Proposed Re-evaluation Decision PRVD2022-02

Flucarbazone (present as flucarbazone-sodium) and Its Associated End-use Products

Consultation Document

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Proposed re-evaluation decision for flucarbazone (present as flucarbazone-sodium) and associated end-use products

Under the authority of the *Pest Control Products Act,* all registered pesticides must be re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Flucarbazone (present as flucarbazone-sodium) is a selective herbicide used on wheat (spring, durum and winter) in Alberta, Manitoba, Saskatchewan, and Peace River region of British Columbia. It is used to control certain annual grasses and broadleaf weeds. Flucarbazone products are formulated as wettable granules, suspension or emulsifiable concentrate and can be applied using ground or aerial equipment. Currently registered products containing flucarbazone can be found in the Pesticide Label Search and in Appendix I.

This document presents the proposed re-evaluation decision for flucarbazone, including the proposed amendments (risk mitigation measures) to protect human health and the environment, as well as the science evaluation on which the proposed decision is based. All products containing flucarbazone that are registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period,[1] during which the public (including the pesticide manufacturers and stakeholders) may submit written comments and additional information to PMRA Publications. The final re-evaluation decision will be published after taking into consideration the comments and information received during the consultation period.

Proposed re-evaluation decision for flucarbazone

Under the authority of the *Pest Control Products Act* and based on an evaluation of available scientific information, Health Canada is proposing continued registration of flucarbazone and associated end-use products registered for sale and use in Canada.

With respect to human health, risks (occupational, dietary, residential/bystander) were shown to be acceptable when flucarbazone is used according to proposed conditions of registration, which include mitigation such as protective clothing and personal protective equipment for mixers, loaders, and applicators, a standard restricted entry interval, and a best practice label statement to minimize the potential for spray drift to limit bystander exposure.

The environmental risk assessment found that flucarbazone and major transformation products flucarbazone sulfonamide, NODT, and flucarbazone sulfonic are expected to be very highly mobile in soil, and may leach to groundwater. A label statement indicating the potential for leaching is proposed for product labels. Flucarbazone does not pose a risk to wild birds, mammals, bees, earthworms, freshwater fish, aquatic invertebrates or algae for the registered

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

uses. Potential risk to non-target terrestrial and aquatic vascular plants were identified during the re-evaluation. Spray buffer zones are required to mitigate potential risks to terrestrial and aquatic vascular plants. When used according to the revised label directions, the risks to the environment have been shown to be acceptable.

Flucarbazone has value as an important weed management tool for Western Canadian wheat growers.

Risk mitigation measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law. The proposed label amendments including any revised/updated label statements and/or mitigation measures, as a result of the re-evaluation of flucarbazone, are summarized below. Refer to Appendix XIII for details.

Human health

Risk mitigation:

To protect workers during mixing, loading and applying and postapplication exposure, the following risk-reduction measures are proposed:

- Protective clothing and personal protective equipment (PPE) requirements consisting of a long-sleeved shirt and long pants plus chemical-resistant gloves, socks and shoes.
- A standard restricted-entry interval (REI) of 12 hours.

To protect bystanders from agriculture application exposure, the following best practice statement is proposed:

- Standard drift statement.

Environment

Risk mitigation:

To protect the environment, the following risk-reduction measures are proposed:

- Precautionary leaching label statements.
- Terrestrial and freshwater aquatic buffer zones to mitigate risk from drift.

International context

Flucarbazone is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States, Chile and Turkey. No decision by an OECD member country to prohibit all uses of flucarbazone for health or environmental reasons has been identified as of 7 May 2021.

Next steps

Upon publication of this proposed re-evaluation decision, the public, including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document,[2] which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with Health Canada's responses.

Refer to Appendix I and II for details on specific products and uses impacted by this proposed decision.

Other Information

The relevant confidential test data on which the proposed decision is based (see References section of this document) are available for public inspection, upon application, in Health Canada's Reading Room. For more information, please contact Health Canada's Pest Management Information Service.

Additional scientific information

No additional scientific data are required at this time.

[2] "Decision statement" as required by subsection 28(5) of the Pest Control Products Act.

