to a bare soil.

5.3 Fate and behaviour in water

5.3.1 Transformation

MKH 6562 is stable to hydrolysis at pH 5, 7, and 9. Chemical hydrolysis will not be an important route of transformation in water under the environmentally relevant range of pH 5–9. Phototransformation of MKH 6562 in water will not be a principal route of transformation in the aquatic environment. One major transformation product, MKH 6562 sulfonamide, was observed in the irradiated samples.

MKH 6562 is persistent in pond water under aerobic conditions. Two major transformation products, MKH 6562 sulfonamide and NODT, were observed under aerobic conditions. In sediment–water systems under anaerobic conditions, MKH 6562 is moderately persistent. At the end of the study period, significant amounts of the applied amount had partitioned from water to the sediment. These results do not agree with those of the adsorption and desorption studies, which indicated little adsorption. Two major transformation products, MKH 6562 sulfonamide and NMT, were identified under anaerobic conditions (Tables 3 and 4 of Appendix III).

5.3.2 Expected environmental concentrations in water

Assuming a scenario in which a body of water of 30 cm deep is oversprayed with an application rate of 30 g a.i./ha, the EEC in water is 0.01 mg a.i./L water. The EEC in pond water (shallow water) owing to runoff from the treated fields is 9.5 Fg a.i./L. The EEC in human drinking water (deep water bodies) is 7 Fg a.i./L water immediately following the application, on the basis of a 4000 m^3 farm dugout 246 cm deep.

5.4 Fate and behaviour in air

MKH 6562 has a very low vapour pressure ($<1 \times 10^{-9}$ Pa at 20EC) and a low Henry's Law Constant ($<1 \times 10^{-11}$ Pa m^3 mol at 20EC; $1/H = 2.48 \times 10^{14}$). These values indicate that MKH 6562 is essentially non-volatile and no significant volatilization is expected. Atmospheric contamination is, therefore, not considered to be a route of exposure for this use pattern.

6.0 Effects on non-target species

6.1 Effects on terrestrial and aquatic non-target species

6.1.1 Terrestrial organisms

MKH 6562 is practically non-toxic to bobwhite quail on an acute basis and slightly toxic on a dietary basis. MKH 6562 significantly affected the reproductive performance of mallard ducks (no observed effect concentration [NOEC] = 223 mg a.i./kg diet). MKH 6562 is non-toxic to rat on an acute basis and on a dietary basis up to 250 mg a.i./kg diet. MKH 6562 is relatively non-toxic to honeybees and earthworms (Table 5 of Appendix III).

6.1.2 Aquatic organisms

The log K_{ow} (<0 at 25EC) value indicates that MKH 6562 has a negligible potential for bioconcentration and bioaccumulation in organisms. MKH 6562 is practically non-toxic to fish on an acute basis and has no affect on the reproductive performance up to 54.3 mg a.i./L. It causes scoliosis and kyphoscoliosis, however, to rainbow trout on a chronic basis. MKH 6562 is practically non-toxic to *Daphnia* sp. on an acute basis and has no effect on the reproductive performance and general health of offspring up to 115 mg a.i./L. MKH 6562 is toxic to freshwater algae. The most susceptible species is green algae. MKH 6562 is not toxic to freshwater and marine diatoms at concentrations up to 90 mg a.i./L (Table 6 of Appendix III).

6.1.3 Non-target plants

MKH 6562 is phytotoxic to the floating aquatic plant, *Lemna gibba* L., with NOEC and effective concentration 5% (EC_5) values of 0.17 and 0.09 g a.i./ha on frond number and dry weight, respectively, under spray conditions (foliar application). MKH 6562 is phytotoxic to seedlings of several plant species and the most sensitive species is onion, with a NOEC of 0.25 g a.i./ha on seedling dry weight. In a vegetative vigour test, MKH 6562 is also phytotoxic to several plant species and will adversely affect plant survival, shoot height, and dry weight. The most sensitive species is onion again, with the plant dry weight NOEC and effective concentration 25% (EC_{25}) values of 0.25 and 0.39 g a.i./ha, respectively.

6.2 Environmental risk assessment

Risk to terrestrial and aquatic organisms with the use of MKH 6562 is assessed using the margin of safety values (toxicity end point/EEC). MKH 6562 will not pose a risk to wild birds, mammals, bees, earthworms, fish, daphnids, and algae with this use pattern. The aquatic and terrestrial non-target vascular plants will be adversely affected, however, by the post-emergence application of MKH 6562 to wheat (Tables 7, 8, and 9 of Appendix III).

6.3 Environmental concerns

An assessment of the environmental safety from the use of MKH 6562 has identified the following concerns:

1. MKH 6562 is toxic to non-target terrestrial plants. MKH 6562 will adversely affect terrestrial wildlife habitat if it is exposed to greater than 1.3% of the label application rate under this use pattern.

2. MKH 6562 is toxic to aquatic plants. MKH 6562 concentration in water will adversely affect aquatic wildlife habitat if it is exposed to greater than 50% of the label application rate under this use pattern. MKH 6562 will adversely affect non-target aquatic plants if greater than 0.3% of the label application rate falls directly on the foliage as a spray deposit.

3. MKH 6562 in the surface runoff water from treated fields will adversely affect non-target aquatic plants if exposed to greater than 55% of the concentration at the maximum application rate.

6.4 Environmental risk mitigation

6.4.1 Buffer zones

To protect the sensitive non-target terrestrial and aquatic plants, buffer zones between the last spray swath and the edge of the sensitive areas are required. These buffer zones were calculated using the Nordby and Skuterud (1975)[1] method.

Terrestrial: To protect the terrestrial non-target plant species from MKH 6562 injury, a buffer zone of 20 m is required between the last spray swath and the edge of sensitive terrestrial areas, such as shelter belts and woodlots.

Aquatic: To protect the non-target aquatic plant species from MKH 6562 injury, a buffer zone of 35 m is required between the last spray swath and the edge of sensitive aquatic areas, such as wetlands, ponds, lakes, streams, and rivers.

6.4.2 Label statement

To protect the non-target aquatic plant species from MKH 6562 in surface runoff water, the following statement has been added to the label:

“Do not apply when rain is forecasted during application or expected in the next 6 hours.”

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[1] Nordby, A. and R. Skuterud. 1975. The effects of boom height, working pressure and wind speed on spray drift. Weed Res. **14**: 385–395.

7.0 Efficacy

MKH 6562 is a Group 2 (ALS inhibitor), post-emergence grass herbicide that was developed by Bayer AG to control wild oats (*Avena fatua*) and biotypes resistant to ACCase (Group 1) and triallate (Group 8) herbicides, and green foxtail (*Setaria viridis*) and biotypes resistant to ACCase (Group 1) and dinitroaniline (Group 3) herbicides in spring wheat (*Triticum aestivum*) and durum wheat (*Triticum durum*).

The initial draft label proposed MKH 6562 not to be applied alone, but tank-mixed with one of five proposed non-ionic surfactant and one of 20 broadleaf herbicide combinations. An application rate of 29 g/ha MKH 6562 70DF (20 g a.i./ha flucarbazone-sodium) plus 0.25% v/v non-ionic surfactant was proposed for the control of green foxtail, and 43 g/ha MKH 6562 70DF (30 g a.i./ha flucarbazone-sodium) plus 0.25% v/v non-ionic surfactant was proposed for the control of wild oats.

Weed control and crop tolerance data from replicated small plot field trials were made available for review to support the registration of the MKH 6562. The study protocol incorporated reduced MKH 6265 application rates to demonstrate that the ones proposed are the lowest to provide effective and consistent weed control. The study protocol also incorporated double the maximum proposed MKH 6265 application rate to demonstrate crop tolerance in an overspray situation.

Adequate data were provided to establish the product performance of two surfactants, Agral 90 and Agsurf, to be agronomically equivalent when tank-mixed with MKH 6562 70DF and a broadleaf herbicide. To this end, the efficacy data bases incorporating Agral 90 and Agsurf were pooled together to support each weed claim listed on the MKH 6562 label. There was insufficient data, however, to make such a determination for the remaining three surfactants proposed as tank-mix partners with MKH 6562 (Citowett Plus, Companion, and Super Spreader Sticker).

Efficacy data made available to support the green foxtail weed claim in spring or durum wheat did not clearly demonstrate that the proposed application rate was the lowest effective rate for consistent pest control results. The data suggested there is little, if any, difference in control results between the proposed and reduced rates of 21.5 g/ha MKH 6562 70DF (15 g a.i./ha flucarbazone-sodium) plus 0.25% v/v Agral 90 or Agsurf and broadleaf herbicide tank-mixes made available for review. The data supported a recommendation that five of 20 broadleaf herbicide combinations with MKH 6562 plus surfactant provided control of green foxtail in spring and durum wheat (2,4-D Amine or Ester, Buctril M, Estaprop, and Refine Extra + 2,4-D Amine). There was insufficient data to support a recommendation for the 15 remaining broadleaf herbicide combinations with MKH 6562 plus surfactant.