Science evaluation

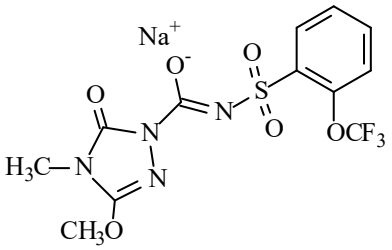
1.0 Introduction

Flucarbazone (present as flucarbazone-sodium) is used on wheat (spring, durum and winter) in Alberta, Manitoba, Saskatchewan, and Peace River region of British Columbia. It is used to control certain annual grasses and broadleaf weeds. There are three sources of flucarbazone technical grade active ingredient and fifteen commercial class end-use products containing flucarbazone currently registered in Canada. Flucarbazone products are formulated as wettable granules, suspension or emulsifiable concentrate and can be applied using ground or aerial equipment.

Flucarbazone is a sulfonyamino-carbonyl-triazolinone herbicide that dissociates to the anion form (flucarbazone) in the presence of moisture. As such, the re-evaluation assessment considered flucarbazone as the active ingredient and is referred to as such throughout the assessment.

2.0 Technical grade active ingredient

2.1 Identity

Common name		Flucarbazone-sodium
Function		Herbicide
Chemical Family		Sulfonylurea
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	sodium [(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)carbonyl]{[2-(trifluoromethoxy)phenyl]sulfonyl}azanide
2	**Chemical Abstracts Service (CAS)**	1*H*-1,2,4-triazole-1-carboxamide, 4,5-dihydro-3-methoxy-4-methyl-5-oxo-*N*-[[2-(trifluoromethoxy)phenyl]sulfonyl]-, sodium salt
CAS Registry Number		181274-17-9
Molecular Formula		$C_{12}H_{10}F_3N_4NaO_6S$
Structural Formula		
Molecular Weight		418.3

Registration number of technical grade active ingredient	Purity as flucarbazone
26446	89.2%
33333	93.2%
34110	91.2%

2.2 Physical and chemical properties

Property	Result
Vapour pressure at 20°C	$<1 \times 10^{-6}$ mPa
Ultraviolet (UV) / visible spectrum	Not expected to absorb at λ >300 nm
Solubility in water at 20°C	44 g/L
n-Octanol/water partition coefficient at 20–25°C	Log K_{ow} for free acid: -2.85 (unbuffered), -1.88 (pH 9), -1.84 (pH 7), -0.89 (pH 4)
Dissociation constant	1.9 (for free acid)

3.0 Human health assessment

3.1 Toxicology summary

Flucarbazone also known as MKH 6562, is a selective herbicide belonging to the triazolone group of chemicals. A detailed review of the toxicological database for flucarbazone was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The toxicology assessment also considered information found in the published scientific literature and a newly submitted guideline short-term inhalation toxicity study. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with flucarbazone.

Both triazolinone- and phenyl-radiolabelled flucarbazone-sodium resulted in rapid systemic absorption and distribution following oral gavage administration in rats. The peak plasma concentrations were achieved within 30 minutes of dosing. Tissue retention was minimal, with the liver and kidney showing the highest tissue concentrations for both radiolabels, followed by plasma and fat. The majority of the administered dose (AD) was excreted within the first day of dosing. Biliary excretion accounted for approximately 2% of the AD. The fecal route was the predominant route of excretion accounting for up to 75% and 85% of the AD in the low and high oral dose levels, respectively, while urinary excretion accounted for up to 30% and 15% of the AD in the low and high oral dose levels, respectively. Approximately 90% of the AD excreted in the urine and feces was unchanged flucarbazone. Overall, the low total biliary and urinary excretion and minimal tissue retention were indicative of poor oral absorption.

The main metabolites of flucarbazone, accounting for trace amounts of the AD, were identified as urazole, methylurethane (also known as methyl carbamate), N-methyltriazolinone, sulfonic acid, hydroxysulfonamide, sulfonamide-N-glucuronide, hydroxysulfonamide-O-glucuronide, N-acetylsulfonamide, carbomethoxy sulfonamide, and carboethoxy sulfonamide. The position of radiolabel, single or repeat dosing did not produce major differences in the kinetic profile and there were no sex-related differences in the absorption, distribution, metabolism or excretion of flucarbazone. Toxicokinetic studies conducted with two major plant metabolites of flucarbazone, MKH 6562 sulfonamide lactate and MKH 6562 sulfonamide alanine, were also considered. The toxicokinetic profiles of these metabolites were similar to that of the flucarbazone, but with higher (greater than 2-fold) absorption of MKH 6562 sulfonamide alanine.