Adequate data were made available to demonstrate the proposed rate of 43 g/ha MKH 6562 70DF (30 g a.i./ha flucarbazone-sodium) plus 0.25% v/v Agral 90 or Agsurf and 12 of 20 broadleaf herbicide tank-mix is the lowest effective rate for consistent

wild oat control results in spring and durum wheat (2,4-D Amine or Ester, Ally + 2,4-D Amine, Buctril M, Estaprop, MCPA Amine or Ester, Refine Extra, Refine Extra + 2,4-D Amine, Target, Thumper, and Unity herbicide tank-mix). There was insufficient data to support a recommendation for the eight remaining broadleaf herbicide combinations with MKH 6562 plus surfactant.

Efficacy trials were also conducted on a selected number of broadleaf weed species, which demonstrated that there is no reduction in weed control results, or reverse antagonism with the addition of 30 g a.i./ha MKH 6562 70DF plus 0.25% v/v Agral 90 or Agsurf as a tank-mix with a recommended broadleaf herbicide. Evaluation of the data suggests the alone treatment of MKH 6562 70DF plus Agral 90 or Agsurf has some herbicidal activity on broadleaf weeds that is enhanced with the addition of a broadleaf herbicide tank-mix. Broadleaf weed control results were consistently high and did not indicate a reduction or reverse antagonism with the addition of 30 g a.i./ha MKH 6562 plus 0.25% v/v Agral 90 or Agsurf tank-mix to the broadleaf herbicide.

Small plot field trials using a randomized complete block design experiment with three or four replicates were conducted between 1994 and 1997 across the prairie provinces of Canada to demonstrate the crop tolerance of spring wheat and durum wheat to the maximum proposed treatment of 43 g/ha MKH 6562 70DF (30 g a.i./ha flucarbazone-sodium) plus 0.25% v/v Agral 90 or Agsurf and a recommended broadleaf herbicide tank-mix partner. Individual trials included crop tolerance assessments, qualitatively as percent visual injury and quantitatively as crop yield (kg/ha).

All broadleaf herbicide tank-mix combinations are by themselves presently accepted for use on spring wheat and durum wheat. While adequate data demonstrated that spring wheat is tolerant to the proposed maximum application rate of MKH 6562 70DF, there was insufficient data to make a determination of crop safety for durum wheat.

In the year following application of flucarbazone-sodium, the initial draft label proposed the re-cropping of four crops within the brown soil zone, and 13 crops in the dark brown, black, and gray-wooded soil zones of the Canadian prairie provinces and the Peace River region of British Columbia. Adequate data were made available to support the re-cropping of spring wheat within the brown soil zone, and the re-cropping of spring wheat, spring barley, canola, and field peas within the dark brown, black, and gray-wooded soil zones in the year following MKH 6562 70DF application.

The management of pesticide resistance development is an important part of sustainable and integrated pest management programs. The current list of available herbicides for use on spring and durum wheat to control green foxtail and wild oats have the same mode of action (inhibitors of ACCase) and are classified as Group 1 herbicides. MKH 6562 represents a new class of Group 2 herbicides that controls green foxtail and wild oats by inhibiting ALS (or AHAS). MKH 6562 will contribute, therefore, to the risk reduction of pesticide resistance developing in these weed species by offering an effective alternative to Group 1 herbicides.

Also as part of the value assessment, the issue of whether this pesticide was registered in the U.S. for the specific use and whether it had a tolerance in the U.S. was considered. Because flucarbazone-sodium is not a registered product in the U.S. and does not have a tolerance or an allowable residue level in the U.S., this could result in the treated wheat not being allowed entry into the U.S. market.

To mitigate this aspect of value considerations, it was required as a condition of registration that a note be put on the label stating: "Registration applications have been filed in the United States. However, this is not yet a registered use in the U.S. and no import tolerance has yet been established in the U.S."

7.1 Label amendments

Amendments to the proposed draft labels for the flucarbazone-sodium technical and end-use products EVEREST 70DF and EVEREST Solupak 70DF are too numerous to list.

The company proposed registration of flucarbazone-sodium for the control of two annual grasses (wild oats and green foxtail) on two crops (durum and spring wheat) with a single post-emergence tank-mix treatment with one of five non-ionic surfactants and one of 20 broadleaf herbicide combinations. In the year following treatment, the draft label recommended the recropping of four crops in the brown soil zone and 13 crops in the dark brown, black, and gray-wooded soil zones.

On the basis of information made available for the registration of flucarbazone-sodium, only 16% of the proposed draft label was supported by data and accepted on the final label. Adequate data was provided to support the use of EVEREST on one of two crops (spring wheat) when tank-mixed with one of two surfactants (Agral 90 and Agsurf) plus one of 12 broadleaf herbicide combinations for wild oat control, and one of five broadleaf herbicide combinations for green foxtail control. The data also supported an application rate reduction of 25% (from 20 to 15 g a.i./ha flucarbazone-sodium) for the control of green foxtail in spring wheat.

In soils treated with flucarbazone-sodium the previous year, only 30% of the crops proposed for recropping on the draft label were supported by data and accepted on the final label. Sufficient data were provided to support one of four crops proposed for recropping in the brown soil zone, and four of 13 crops proposed in the dark brown, black, and gray-wooded soil.

The Agency has informed the registrant of the necessary label amendments to reflect the evaluation of data and information made available for review. These amendments are also reflected on the product labels for commercial use.

8.0 Toxic Substances Management Policy considerations

During the review of MKH 6562, the PMRA has considered the implications of the TSMP and the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, and has concluded the following:

MKH 6562 does not meet the TSMP criteria for persistence in soil and anaerobic water–sediment systems. The half-life values of MKH 6562 in soil (31 days) and anaerobic water–sediment systems (104 days) are below the TSMP Track-1 cut-off criteria for water (≥182 days), sediment (≥365 days), and soil (≥182 days). In aerobic water–sediment systems, however, the half-life of MKH 6562 (>800 days) meets the TSMP criteria for persistence. No data were provided for MKH 6562 persistence in air.

MKH 6562 is not bioaccumulative. The log K_{ow} of MKH 6562 is less than zero, which is below the TSMP Track-1 cut-off criterion of 5.0 or higher.

MKH 6562 does not meet the criteria for Canadian *Environmental Protection Act* (CEPA) toxic or CEPA-toxic equivalent under the TSMP.

MKH 6562 does not contain any by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concerns as identified in Section 2.13.4 of the PMRA Regulatory Directive DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process. The formulated product does not contain any formulants that are known to be TSMP Track-1 substances.

MKH 6562 forms two major transformation products, MKH 6562 sulfonamide and *O*-desmethyl MKH 6562, in soil under field conditions. MKH 6562 sulfonamide is persistent in soil (half-life > 400 days) and meets the TSMP Track-1 cut-off criteria for persistence in soil (≥182 days).

In aerobic and anaerobic water–sediment systems, MKH 6562 forms MKH 6562 sulfonamide, NODT, and NMT under laboratory conditions. Residues of these transformation products did not decline during the study period, which indicates that these products are persistent in aquatic systems. MKH 6562 sulfonamide, NODT, and NMT are, however, not bioaccumulative, as their log K_{ow} values (1.11, –1.24, and –0.74, respectively) are below the TSMP Track-1 cut-off criterion of 5.0 or higher.

9.0 Regulatory Decision

A temporary registration has been granted under Section 17 of the Pest Control Products Regulations for the flucarbazone-sodium technical and end-use products EVEREST 70DF and EVEREST Solupak 70DF, conditional on the generation of the data requirements as outlined below:

Flucarbazone-sodium technical:

Establishing certified limits: more precise limits supported by batch data

Control Product Specification Form: confirm and support the specifications with data from five batches of full scale production when the full scale production begins

EVEREST end-use products:

Confine Crop Rotation Trial Study: storage stability data required to confirm the stability of flucarbazone-sodium residues in kale and turnip tops

Enforcement Analytical Method: an adequate enforcement method specific to flucarbazone-sodium in animal tissues

Freezer Storage Stability Tests: additional storage stability data required on flucarbazone-sodium in wheat grain

Efficacy Trials: additional efficacy data to support an application rate of 21.5 g/L EVEREST (15 g a.i./ha flucarbazone-sodium) for the control of green foxtail in spring and durum wheat

List of abbreviations

ACCase	acetyl CoA carboxylase
ADI	acceptable daily intake
AFC	antibody-forming cell
AHAS	acetohydroxyacis synthase
a.i.	active ingredient
ALS	acetolactic synthase
AP	alkaline phosphatase
bw	body weight
B-cells	bursa derived lymphocytes
CAS	Chemical Abstracts Service
CD	cluster of differentiation (for naming cell surface molecules expressed on lymphocytes in immunology)
CEPA	Canadian *Environmental Protection Act*
d	day
DAT	days after treatment
DEEM™	Dietary Exposure Evaluation Model™
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EC_5	effective concentration 5%
EC_{25}	effective concentration 25%
EC_{50}	effective concentration 50%
EEC	expected environmental concentration
FOB	functional observational battery
F_0	parental animals
F_1	first generation offspring
F_2	second generation offspring
GAP	good agricultural practices
GIT	gastrointestinal tract
h	hour
ha	hectare
HPLC	high-performance liquid chromatography
ILV	interlaboratory validation
K_d	adsorption coefficient
K_{oc}	adsorption coefficient (relates K_d to the organic content of soils)
K_{ow}	*n*-octanol–water constant
LC	liquid chromatography
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score (at 24, 48, and 72 hours)
MIS	maximum irritation score
MMAD	mass median aerodynamic diameter
MOE	margin of exposure

MRL	maximum residue limit
MS	mass spectrometry
n	number of trials
NK	natural killer cell
NMT	*N*-methyl triazolinone
NOAEL	no observed adverse effect level
NODT	*N*,*O*-dimethyl triazolinone
NOEC	no observed effect concentration
NOEL	no observed effect level
OMT	*O*-methyl triazolinone
PDI	potential daily intake
PFC	plaque-forming-cell assay
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
PVA	polyvinyl alcohol
r	correlation coefficient
ROC	residue of concern
SD	standard deviation
sRBC	sheep red blood cell preparation (T-cell dependent antigen)
$t_{½}$	half-life
T-cells	thymic derived lymphocytes
T_3	tri-iodothyronine
T_4	thyroxine
TBC	thyroxine binding capacity
TGAI	technical grade active ingredient
TRR	total radioactive residue
TS	test substance
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDPGT	uridine 5'-diphosphatase-glucuronyl transferase
UDS	unscheduled DNA synthesis
U.S.	United States
Fg	microgram
FL	microlitre
v/v	volume per volume

Appendix I Toxicological summary table

Rat metabolism: Technical MKH 6562 ([phenyl-UL-^{14}C] MKH 6562)
Rate and extent of absorption and excretion: Following a single oral dose, [phenyl-UL-^{14}C] MKH 6562 was rapidly absorbed in rats, with plasma concentrations reaching a maximum within 30 minutes. The high fecal excretion rate, low biliary excretion rate, and high levels of the unchanged parent compound in the fecal extracts suggest that absorption was low (approximately 25–30% at the low dose and 15% at the high). MKH 6562 residues were rapidly excreted with 84–95% of the administered dose being excreted within 24 hours. Fecal excretion (64–78% of the administered dose) was greater than urinary excretion (15–30%). Urinary excretion was lower at the high dose experiment (15% of the administered dose) than at the low dose (24–30%). Biliary excretion accounted for 1–5% (average 2%) of the administered dose. Less than 1% of the administered dose was excreted in expired air. There were no sex-related differences in the absorption, distribution, metabolism, or excretion of MKH 6562 following a single low-dose exposure. The absorption, distribution, metabolism, and excretion do not appear to be influenced by repeat low-dose oral administration. **Distribution and target organ(s)**: The highest tissue residues were found in the liver. Less than 1% of the administered dose, however, remained in the carcass and tissues at sacrifice (after 72 or 96 hours post-dosing). The low mean recovery of radioactivity in the tissues and carcass at sacrifice indicates little potential for accumulation. **Toxicologically significant compound(s)**: Approximately 89% of the administered dose was excreted in the urine and feces as the parent compound, MKH 6562. No other residue present in the feces or urine comprised greater than 1% of the administered dose. Other metabolites found in the excreta that were identified included sulfonic acid, hydroxysulfonamide, sulfonamide-*N*-glucuronide, hydroxysulfonamide-*O*-glucuronide, *N*-acetylsulfonamide, carbomethoxy sulfonamide, and carboethoxy sulfonamide. The major metabolite found in the blood, fat, liver, and muscle was MKH 6562 sulfonamide, although this accounted for less than 1% of the administered dose.
Rat metabolism: Technical MKH 6562 ([triazolinone-3-^{14}C] MKH 6562)
Rate and extent of absorption and excretion: Following a single oral dose [triazolinone-3-^{14}C] MKH 6562 was rapidly absorbed in male rats, with maximal plasma concentrations being achieved within 15–30 minutes. The high fecal excretion rate, low urinary excretion rate, and high levels of the unchanged parent compound, MKH 6562, in fecal extracts suggest that absorption was low (approximately 27% on the basis of the available urinary data: radioactivity detected in the urine, cage washes, tissues, and carcass). The major route of elimination was via the feces, with approximately 70% of the administered dose being found in the fecal extract. The urinary recovery was approximately 27% of the administered dose. The majority of the activity was eliminated via the feces and urine within 24 and 6–12 hours, respectively. The total recovery was approximately 97% of the administered dose; the majority of this was eliminated within 24 hours (95% of the administered dose). **Distribution and target organ(s)**: The highest tissue residues were found in the liver. The mean recovery of radioactivity in the tissues and carcass at sacrifice was less than 1% of the administered dose, however, indicating that the potential for accumulation was low. **Toxicologically significant compound(s)**: The major component in both the urine and fecal extracts was identified as the unchanged parent compound MKH 6562; this represented 94% of the administered dose. Other metabolites found in the excreta and identified included urazole, methylurethane, NMT, OMT, and NODT. Each of these represented less than 1% of the administered dose.

Acute toxicity studies	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Acute studies: Technical MKH 6562			
Oral	Wistar rat 5 animals/sex Dose level: 5000 mg/kg bw	lethal dose 50% (LD_{50}) > 5000 mg/kg bw for both sexes	No mortalities and no treatment-related gross pathological findings or changes in body weight. Clinical observations included moist anus, lightly coloured and mucoid feces in both sexes. Resolved by day 4. Low toxicity
Dermal	Wistar rat 5 animals/sex Dose level: 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw for both sexes	No mortalities and no treatment-related clinical or gross pathological findings. Slight transient decreased body weight in females on day 4, although all animals gained weight by end of study. Low toxicity
Inhalation 4-h nose-only	Wistar rat 5 animals/sex/group Dose levels Analytical: 0, 0.51, or 5.13 mg/L air	lethal concentration 50% (LC_{50}) > 5.13 mg/L air for both sexes	No mortalities and no treatment-related gross pathological findings or changes in body weight. Clinical observations included ungroomed coat, piloerection, decreased motility, and red encrustation of nose. Resolved by day 6. Low toxicity
Skin irritation	New Zealand White rabbit 3 adult females Dose level: 500 mg	maximum irritation score (MIS) and maximum average score (MAS) (at 24, 48, and 72 hours = 0/8	There were no signs of dermal irritation at any time point. Non-irritating
Eye irritation	New Zealand White rabbit 6 adult females Dose level: 100 FL (.26 mg)	MIS = 5.0/110 at 1 hour MAS (at 24, 48, and 72 hours) = 1.7/110	Slight to moderate conjunctival redness, chemosis, and discharge were evident at 1 hour. Resolved by day 7. No corneal opacity observed. Transient iritis observed in one animal at 24 hours Minimally irritating
Skin sensitization (Maximization test)	SPF bred guinea pigs 20 females in treatment group 10 females in control group Dose levels Intradermal induction treatment: 20 mg MKH 6562 Topical induction treatment: 250 mg/animal Challenge treatment: 125 and 250 mg/animal	No dermal reactions observed at 48 or 72 hours following challenge treatment at either test site in the control or treatment group. Positive control produced sensitization, demonstrating the responsiveness of the assay.	Not a skin sensitizer

Acute toxicity studies	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Acute studies: Formulation (MKH 6562 70DF and MKH 6562 Solupak 70DF)			
Oral (limit test)	Wistar rat 5 animals/sex Dose level: 5000 mg/kg bw/d	LD_{50} > 5000 mg/kg bw for both sexes	No mortalities, treatment-related gross pathological findings, or changes in body weight. Clinical signs of toxicity included decreased motility, diarrhea, and increased salivation on day of dosing only. Low toxicity No labelling recommendations
Dermal (limit test)	Wistar rat 5 animals/sex Dose level: 2000 mg/kg bw/d	LD_{50} > 2000 mg/kg bw for both sexes	No mortalities, treatment-related clinical or gross pathological findings, or changes in body weight. Low toxicity No labelling recommendations
Inhalation (4-h nose-only)	Wistar rat 5 animals/sex Dose levels Nominal: not determined owing to technical problems Actual: 0, 0.201, or 5.113 mg/L air	LC_{50} > 5.113 mg/L air for both sexes	No mortalities, treatment-related gross pathological findings, or changes in body weight. Clinical signs of toxicity observed at the high dose were indicative of respiratory tract irritation. Resolved by day 6. Low toxicity No labelling recommendations
Skin irritation	Himalayan rabbit 3 males Dose level: 500 mg test substance (TS) moistened with water	MIS and MAS (at 24, 48, and 72 hours) = 0/8	There were no signs of dermal irritation at any time point. Non-irritating No labelling recommendations
Eye irritation	Himalayan rabbit 3 males Dose level: 100 mg of TS	MIS = 10/110 at 1 hour MAS (at 24, 48, and 72 hours) = 0/110	Diffuse corneal opacity and iritis observed in 2/3 animals at 1 hour. Resolved by 24 hours. No conjunctival irritation observed. Minimally irritating No labelling recommendations
Skin sensitization (Buehler method)	SPF bred guinea pigs 20 females in treatment group and 10 females in control group Dose levels: 0.5 mL of 71.4% preparation of TS in physiological saline (.500 mg TS/animal) for both induction (left flank region) and challenge treatment (right flank caudal region)	No dermal reactions observed at 30 or 50 hours following challenge treatment in either the control or treatment group. Positive control substance produced sensitization, demonstrating the responsiveness of the assay.	Not a skin sensitizer No labelling recommendations