Flucarbazone was of low acute oral, dermal and inhalation toxicity in rats. It was non-irritating to rabbit skin, minimally irritating to the rabbit eye, and did not cause skin sensitization in guinea pigs using the Maximization test method. Several plant metabolites of flucarbazone tested in acute oral toxicity studies in rats also exhibited low acute toxicity.

Administration of flucarbazone in repeat dose dietary toxicity studies revealed the liver, stomach, and immune system as the principal target sites of toxicity. With the exception of short-term toxicity studies in mice, decreased body weight and increased clinical signs of toxicity such as fecal changes were noted across several studies and species. Dogs were the most sensitive species to the toxicological effects induced by flucarbazone. However, there was no notable evidence of increased toxicity with increased duration of dosing in any test species. The most sensitive oral endpoints for risk assessment were reductions in body weight gain and body weight observed in the 12-month dietary toxicity study in dogs. Decreased T4 levels were also observed in short-term dietary toxicity studies in dogs. The induction of several liver enzymes and increased incidence of cytoplasmic changes in the liver were noted in the supplemental 28-day and the guideline 90-day dietary toxicity studies in dogs, but not in the 12-month dietary toxicity study. Liver enzyme induction, which could cause increased hepatic clearance of T4 levels resulting in decreased circulating T4, was considered an adaptive response, as it was not seen in the 12-month dietary toxicity study. Thus, the level of concern was low for the decreased T4 levels, which was further supported by the absence of any effects on other thyroid biomarkers, such as triiodothyronine (T3), and thyroid-stimulating hormone (TSH), and a lack of corroborative histopathological findings in the thyroid gland.

Effects on the stomach included increased incidences of red discolouration or red areas in the gastric mucosa in both sexes at the mid- and higher dose levels in the 90-day dietary toxicity study in dogs. These findings were accompanied by increased incidences of glandular cell degeneration, round cell infiltrates, and foveolar hyperplasia of the stomach in females at the same dose level and in males at higher dose levels. These effects on the stomach in dogs were supported by evidence in rat dietary toxicity studies where increased incidence of vacuolation of the forestomach squamous epithelium or thickened mucosa of the glandular stomach were observed at or above limit doses in the 90-day dietary toxicity study and the dietary chronic toxicity/carcinogenicity studies. However, there were no treatment-related findings in the stomach in the 12-month dietary toxicity study in dogs. Overall, the effects on the stomach were suggestive of a local irritative effect of the test substance.

Within the standard short-term dietary toxicity studies and the dietary chronic toxicity/carcinogenicity study in rats, additional immunological investigations were conducted that are typically not required by the respective test guidelines for these studies. Evidence of treatment-related immunological changes were observed, consisting of decreased cell counts in the spleen and lymph nodes, decreased serum antibody titers of subclasses IgA and IgG, and altered responsiveness of spleen or lymph node cells (B cell, T cell, macrophage) to stimulation by various mitogens such as phorbol 12-myristate 13-acetate (PMA), and concavalin A (ConA). These findings occurred at similar dose levels across all studies, irrespective of the duration of the study and were noted in both sexes in the short-term toxicity studies. However, only minimal findings were observed at the end of the recovery period in the 90-day study. In addition, in the dietary chronic toxicity/oncogenicity study, the majority of the immunological changes were clustered in males reserved for the chronic toxicity/interim necropsy portion of the study. There was no evidence of durational or progression to more severe effects in these studies.

The immunotoxic potential of flucarbazone was further investigated in five (four guideline; one non-guideline) rat immunotoxicity studies which utilized assays examining immunization response (antibody-forming cell count (AFC)), splenic immune cell sub-populations, a cell-mediated immune response (anti-CD3 proliferation response), and natural killer (NK) cell function. At dose levels reaching or exceeding the limit dose of testing, decreased spleen weight and/or cellularity were observed across each of these studies. In addition, a decreased immunization response was noted in one study, and decreased T and B lymphocyte counts were noted in another study. Overall, clear indications of immunotoxicity were not observed in these assays at dose levels below the limit dose of testing and based on a weight of evidence assessment, there was a low level of concern for the immunotoxic potential of flucarbazone.

No treatment-related systemic effects were observed in the short-term dermal toxicity study in rats, which only tested a limit dose. In the short-term nose-only inhalation toxicity study in rats, treatment-related histopathological findings in the upper respiratory tract were observed in both sexes. These findings consisted of increased incidences of eosinophilic globules in the nasal cavity and focal inflammatory infiltration and squamous cell metaplasia in the larynx. Increased incidence of goblet cell hyperplasia in the nasal cavity was also observed at the same dose level in female animals. At the highest dose level, these effects were more pronounced; additionally an increased incidence of goblet cell hyperplasia in the nasal cavity of male animals and increased/hypertrophic mucous neck cells in the stomach were observed.

In the long-term rat and mouse dietary toxicity studies, there was no evidence of oncogenicity at any dose level and no evidence of systemic toxicity at doses below the limit dose. Flucarbazone was not genotoxic in a battery of in vitro genotoxicity studies that included a bacterial gene mutation assay, a chromosome aberration assay in Chinese hamster V79 cells, a mammalian gene mutation assay in hamster lung V79 cells, and an unscheduled DNA synthesis assay in rat hepatocytes. An in vivo mouse micronucleus test was also negative for genotoxicity. MKH 6562 sulfonic acid sodium salt, a metabolite of flucarbazone, also produced negative results when tested in a bacterial reverse mutation assay.

In the dietary 2-generation reproductive toxicity study in rats, systemic toxicity in the parental generations consisted of increased incidences of clinical signs of toxicity, such as diarrhea, discoloured faeces, and increased water intake observed at the highest dose level, which approached the limit dose of testing. Treatment-related decreased body weight and body weight gain were also observed at the highest dose level until this dose was adjusted to a lower level. Additional treatment-related findings at this dose level included decreased liver weights in males and increased incidence of severe cecal enlargement in F1 females. In the offspring, body weight was decreased on postnatal day (PND) 21 and incidences of air-filled stomach and marbled liver surface were increased in both generations. Decreased liver weight was also observed in F2 male pups. Histopathology was not conducted in the pups. There was no evidence of increased sensitivity of the young in this study. Effects on the reproductive system were limited to decreased uterine weight at the highest dose tested, that, in absence of any other findings, was not considered adverse on its own. In addition, no treatment-related effects were observed on ovarian follicle counts, estrous cycle length and periodicity, sperm parameters (motility and morphology), or on the reproductive indices.

In the rat gavage developmental toxicity study, there were no treatment-related maternal or developmental effects at dose levels up to and including the limit dose of testing. In the rabbit gavage developmental toxicity study, systemic toxicity was observed in both dams and offspring at the same dose level. Maternally, body weight loss and food consumption, as well as increased incidence and frequency of clinical signs of toxicity, such as cold ears and faecal changes, were noted. These effects were observed within the first few days of dosing and, at the higher dose levels, were accompanied by other clinical signs of toxicity, such as anal and vaginal prolapse and diarrhea. Hepatocytic cytoplasmic changes and fatty change in the liver, and gross pathological changes in the GI tract were also observed at the two higher dose levels. Abortions occurred at the limit dose of testing. Developmental toxicity consisted of decreased fetal body weight and increased incidences of incomplete skeletal ossification noted at maternally toxic dose levels. Overall, there was no evidence of treatment-related malformations or sensitivity of the young in either rat or rabbit developmental toxicity studies.

The neurotoxic potential of flucarbazone was examined in rats following acute or short-term exposures. In the acute gavage neurotoxicity study, decreased motor activity levels, as well as a decreased level of activity in the open field, were observed in both sexes above the limit dose of testing. While decreased activity levels may be suggestive of neurotoxicity, they are also commonly associated with general malaise following treatment with excessively high dose levels. In the dietary short-term neurotoxicity study, there were no signs of neurotoxicity. Systemic toxicity was only observed above the limit dose in the form of decreased body weight and food consumption. Overall, there was no evidence of selective neurotoxicity.