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Short term: Technical MKH 6562			
28-d dietary mouse	5 B6C3 F_1 mice/sex/dose Dose levels: 0, 100, 1000, or 10 000 ppm (equal to 0/0, 45.2/61.2, 472/603, or 4554/6429 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 4554/6429 mg/kg bw/d LOAEL: not determined	There were no adverse treatment-related findings in either sex at any dose level.
90-d dietary mouse	10 B6C3 F_1 mice/sex/dose Dose levels: 0, 260, 780, 2340, or 7000 ppm (equal to 0/0, 77/115, 209/337, 696/1038, or 2083/3051 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 2038/3051 mg/kg bw/d LOAEL: not determined	There were no adverse treatment-related findings in either sex at any dose level. Control terminal body weight (week 13): males and females 26.0/22.9 g Control terminal daily food consumption (week 13): males and females 5.7/8.1 g/mouse
28-d dietary rat *For guideline immunotoxicity study findings in the rat and weight of evidence refer to Section 3.1: Subacute immunotoxicity (28-d dietary) studies.	5 SPF bred Wistar rats/sex/dose Dose levels: 0, 100, 250, 2500, or 10 000 ppm (equal to 0/0, 10.3/10.8, 27.0/25.2, 266/251, or 1134/1150 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 27.0/25.2 mg/kg bw/d LOAEL: males and females 266/251 mg/kg bw/d	$266/251 mg/kg bw/d: decreased splenic cell counts (males), increased macrophage activation in spleen (females) and decreased IgA titer (males and females) 1134/1150 mg/kg bw/d: decreased surface markers for T lymphocytes (CD45) and B cells (PanB) in lymph nodes (males and females), increased macrophage activation in spleen (males), slight decreased macrophage activity in lymph node (males), slight decreased lymph node cell count (males) and increased water consumption (males)

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Short term: Technical MKH 6562			
90-d dietary rat (with 5-week recovery) *For guideline immunotoxicity study findings in rat and weight of evidence refer to Section 3.1: Subacute immunotoxicity (28-d dietary) studies.	10 SPF bred Wistar rats/sex/dose Dose levels: 0, 250, 1000, 4000, or 20 000 ppm (equal to 0/0, 17.6/21.4, 73.5/102, 287/358, or 1669/2314 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 73.5/102 mg/kg bw/d LOAEL: males and females 287/358 mg/kg bw/d	$73.5/102 mg/kg bw/d: decreased spleen weights (males), reversible, no gross pathological or histopathological findings $287/358 mg/kg bw/d: immunological changes (males and females) 1669/2314 mg/kg bw/d: discoloured feces (males and females), slight transient retardation in body weight development (males), increased food and water consumption (males and females), reversible vacuolation of the fore-stomach squamous epithelium (males and females) Immunological changes appeared to be reversible; only minimal findings were observed at the end of the recovery period. Control body weight (week 13): males and females 431/234 g Control daily food consumption (week 13): males and females 21.8/15.7 g/rat
28-d dietary dog	2 dogs/sex/dose (Bor. beagle) Dose levels: 0, 1000, 5000, or 50 000 ppm (equal to 0/0, 33.1/36.1, 164/171, or 1614/1319 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 164/171 mg/kg bw/d LOAEL: males and females 1614/1319 mg/kg bw/d	1614/1319 mg/kg bw/d (males and females): decreased body-weight gain and food consumption (males and females); decreased T_4 and increased TBC (males and females); induction of microsomal liver enzymes Phases I and II (males and females); slight increased liver weights (males and females); “cytoplasmic changes” in centrilobular cells of liver (males and females)

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Short term: Technical MKH 6562			
90-d dietary dog	4 dogs/sex/dose (Bor. beagle) Dose levels: 0, 1000, 5000, or 50 000 ppm (equal to 0/0, 33.8/35.2, 162/170, or 1674/1750 mg/kg bw/d, respectively, in males and females)	NOAEL: males and females 33.8/35.2 mg/kg bw/d LOAEL: males and females 162/170 mg/kg bw/d	33.8/35.2 mg/kg bw/d: induction of microsomal liver enzymes Phases I and II (males and females), considered to be an adaptive response owing to metabolism and excretion of TS $162/170 mg/kg bw/d: decreased T_4 and increased TBC (males and females); induction of microsomal liver enzymes Phases I and II (males and females); eosinophilic hepatocellular cytoplasm (males and females); red discolourations and red areas in gastric mucosa, rarefaction of glandular cells of the fundic mucosa accompanied by round cell infiltrates, congestion and foveolar hyperplasia, suggest local irritation in the stomach (males and females) 1674/1750 mg/kg bw/d: transient decreased food consumption (males and females); decreased serum protein and albumen and increased alkaline phosphatase (males and females) and increased liver tissue triglyceride level (males); increased liver and adrenal weights (males); slight vacuolation if inner cortex of adrenals and slight lipofuscin storage proximal tubular epithelia of kidneys (males and females)
12-month dietary dog	4 dogs/sex/dose (Bor. beagle) Dose levels: 0, 200, 1000, or 5000 ppm (equal to 0/0, 6.7/7.43, 35.9/37.1, or 183/187 mg/kg bw/d, respectively in males and females)	NOAEL: males and females 35.9 and 37.1 mg/kg bw/d LOAEL: males and females 183 and 187 mg/kg bw/d	183 and 187 mg/kg bw/d: impaired body weight development (males and females); decreased T_4 levels (females); increased *N*-demethylase levels (males and females); marginally increased liver weight (females)
4-week dermal rat	5 SPF bred Wistar rats/sex/dose Dose levels: 0 or 1000 mg/kg bw/d	Systemic NOAEL: 1000 mg/kg bw/d in both sexes LOAEL: not determined	There were no treatment-related systemic findings in either sex. Local irritation: increased skinfold thickness (males and females) and minimal to slight acanthosis (males)

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Chronic toxicity and oncogenicity: Technical MKH 6562			
2-year dietary mouse	50 B6C3 F_1 mice/sex/dose Dose levels: 0, 50, 1000, or 7000 ppm (equal to 0/0, 12.2/22.6, 275/459, or 2066/3212 mg/kg bw/d, respectively, in males and females)	Chronic toxicity NOAEL: males and females 275/459 mg/kg bw/d LOAEL: males and females 2066/3212 mg/kg bw/d	2066 and 3212 mg/kg bw/d: retarded body-weight development (males and females); increased food consumption (males) No evidence to indicate any carcinogenic potential of MKH 6562 up to and including the highest dose tested (males and females 2066 and 3212 mg/kg bw/d, respectively)
2-year dietary rat *For guideline immunotoxicity study findings in rat and weight of evidence refer to Sect. 3.1: subacute immunotoxicity (28-d dietary) studies	Wistar (Hsd Cpb: WU) rats 60 rats/sex/dose (10 rats/sex/dose interim sacrifice + 50 rats/sex/dose terminal sacrifice) Dose levels: 0, 2.5, 7.5, 125, or 1000 mg/kg bw/d	Chronic toxicity NOAEL: 125 mg/kg bw/d in both sexes LOAEL: 1000 mg/kg bw/d in both sexes	1000 mg/kg bw/d: increased food consumption (males and females); decreased body weight and body-weight gain (males); immunotoxicological findings (males) including decreased splenic T-helper cells, lymphocytes, T-cells, and interleukin-2 receptor expressing cells, decreased response to mitogen stimulation (concavalin A and lipopolysaccharide) in splenic cells (with a possible decreased in lymph node cells) and increased serum IgM titers at interim sacrifice but not at terminal sacrifice; slight increased incidence of inflammatory infiltrates (males, interim necropsy), thickened mucosa of the glandular stomach (males and females, terminal necropsy), and mild vacuolation of the fore-stomach epithelium (females, terminal necropsy) No evidence to indicate any carcinogenic potential of MKH 6562 up to and including 1000 mg/kg bw/d, the highest dose tested