Results of the toxicology studies conducted on laboratory animals with flucarbazone are summarized in Appendix III, Table 3.1. The toxicology reference values for use in the human health risk assessment are summarized in Appendix III, Table 3.2.

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database contains the full complement of required studies including oral developmental toxicity studies in rats and rabbits and a dietary 2-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased sensitivity of offspring or fetuses compared to parental animals in the dietary 2-generation reproductive toxicity study and gavage developmental toxicity studies. There were no treatment-related developmental effects up to and including the limit dose of testing in the rat gavage developmental toxicity study. In the rat dietary 2-generation reproductive toxicity study, decreased pup body weights, as well as increased incidences of air-filled stomach and marbled liver, were observed in the offspring of both generations; however, these occurred in the presence of maternal toxicity and at a dose level that approached the limit dose of testing. In the rabbit gavage developmental toxicity study, all developmental effects, including decreased fetal weights observed at the lowest-observed-adverse-effect-level (LOAEL) and an increased incidence of incomplete skeletal ossification observed at higher dose levels, were observed in the presence of maternal toxicity. At the highest dose level, which was the limit dose of testing, abortions were noted in the presence of maternal toxicity.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young as effects on the young are well characterized and occurred in the presence of maternal toxicity. The observed effects in the young, decreased body weight and delayed ossification in rabbit fetuses, and decreased body weight, stomach and liver effects in rat pups were not considered serious in nature. The level of concern for abortions in the rabbit, a serious effect, was tempered by the presence of significant maternal toxicity, the occurrence of these effects at the limit dose of testing, and an inherent 10-fold difference between the dose at which this effect occurred and the NOAEL selected for developmental effects in this study.

On the basis of this information, the *Pest Control Products Act* factor (PCPA factor) was reduced to onefold.

3.2 Dietary exposure and risk assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in meat and milk, may be ingested with the daily diet. Exposure to flucarbazone from potentially treated imported foods is also included in the assessment. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For

example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

Health Canada considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. Health Canada's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (in other words, are high-end estimates) on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and empirical processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Sufficient information was available to adequately assess the dietary exposure and risk from flucarbazone. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). Further details on the consumption data are available in Health Canada's Science Policy Note SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. Information on the residue chemistry of flucarbazone is published in the Regulatory Note REG2000-09 and the Proposed Registration Decision PRD2008-13, *Flucarbazone*, and in subsequent Evaluation Reports for the use expansions since then. For more information on dietary risk estimates and the residue chemistry information used in the dietary assessment, see Appendix IV.

Canadian MRLs for flucarbazone are currently specified for plant and animal commodities at the limits of quantitation (LOQs) of the enforcement analytical methods. The current MRLs and enforcement residue definition for flucarbazone (that is flucarbazone per se) can be found on the Pesticides section of the Canada.ca website. No changes are being proposed as a result of this re-evaluation. The only registered food use is weed control in wheat.

The residue definition in drinking water (for risk assessment) is proposed to be expressed as the combined residue of parent flucarbazone and five of its major transformation products, assumed to be of equal toxicity to the parent.

3.2.1 Determination of acute reference dose

To estimate acute dietary risk, the maternal NOAEL of 100 mg/kg bw/day from the developmental toxicity study in the rabbit was selected for risk assessment. At the LOAEL of 300 mg/kg bw/day, effects on clinical signs of toxicity, such as cold ears, fecal changes, as well as body weight loss and decreased food consumption were observed. Given that these effects were observed during the first few days of dosing, they were considered relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization Section (Section 3.1.1), the PCPA factor was reduced to onefold. **The composite assessment factor (CAF) is thus 100.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{100} = 1.0 \text{ mg/kg bw of flucarbazone}$$

3.2.2 Acute dietary exposure and risk assessment

The acute dietary risk was calculated considering the highest ingestion of flucarbazone that would be likely on any one day, and using food and drinking water consumption and residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure has been shown to be acceptable.