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Reproduction and developmental toxicity: Technical MKH 6562			
Multigeneration rat	30 Wistar rats/sex/group Dose levels: 0, 50, 4000, or 20 000 (12 000)* ppm, equal to 0/0, 3.5/4.2, 287/340, or 2244(800)/3130(991) mg/kg bw/d, respectively, in F_0 males and females; equal to 0/0, 4.2/5.5, 346/453, or 1059/1249 mg/kg bw/d, respectively, in F_1 males and females *dose reduced in week 6	Parental NOAEL: F_0 males and females 287/340 mg/kg bw/d F_1 males and females 346/453 mg/kg bw/d LOAEL: F_0 males and females 800/991 mg/kg bw/d F_1 males and females 1059/1249 mg/kg bw/d Offspring NOAEL: F_0 males and females 287/340 mg/kg bw/d F_1 males and females 346/453 mg/kg bw/d LOAEL: F_0 males and females 800/991 mg/kg bw/d F_1 males and females 1059/1249 mg/kg bw/d Reproductive NOAEL: F_0 males and females 800/991 mg/kg bw/d F_1 males and females 1059/1294 mg/kg bw/d LOAEL: not determined	Parental $4000 ppm (287/340 mg/kg bw/d in F_0 males and females and 346/453 mg/kg bw/d in F_1 males and females): non-adverse increased incidence of cecal enlargement (F_1 females) 12 000 ppm (800/991 mg/kg bw/d in F_0 males and females and 1059/1249 mg/kg bw/d in F_1 males and females): decreased liver weight (F_1 males); decreased uterus weight (F_1 and F_2 females) Offspring 12 000 ppm (800/991 mg/kg bw/d in F_0 males and females and 1059/1249 mg/kg bw/d in F_1 males and females): decreased pup body weight (F_1 males and females); decreased liver weight (F_2 males); marbled liver surface (F_1 and F_2 pups); air-filled stomach (F_1 pups) Reproductive: No adverse treatment-related effects on reproductive parameters up to and including 12 000 ppm, the highest dose tested
Teratogenicity rats	30 sexually mature female Sprague-Dawley rats/dose Dose levels: 0, 100, 300, or 1000 mg/kg bw/d	Maternal toxicity LOAEL: not determined NOAEL: 1000 mg/kg bw/d Developmental toxicity LOAEL: not determined NOAEL: 1000 mg/kg bw/d	Maternal toxicity: There were no treatment-related effects at any dose level up to and including the limit dose, 1000 mg/kg bw/d Developmental toxicity: There were no treatment-related effects at any dose level up to and including the limit dose, 1000 mg/kg bw/d. Teratogenicity: There was no evidence of any treatment-related irreversible structural changes; therefore, under the conditions of the study, MKH 6562 was not teratogenic.

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Teratogenicity rabbit	22 sexually mature female Himalayan (CHBB:HM) rabbits/dose Dose levels: 0, 100, 300, 500, or 1000 mg/kg bw/d	Maternal toxicity LOAEL: 300 mg/kg bw/d NOAEL: 100 mg/kg bw/d Developmental toxicity LOAEL: 500 mg/kg bw/d NOAEL: 300 mg/kg bw/d	Maternal toxicity $300 mg/kg bw/d: decreased food consumption $500 mg/kg bw/d: gross pathological changes in the cecum (cecal enlargement); histopathological changes in the liver 1000 mg/kg bw/d: one treatment-related mortality; decreased body weight gain (not significantly different when corrected for gravid uterine weight); gross pathological changes in the liver and GIT (stomach, small and large intestines and cecum); decreased placental weight, increased incidence of coarse grained and light discoloured placentas; decreased gestation index and increased number of abortions Developmental toxicity $500 mg/kg bw/d: decreased fetal body weight; increased incidence of delayed fetal development (skeletal ossification) Teratogenicity: There was no evidence of any treatment-related irreversible structural changes; therefore, under the conditions of the study, MKH 6562 was not teratogenic.

Study	Species and strain and cell type	Dose levels	Significant effects and comments
Genotoxicity: Technical MKH 6562			
Salmonella (Ames test)	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537	0, 8, 40, 200, 1000, or 5000 Fg/plate in the initial trial and 0, 5, 10, 20, 40, 80, or 160 Fg/plate in a confirmatory trial	Negative
In vitro mammalian (cell) point mutation	V79 cells (Chinese hamster lung fibroblasts)	5–5000 Fg/plate	Negative
Mammalian chromosomal aberration (in vitro)	Chinese hamster V79 cells	100, 1000, or 5000 Fg/mL	Negative
Micronucleus assay (in vivo)	Mouse (male and female) bone marrow erythroblasts	2000 mg/kg bw	Negative
UDS in vitro	Rat primary hepatocytes	1.0–1250 Fg/mL	Negative

Study	Species and strain and dose level	NOAEL and LOAEL (mg/kg bw/d)	Target organs and significant effects and comments
Special studies: Technical MKH 6562			
Acute neurotoxicity screening battery: rat	12 young adult Fischer 344 CDF(F-344) rats/sex/dose Dose level: 0, 125, 500, or 2000 mg/kg bw	Systemic toxicity LOAEL: 2000 mg/kg bw NOAEL: 500 mg/kg bw Neurotoxicity LOAEL: not determined NOAEL: 2000 mg/kg bw	Systemic toxicity 2000 mg/kg bw: transient decreased in motor and locomotor activity in figure-eight maze and lower level of activity in open field, not considered to be due to neurotoxicity per se (males and females) Neurotoxicity: There was no evidence of neurotoxicity in either sex up to and including the highest dose tested (2000 mg/kg bw).
Subchronic neurotoxicity screening battery: rat	12 young adult Fischer 344 CDF(F-344) rats/sex/dose Dose levels: 0, 250, 2000, or 20 000 ppm (equal to 0/0, 18.5/21.9, 147/174, or 1482/1736 mg/kg bw/d, respectively, in males and females)	Systemic toxicity LOAEL: males 1482 mg/kg bw/d (females not determined) NOAEL: males and females 147/1736 mg/kg bw/d Neurotoxicity LOAEL: not determined NOAEL: males and females 1482/1736 mg/kg bw/d	Systemic toxicity 1482/1736 mg/kg bw/d: decreased body weight, body-weight gain and food consumption (males) Neurotoxicity: there was no evidence of neurotoxicity in either sex up to and including the highest dose tested (1482/1736 mg/kg bw/d)
Subacute immunotoxicity (28-d dietary)			
Antibody plaque-forming cell assay	10 female Wistar [Crl:WI(Glx/Brl/Han) IGSRB] rats/dose Dose levels: 0, 15, 150, or 1000 mg/kg bw/d (equal to 0, 13.8, 134, or 966 mg/kg bw/d, respectively)	Immunotoxicity LOAEL: not determined NOAEL: 966 mg/kg bw/d	Immunotoxicity: no treatment-related findings Systemic: no treatment-related systemic findings
Antibody plaque-forming cell assay	10 male Wistar [Crl:WI(Glx/Brl/Han) IGSRB] rats/dose Dose levels: 0, 15, 150, or 1000 mg/kg bw/d (equal to 0, 16.5, 157, or 1106 mg/kg bw/d, respectively)	Immunotoxicity LOAEL: not determined NOAEL: 1106 mg/kg bw/d	Immunotoxicity: no treatment-related findings; however, there appears to be a dose-related trend in the antibody-forming cell response, which suggests that exposures to high concentrations of MKH 6562 (>1000 mg/kg bw/d) may have the potential to affect the humoral response in males Systemic: no treatment-related systemic findings
Splenic T-cells, B-cells, and NK-cell assay	10 female Wistar [Crl:WI(Glx/Brl/Han) IGSRB] rats/dose Dose levels: 0, 15, 150, or 1000 mg/kg bw/d (equal to 0, 16.9, 167, or 1131 mg/kg bw/d, respectively)	Immunotoxicity LOAEL: not determined NOAEL: 1131 mg/kg bw/d	Immunotoxicity: no treatment-related findings Systemic: increased absolute and relative liver weights at 167 and 1131 mg/kg bw/d

Study	Species and strain and dose level	NOAEL and LOAEL (mg/kg bw/d)	Target organs and significant effects and comments
Special studies: Technical MKH 6562			
Splenic T-cells, B-cells, and NK-cell assay	10 male Wistar [Crl:WI(Glx/Brl/Han) IGSRB] rats/dose Dose levels: 0, 15, 150, or 1000 mg/kg bw/d (equal to 0, 17.7, 177, or 1222 mg/kg bw/d, respectively)	Immunotoxicity LOAEL: not determined NOAEL: 1222 mg/kg bw/d	Immunotoxicity: no treatment-related findings Systemic: decreased terminal body weight at 1222 mg/kg bw/d

Rat metabolism: MKH 6562 sulfonamide alanine (plant metabolite of MKH 6562)

Rate and extent of absorption and excretion: The excretion of [phenyl-^{14}C] MKH 6562 sulfonamide alanine residues in the urine and feces (approximately 75 and 90% of the administered dose at 24 and 48 hours, respectively) suggest that absorption of [phenyl-^{14}C] MKH 6562 sulfonamide alanine appears to be rapid. The high urinary excretion rate (69% of the administered dose) suggest that absorption was high. On the basis of the available urinary data (radioactivity detected in the urine, cage washes, tissues, and carcass) the estimated proportion of the dose administered that was absorbed was approximately 70%. The mean overall recovery of administered radioactivity was 98%. The major route of excretion was via the urine with approximately 69% of the administered dose being found in the urine (with 51 and 64% excreted within 24 and 48 hours, respectively). Fecal excretion accounted for 27% of the administered dose (with 24 and 26% excreted within 24 and 48 hours, respectively).

Distribution and target organ(s): The total radioactive residues were highest in the liver (0.080 ppm), kidney (0.079 ppm), and GIT (0.073 ppm). However, a combined total of 1% of the administered dose remained in the blood, tissues, GIT, and residual carcass 96 hours after dosing, indicating that the potential for accumulation was low.

Toxicologically significant compound(s): Data suggests that [phenyl-^{14} C] MKH 6562 sulfonamide alanine was extensively and rapidly metabolized by rats. The major metabolites in the urine were identified as *N*-acetyl sulfonamide alanine (17%), sulfonamide (11%), sulfinic acid (10%), a glucuronide of sulfohydroxamic acid (10%), sulfonamide *N*-glucuronide (7%), sulfohydroxamic acid (2%), *N*-acetyl sulfonamide (2%), hydroxysulfonamide (2%), sulfonamide alanine (1%), hydroxysulfonamide glucuronide (1%), and sulfonic acid (<1%). The major fecal metabolites were identified as sulfonamide alanine (13%), sulfonamide (7%), sulfohydroxamic acid (<1%), *N*-acetyl sulfonamide alanine (<1%), and *N*-acetyl sulfonamide (<1%).

Rat metabolism: MKH 6562 sulfonamide lactate (plant metabolite of MKH 6562)

Rate and extent of absorption and excretion: The rapid excretion of [phenyl-UL-^{14}C] MKH 6562 sulfonamide lactate residues in the feces and urine (at 24 hours approximately 99% of the dose had been eliminated) suggest that absorption of [phenyl-UL-^{14}C] MKH 6562 sulfonamide lactate appears to be rapid. However, the high fecal excretion rate (65% of the administered dose), low urinary excretion rate (35% of the administered dose) and high levels of the unchanged parent compound, MKH 6562 sulfonamide lactate, in fecal extracts (65% of the administered dose) suggest that absorption was low. On the basis of the available urinary data (radioactivity detected in the urine, cage washes, tissues and carcass) the estimated proportion of the dose administered that was absorbed was approximately 35%. The major route of excretion was via the feces with approximately 65% of the administered dose being found in the fecal extract. Urinary excretion accounted for 35% of the administered dose.

Distribution and target organ(s): Less than 1% of the administered dose remained in the carcass and tissues at sacrifice (at 72 hours) indicating that the potential for accumulation was low.

Toxicologically significant compound(s): The parent compound, MKH 6562 sulfonamide lactate, was the major residue found in both the urine (22% of the administered dose) and feces (65% of the administered dose). The metabolites found in the urine were sulfonamide (10% of the administered dose) and sulfonamide acetate (3% of the administered dose). No metabolites were found in the feces.

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Acute studies: MKH 6562 metabolites			
Oral (limit test) Trifluoromethoxy sulfonamide (animal and plant metabolite of MKH 6562)	Wistar rats 5 animals/sex Dose level: 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw for both sexes	No mortalities or treatment-related gross pathological findings. Slight transient decreased body weight in females. Non-specific clinical signs observed in both sexes, first apparent immediately after administration and lasted up to day 13. Low toxicity

Study	Species and strain and doses	NOAEL and LOAEL (mg/kg bw/d)	Target organ and significant effects and comments
Acute studies: MKH 6562 metabolites			
Oral (limit test) MKH 6562 lactate conjugate (plant metabolite of MKH 6562)	Wistar rats 5 animals/sex Dose level: 0 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw for both sexes	No mortalities and no treatment-related gross pathological findings or changes in body weight. Diarrhea was observed in all animals at 1 hour after administration, completely resolved by 7 hours. Low toxicity
Oral (limit test) MKH 6562 sulfonamide alanine (plant metabolite of MKH 6562)	Wistar rats 5 animals/sex Dose level: 0 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw for both sexes	No mortalities or treatment-related gross pathological findings or changes in body weight. Lightly discoloured feces observed in all animals, first apparent 2 days after administration, completely resolved by day 7. Low toxicity
Oral (limit test) MKH 10868 (animal, plant, and soil metabolite of MKH 6562)	Wistar rats 5 animals/sex Dose level: 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw for both sexes	No mortalities, clinical signs, necropsy findings, or changes in body weight Low toxicity
Oral (limit test) *O*-desmethyl MKH 6562 (a soil metabolite of MKH 6562)	Wistar rats 5 animals/sex Dose levels: 2500 or 5000 mg/kg bw	LD_{50} > 2500 and < 5000 mg/kg bw for both sexes	At 5000 mg/kg bw, 3/5 males and 5/5 females died. All deaths occurred by day 4. Non-specific clinical signs were observed in both sexes at 2500 and 5000 mg/kg bw, first apparent 1 hour after administration and lasted up to day 11. Transient decreased body weight in males at 5000 mg/kg bw. No treatment-related gross pathological findings. Low toxicity

Study	Species and strain and cell type	Dose levels	Significant effects and comments
Genotoxicity: MKH 6562 metabolite (MKH 10868, an animal, plant, and soil metabolite of MKH 6562)			
Salmonella (Ames test)	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, and TA 1537	0, 16, 50, 158, 500, 1581, or 5000 Fg/plate	Negative

Appendix II Residues

Plant metabolism
Flucarbazone-sodium is readily metabolized in wheat. The major metabolites detected in wheat matrices were *N*-desmethyl flucarbazone, sulfonamide conjugates (lactate, acetate, and glucosides), sulfonic acid, and NODT glycoside. The sulfonamide conjugates, sulfonic acid, and NODT were adequately tested in the rat, and were found not to be of toxicological concern.
ROC defined as flucarbazone-sodium + *N*-desmethyl flucarbazone

Matrix	PHI (days)	[phenyl-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 30 g a.i./ha (1 × GAP)	[triazolinone-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 45 g a.i./ha (1.5 × GAP)
wheat forage	7, 21	0.495	0.68
wheat hay	38, 48	2.895	0.217
wheat straw	64, 75	2.757	0.222
wheat grain	64, 75	0.271	0.023

Confined crop rotation studies
11 month plantback restriction on label

Crop fraction	[phenyl-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 30 g a.i./ha (1 × GAP)			[triazolinone-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 45 g a.i./ha (1.5 × GAP)		
	Planting interval (days after treatment [DAT])			Planting interval (DAT)		
	30	**120**	**371**	**31**	**120**	**368**
Wheat forage	0.34	0.096	0.037	0.01	0.003	0.001
Wheat hay	0.27	0.57	0.21	0.045	0.01	0.003
Wheat straw	1	0.33	0.05	0.044	0.003	0.004
Wheat grain	—	0.028	0.012	0.006	0.001	0.001
Turnip tops	0.094	0.053	0.017	0.01	0.003	0.002
Turnip roots	0.04	0.021	0.007	0.001	<0.001	<0.001
Kale	0.062	0.036	0.012	0.004	0.002	0.002

Freezer storage stability tests
Stability of flucarbazone-sodium + *N*-desmethyl flucarbazone residues in wheat forage, hay, straw, and grain at –20EC for 34, 33, 28, and 24 months, respectively.
Plant metabolism and residue samples were stored within the time periods studied.