Acute food residue estimates for flucarbazone were based on Canadian MRLs or American Tolerances. There are no Codex MRLs established for flucarbazone. Residues in drinking water were estimated using environmental concentrations from modelling discussed in Section 3.3. Default processing factors were applied for relevant processed commodities. The assessment considered all foods that may potentially be treated with flucarbazone including foods that may be treated in the United States and imported to Canada. All commodities were assumed to be 100% treated.

The acute dietary risk assessment was conducted for the general population and all population subgroups. The acute dietary (food and drinking water) exposure estimates for flucarbazone were shown to be acceptable for all populations, representing less than 1% of the ARfD. The dietary risk estimates are presented in Appendix IV.

3.2.3 Determination of acceptable daily intake

To estimate risk following repeated dietary exposure, the NOAEL of 36 mg/kg bw/day from the 12-month dietary toxicity study in the dog was selected. At the LOAEL of 183 mg/kg bw/day, reductions in body weight gain and body weight were observed in both sexes. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* hazard characterization Section (Section 3.1.1), the PCPA factor was reduced to onefold. **The CAF is thus 100.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{\text{36 mg/kg bw/day}}{100} = 0.4 \text{ mg/kg bw/day of flucarbazone}$$

The ADI provides a margin of 1250 to the NOAEL of 500 mg/kg bw/day for abortions noted at 1000 mg/kg bw/day in the rabbit developmental toxicity study.

3.2.4 Chronic dietary exposure and risk assessment

Generally, the chronic dietary risk (from food and drinking water) is calculated using average consumption of different foods and drinking water, and the average residue values on those foods and drinking water. For flucarbazone specifically, the average consumption values were used and the maximum potential residues in food as noted below were used. This would result in conservative (high-end) estimates of exposure from food. The estimated exposure was then compared to the ADI, which is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is shown to be acceptable.

Chronic food residue estimates for flucarbazone were based on Canadian MRLs or American Tolerances. Residues in drinking water were estimated using environmental concentrations from modelling discussed in Section 3.3. Default processing factors were applied for processed commodities. The assessment considered all foods that may potentially be treated with flucarbazone including foods that may be treated in the United States and imported to Canada. All commodities were assumed to be 100% treated.

The chronic dietary risk assessment (from food and drinking water) was conducted for the general population and all population subgroups. The chronic exposure estimates were shown to be acceptable for all populations, representing less than 1% of the ADI. The dietary risk estimates are presented in Appendix IV.

3.2.5 Cancer assessment

There was no evidence of oncogenicity and therefore, a cancer risk assessment was not necessary for flucarbazone.

The USEPA recently used a linear, low-dose extrapolation method to quantify the cancer risk for methyl carbamate, which was identified as a residue of concern for flucarbazone in livestock commodities. The PMRA considered the USEPA cancer slope factor q_1^* of 2.88×10^{-3} $(\text{mg/kg bw/day})^{-1}$ in conducting a cancer risk assessment for this metabolite within the context of all available information. A screen of published toxicity studies including genotoxicity studies and a cancer bioassay conducted by the National Toxicology Program (NTP) did not identify a genotoxic concern for methyl carbamate.

In their registration review of flucarbazone, the USEPA conducted a cancer risk assessment for methyl carbamate, which may occur at very low levels in animal commodities following consumption of feed commodities derived from crops treated with flucarbazone; cancer risks were shown to be acceptable ($\sim 1 \times 10^{-7}$).

In the Canadian context and assuming the same cancer slope factor as the USEPA, the potential cancer risk would be lower, given the smaller use pattern in Canada (that is, grazing of treated fields or using treated green crop for feed is prohibited in Canada).

3.3 Exposure from drinking water

Combined residues of flucarbazone and its major transformation products in potential sources of drinking water were estimated from modelling.

3.3.1 Concentrations in drinking water

The estimated environmental concentrations (EECs) in potential sources of drinking water were modelled for the combined residues of flucarbazone (development code name: MKH 6562) and five of its transformation products: MKH 6562 sulfonamide; MKH 6562 sulfonic acid; *O*-desmethyl MKH 6562; *N,O*-dimethyl triazolinone (NODT) and *N*-methyl triazolinone (NMT). The EECs were calculated for surface water and groundwater using the Pesticide Water Calculator model (PWC, version 1.52).