[triazolinone-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm)

Commodity	Flucarbazone-sodium residues			*N*-desmethyl flucarbazone residues		
	Initial residue level (ppm)	Initial residues recovered (%)	Stored samples residues recovered (%)	Initial residue level (ppm)	Initial residues recovered (%)	Stored samples residues recovered (%)
Wheat forage	0.48	100	96	0.75	92	95
Wheat hay	0.471	94	74	1.501	71	80
Wheat straw	0.237	76	72	0.558	72	90
Wheat grain	—	—	—	0.003	100	90

Animal metabolism
In the goat and poultry metabolism studies, flucarbazone-sodium was extensively metabolised via hydrolysis to NODT and sulfonamide metabolites and via the apparent conjugation to proteins in the liver. A minor route observed in muscle and liver was the *N*-dealkylation of the parent compound to the *N*-desmethyl flucarbazone. Excretion was rapid and occurred mostly through the feces, but also in the urine. The minor metabolic routes differ slightly between the animals; however, all metabolites observed in the goat and poultry have been identified or accounted for in the rat metabolism and have therefore been adequately tested.
ROC defined as flucarbazone-sodium

Goat

Matrix	[phenyl-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 3 mg/kg bw/d (1709 × expected feeding rate)	[triazolinone-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 3 mg/kg bw/d (1454 × expected feeding rate)
	% of recovered dose (ppm)	% of recovered dose (ppm)
Tissues	1.7 (4.977)	0.4 (2.471)
Milk	0.3 (0.481)	0.5 (1.143)
Feces	53.6	69.4
Urine	44.4	29.7

Poultry

Matrix	% of recovered dose (ppm)	
	[phenyl-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 3 mg/kg bw/d (6450 × expected feeding rate)	[triazolinone-UL-^{14}C] flucarbazone-sodium label, TRRs (ppm) 3 mg/kg bw/d (4688 × expected feeding rate)
Tissues	0.3 (0.883)	0.4 (0.648)
Eggs	0.01 (0.042)	0.1 (0.259)
Excreta	99.5	99.5

Cattle feeding study
The maximum anticipated dietary burdens of flucarbazone-sodium and *N*-desmethyl flucarbazone to dairy cattle was 0.057 ppm, on the basis of diets consisting of wheat hay (0.78 ppm) and wheat grain (LOQ, 0.01 ppm), treated at the Canadian maximum seasonal application rate (30 g a.i./ha).

Dose (ppm)	Residues (ppm)						
	Raw milk	Skim milk	Cream	Fat	Muscle	Kidney	Liver
13× (0.73)	n.a.	n.d.	n.d.	n.a.	n.a.	0.004	0.532
33× (1.89)	n.a.	n.d.	n.d.	n.a.	n.a.	0.008	1.211
120× (6.82)	<0.005	<0.005	<0.005	<0.01	<0.01	0.025	3.638

n.a., not analysed, since no residues found in higher feeding level; n.d., not detected.
At the 120× feeding level, residues in milk plateaued by day 14 and appeared to decline by day 28.
On the basis of the 13× feeding level, residues in meat (excluding liver), liver, and milk are expected to be 0.02 ppm and higher, 0.05 ppm and higher, and 0.005 ppm and higher at the 1× feeding level.

Poultry feeding study
Petitioner requested a waiver from the requirements for a poultry feeding study. The maximum anticipated dietary burden of flucarbazone-sodium and *N*-desmethyl flucarbazone to poultry is 0.008 ppm. On the basis of the supervised field trials, residue of flucarbazone-sodium and *N*-desmethyl flucarbazone in wheat grain did not exceed the method LOQ (0.01 ppm), when treated at a rate of 1× the Canadian maximum seasonal application rate. The poultry metabolism study demonstrated that it is unlikely that quantifiable residues of flucarbazone-sodium or any compound of toxicological interest be transferred to poultry tissues or eggs at the anticipated dietary burden, no poultry feeding study was required.

Number of field trials by region									
Zones	**2**	**4**	**5**	**6**	**7**	**8**	**9**	**14**	**Total**
Required			2		8			10	20
Submitted	2	1	6	1	9	6	1	10	36

Supervised residue trials on wheat						
Commodity and portion analysed	**Formulation**	**Application**			**PHI (days)**	**Residues (ppm) (*represents highest average field trial value)**
		No.	**Total rate (kg a.i./ha)**	**% GAP**		
Wheat grain	70WG	1	0.3	100	60–127	<0.01
Wheat forage	70WG	1	0.3	100	15	0.27*
Wheat hay	70WG	1	0.3	100	51	0.08*
Wheat straw	70WG	1	0.3	100	77	0.04*

Processing studies
The petitioner requested a waiver from the requirements for data for processed wheat commodities. As residues in wheat grain, grown in zone 5 and treated with flucarbazone-sodium 70WG at 5× the Canadian maximum seasonal application rate (0.155 kg a.i./ha), did not exceed the method LOQ (0.01 ppm), a wheat grain processing study was not required to support this petition.

Proposed MRLs	
Commodity	**Proposed Canadian MRLs (ppm)**
Wheat grain	0.01
Meat and meat by-products of cattle, goat, hogs, horses, sheep, and poultry	0.1*
Milk	0.1*
Eggs	0.1*
*Owing to the lack of an adequate enforcement method for animal tissues, MRLs cannot be established on animal tissues. Residues occurring in meat, meat by-products (excluding liver), and liver and milk are not expected to exceed 0.02 ppm, 0.05 ppm, and 0.005 ppm, respectively. No quantifiable residues are expected in poultry and eggs.	

Chronic dietary risk assessment using DEEM™ software on the basis of the 1994–1996 Continuing Survey of Food Intake by Individuals, ADI = 0.36 mg/kg bw; using the proposed MRLs on wheat grain (0.01 ppm), the expected residues on animal commodities, and the EEC for drinking water (7.1 Fg a.i./L).

	All populations	**All infants (<1 year)**	**Children (1–6 years)**	**Children (7–12 years)**	**Adolescents (13–19 years)**	**Adults (20+ years)**	**Seniors (55+ years)**
% of ADI	<1%	<1%	<1%	<1%	<1%	<1%	<1%

Worst case scenario chronic dietary risk assessment using DEEM™ software on the basis of the 1994–1996 Continuing Survey of Food Intake by Individuals ADI = 0.36 mg/kg bw; using the proposed MRLs on wheat grain (0.01 ppm), the general regulations (0.1 ppm) on animal commodities, and the EEC for drinking water (7.1 Fg a.i./L).

	All populations	**All infants (<1 year)**	**Children (1–6 years)**	**Children (7–12 years)**	**Adolescents (13–19 years)**	**Adults (20+ years)**	**Seniors (55+ years)**
% of ADI	<1%	<1%	<1%	<1%	<1%	<1%	<1%

Appendix III Environmental assessment summary tables

Table 1 Summary of terrestrial fate and transformation data

Fate process	End point	Major transformation product
Hydrolysis	$t_{½}$ pH 5 = 525 days $t_{½}$ pH 7 = 521 days $t_{½}$ pH 9 = 753 days	MKH 6562 is stable to hydrolysis. Chemical hydrolysis is not a principal route of transformation in the terrestrial environment.
Phototransformation	$t_{½}$ (irradiated) = 214, 287 days $t_{½}$ (control) = 157, 211 days	Phototransformation on soil is not a principal route of transformation in the environment.
Aerobic biotransformation	$t_{½}$ = 28, 31, and 76 days $t_{½}$ sterile = 1173 days	MKH 6562 is slightly to moderately persistent in soil under aerobic conditions. Aerobic biotransformation is a principal route of transformation in the environment.
Anaerobic biotransformation	no data were submitted	
Adsorption or desorption	MKH 6562 K_d = 0.02–0.57 K_{oc} = 11–20 Transformation products K_d = 0.06–0.89 K_{oc} = 11–49	MKH 6562 and its transformation products have a high to very high mobility in silt clay, sandy clay loam, silt clay loam, sandy loam, and sandy soils.
Aged soil column leaching	radioactivity = 57–69% parent compound = 78–89% transformation products > 70%	MKH 6562 and its transformation products have a very high mobility in sandy loam soils.
Field dissipation and leaching	DT_{50} = 13–31 days Dissipation time 90% = 5994 days No residues of parent compound and transformation products were detected below the 30 cm soil depth.	MKH 6562 is non persistent to slightly persistent in soil under field conditions and has a low potential for carryover into the following season. MKH 6562 and its transformation products have a low potential to leach under field conditions.
EEC in soil	0.013 mg a.i./kg dry soil	

Table 2 Summary of transformation products in the terrestrial fate studies

Fate process	Major transformation products (% of applied MKH 6562)	Minor transformation products (% of applied MKH 6562)
Hydrolysis	none	MKH 6562 sulfonamide (3.9–4.2%)
Phototransformation on soil	none	unidentified (8.18%)
Aerobic biotransformation	MKH 6562 sulfonamide (46–69%) MKH 6562 sulfonic acid (11%) *O*-desmethyl MKH 6562 (15%) NMT (14.4%)	MKH 6562 sulfonyl urea (2%) NODT (4.7%)
Aged soil column leaching	MKH 6562 sulfonamide (54.5%) *O*-desmethyl MKH 6562 (17.1%) NMT (14.2%)	MKH 6562 sulfonic acid (1.6%) NODT (4.4%)
Terrestrial field dissipation	MKH 6562 sulfonamide (24%) *O*-desmethyl MKH 6562 (28%)	MKH 6562 sulfonic acid (9%) NODT (4%)

Table 3 Summary of aquatic fate and transformation data

Fate process	Half-life	Interpretation
Hydrolysis	$t_{½}$ pH 5: 525 days $t_{½}$ pH 7: 521 days $t_{½}$ pH 9: 753	Chemical hydrolysis is not a principal route of transformation in the aquatic environment
Phototransformation	$t_{½}$ = 61, 82 days	Phototransformation on water is not a principal route of transformation in the aquatic environment
Aerobic biotransformation: pond	$t_{½}$ = 878–1632 days $t_{½}$ sterile = 1002 days	MKH 6562 is persistent in water under aerobic conditions.
Anaerobic biotransformation	$t_{½}$ DT_{50} = 66, 104 days $t_{½}$ sterile = 1421, 4226 days	MKH 6562 is moderately persistent in sediment–water system under anaerobic conditions. Biotransformation is a principal route of transformation in the anaerobic aquatic environment.
EEC in water	0.01 mg a.i./L	
EEC in pond water owing to runoff	9.5 Fg a.i./L	
EEC in drinking water owing to runoff	7 Fg a.i./L	

Table 4 Summary of transformation products formed in aquatic fate studies

Fate process	Major transformation products (% of applied MKH 6562)	Minor transformation products (% of applied MKH 6562)
Hydrolysis	none	MKH 6562 sulfonamide (3.9–4.2%)
Phototransformation	MKH 6562 sulfonamide (22.6%)	MKH 6562 sulfonic acid (1.32%)
Aerobic biotransformation	MKH 6562 sulfonamide (14.9–16.1%) NODT (19%)	MKH 6562 sulfonic acid (<0.8%)
Anaerobic biotransformation	MKH 6562 sulfonamide (89%) NMT (65%)	NODT (3.7–7%)

Table 5 Summary of toxicity of MKH 6562 to terrestrial organisms

Group	Organism	Study	NOEC	LD_{50} or LC_{50} or EC_{25}	Interpretation
Birds	bobwhite quail	acute oral	2000 mg a.i./kg bw	LD_{50} > 2000 mg a.i./kg bw	non-toxic
		dietary	4646 mg a.i./kg diet	LC_{50} > 4646 mg a.i./kg diet	slightly toxic
	mallard ducks	dietary	4969 mg a.i./kg diet	LC_{50} > 4969 mg a.i./kg diet	non-toxic
	bobwhite quail	reproduction	1311 mg a.i./kg diet		no effect
	mallard ducks	reproduction	223 mg a.i./kg diet		no effect up to 223 mg a.i./kg diet
Mammals	rats	acute oral		LD_{50} > 5000 mg a.i./kg bw	non-toxic
	rats	dietary	250 mg a.i./kg diet		
	rats	subchronic	250 mg a.i./kg diet		
	mice	subchronic	7000 mg a.i./kg diet		
	rats	two-generation reproduction	4000 mg a.i./kg diet (parental and offspring)		
			12 000 mg a.i./kg diet (reproduction)		
Soil organisms	earthworms	acute	1000 mg a.i./kg soil	LC_{50} > 1000 mg a.i./kg soil	no effect
Predators and parasites	honeybees	acute contact		LD_{50} > 200 Fg a.i./bee	non-toxic
		acute oral		LD_{50} > 445 Fg a.i./bee	non-toxic
Terrestrial plants	seedlings	emergence	0.25 g a.i./ha (onion*)	EC_{25} = 1.34 g a.i./ha (onion*)	significant effect
		shoot height	0.74 g a.i./ha (canola*)	EC_{25} = 1.32 g a.i./ha (canola*)	significant effect

Group	Organism	Study	NOEC	LD_{50} or LC_{50} or EC_{25}	Interpretation
		dry weight	0.25 g a.i./ha (onion*)	EC_{25} = 0.30 g a.i./ha (canola*)	significant effect
		phytotoxicity	0.74 g a.i./ha (flax*)	EC_{25} = 1.21 g a.i./ha (canola*)	phytotoxic
	vegetative vigour	plant survival	2.2 g a.i./ha (oat*)	EC_{25} > 6.7 g a.i./ha** (corn*)	significant effect
		shoot height	0.25 g a.i./ha (buckwheat*)	EC_{25} = 0.54 g a.i./ha (buckwheat*)	significant effect
		dry weight	0.25 g a.i./ha (onion*)	EC_{25} = 0.39 g a.i./ha (onion*)	significant effect
		phytotoxicity	0.25 g a.i./ha (buckwheat*)	EC_{25} = 0.93 g a.i./ha (buckwheat*)	phytotoxic

* most sensitive species; ** highest application rate tested.

Table 6 Summary of toxicity of MKH 6562 to aquatic organisms

Group	Organism	Study	NOEC	LC_{50} or EC_{50} or EC_{25}	Interpretation
Fish	rainbow trout	acute	96.7 mg a.i./L	LC_{50} > 96.7 mg a.i./L	non-toxic
	bluegill sunfish	acute	99.3 mg a.i./L	LC_{50} > 99.3 mg a.i./L	non-toxic
	rainbow trout	chronic	2.75 mg a.i./L		
Invertebrates	water flea	acute	25.1 mg a.i./L	LC_{50} > 109 mg a.i./L effective concentration 50% (EC_{50}) = 38.8 mg a.i./L	non-toxic
	water flea	chronic	114.64 mg a.i./L		no effect
Algae	blue-green alga	acute	5.43 mg a.i./L	EC_{50} = 12 mg a.i./L EC_{25} = 9.1 mg a.i./L	toxic
	green alga	acute	2.5 mg a.i./L	EC_{50} = 3.8 mg a.i./L EC_{25} = 6.4 mg a.i./L	toxic
	freshwater diatom	acute	115 mg a.i./L	EC_{50} > 115 mg a.i./L EC_{25} > 115 mg a.i./L	non-toxic
	marine diatom	acute	89.2 mg a.i./L	EC_{50} > 89.2 mg a.i./L EC_{25} > 89.2 mg a.i./L	non-toxic
Plants	duck weed	acute	5.3 Fg a.i./L	EC_{50} = 12.3 Fg a.i./L EC_{25} = 9.4 Fg a.i./L	phytotoxic
	duck weed	foliar spray	0.17 g a.i./ha (frond number)	EC_{50} = 1.12 g a.i./ha EC_{25} = 0.55 g a.i./ha	phytotoxic
			EC_5 = 0.09 g a.i./ha (frond dry weight)	EC_{50} = 1.76 g a.i./ha EC_{25} = 0.53 g a.i./ha	

Table 7 Summary of risk assessment to terrestrial organisms

Organism	Effect	NOEC or NOEL	EEC	Margin of safety	Risk	Mitigatory measures
Bobwhite quail	acute oral	2000 mg a.i./kg bw 490 mg a.i./ind	3.6 mg a.i./kg dw DI = 0.06 mg a.i./ind/d	>8000 days	no risk	not required
	dietary	4646 mg a.i./kg dw	3.6 mg a.i./kg dw	129	no risk	not required
Mallard ducks	reproduction	223 mg a.i./kg dw	1.01 mg a.i./kg dw	221	no risk	not required
Rats	acute	500 mg a.i./kg bw 175 mg a.i./ind.	15.13 mg a.i./kg dw DI = 0.9 mg a.i./ind/d	193 days	no risk	not required
Rats	dietary	250 mg a.i./kg dw	15.13 mg a.i./kg dw	16.5	no risk	not required
Rats	parental	4000 mg a.i./kg bw	15.13 mg a.i./kg dw	264	no risk	not required
	reproduction	12000 mg a.i./kg bw	15.13 mg a.i./kg dw	793	no risk	not required
Earthworms	acute	1000 mg a.i./kg	0.013 mg a.i./kg dw	76900	no risk	not required
Honeybees	acute contact	220 Fg/bee 224 mg/ha*	30 g a.i./ha	7.5	no risk	not required
	acute oral	445 Fg/bee 499 mg/ha*	30 g a.i./ha	16.6	no risk	not required

* Fg/bee is converted to g/ha by multiplying by 1.2 (Atkins et al., 1981[2]).

Table 8 Summary of risk assessment to aquatic organisms

Organism	Effect	NOEC or NOEL (mg a.i./L)	EEC (mg a.i./L)	Margin of safety	Risk	Mitigatory measures
Water flea	acute	25.1	0.01	2510	no risk	not required
	chronic	115	0.01	11500	no risk	not required
Fish: Rainbow trout	acute	96.7	0.01	9670	no risk	not required
	chronic	2.75	0.01	275	no risk	not required

[2] Atkins, E.L., D. Kellum, and K.W. Atkins. 1981. Reducing pesticide hazards to honey bees: Mortality prediction techniques and integrated management strategies. Univ. Calif. Div. Agric. Sci. Leaflet 2883. 22 pp.

Table 9 Summary of risk assessment to non-target plants

Organism	Effect	NOEC	EEC	Margin of safety	Risk	Mitigatory measures
Green algae	acute	2.5 mg a.i./L	0.01 mg a.i./L	250	no risk	not required
Duckweed	acute	0.0053 mg a.i./L	0.01 mg a.i./L	0.53	risk	buffer zone required
	spray	0.09 g a.i./ha	30 g a.i./ha	0.003	risk	buffer zone required
Onion	dry weight	EC_{25} = 0.39 g a.i./ha	30 g a.i./ha	0.013	risk	buffer zone required