Modelling for surface water used a standard Level 1 scenario, a small reservoir adjacent to agricultural fields. EECs in groundwater were calculated by selecting the highest EEC from a set of standard Level 1 scenarios representing different regions of Western Canada. The scenario for surface water modelling was run for 50 years and scenarios for groundwater modelling were run for 100 years due to low throughputs.

Level 1 EECs are conservative values intended to screen out pesticides that are not expected to pose any concern related to drinking water. These are calculated using conservative inputs with respect to application rate, application timing, and geographic scenario. Given the currently registered use pattern of flucarbazone, the scenarios selected for the modelling cover uses in Western Canada only (Peace River Region in British Columbia, Alberta, Saskatchewan and Manitoba). The EECs are presented in Table 1. The groundwater EEC of 0.039 ppm (daily value = yearly value) were used in the acute and chronic dietary exposure assessments.

Table 1 Level 1 EECs of the combined residue of flucarbazone in potential sources of drinking water, reported as parent equivalent

Use pattern	Groundwater (µg a.i./L)		Surface Water (µg a.i./L)		
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Overall[5]
A single application of 28.8 g a.i./ha per year	39	39	2.4	0.38	0.24

[1] 90th percentile of daily concentrations
[2] 90th percentile of 365-day moving average concentrations
[3] 90th percentile of the highest 1-day average concentration from each year
[4] 90th percentile of yearly average concentrations
[5] Average of all yearly average concentrations

3.3.2 Drinking water exposure and risk assessment

Exposure from drinking water and food sources were combined to determine the total dietary exposure and risk. Refer to Sections 3.2.3 and 3.2.4 for the results of the acute and chronic dietary exposure and risk assessments.

3.4 Occupational and non-occupational exposure and risk assessment

Occupational and non-occupational (residential) risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicology endpoint selection for residential and occupational exposure

3.4.1.1 Short-term dermal

The available route-specific 28-day dermal toxicity study in rats was not used for risk assessment as the dog was considered the most sensitive species to the toxicological effects of flucarbazone. These effects in dogs included decreased body weight and histopathological findings in the stomach following repeated oral dosing. Furthermore, the target organs of toxicity, such as the stomach, were not examined histopathologically in the 28-day dermal toxicity study in rats in part due to the limit test study design. Thus, for short-term dermal risk assessment, an oral point of departure (POD) was selected for use in risk assessment. The 90-day and 12-month dietary toxicity studies in dogs were considered co-critical because they examined the most sensitive test species and primary target organ. The NOAEL of 36 mg/kg bw/day was selected. At the LOAEL of 162 mg/kg bw/day, an increased incidence of red discolouration/red areas in the gastric mucosa of the stomach in both sexes, as well as increased incidences of glandular cell degeneration, round cell infiltrates and foveolar hyperplasia in the stomach of the female animals was noted.

Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied, resulting in a target Margin of Exposure (MOE) of 100. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

The short-term dermal toxicological reference value provides a margin of 1250 to the NOAEL of 500 mg/kg bw/day for abortions noted at 1000 mg/kg bw/day in the rabbit developmental toxicity study.

3.4.1.2 Short-term inhalation

For short-term inhalation risk assessment, the NOAEC of 0.03 mg/L (equivalent to 8 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected. At the LOAEC of 0.18 mg/L (equivalent to 48 mg/kg bw/day), treatment-related histopathological findings in the upper respiratory tract were observed including increased incidences of eosinophilic globules in the

nasal cavity and focal inflammation infiltrates and squamous cell metaplasia in the larynx. An increased incidence of goblet cell hyperplasia in the nasal cavity was also observed at this dose level in the female animals. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied resulting in a target MOE of 100. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

The short-term inhalation toxicological reference value provides a margin of 6250 to the NOAEL of 500 mg/kg bw/day for abortions noted at 1000 mg/kg bw/day in the rabbit developmental toxicity study.

3.4.1.3 Combined short-term dermal and short-term inhalation

Given that treatment-related histopathological findings in the stomach were noted in toxicity studies using different routes of administration, a combined short-term dermal and short-term inhalation risk assessment was undertaken. For the dermal component, the route-specific 28-day dermal toxicity study in rats was not considered appropriate since it was conducted using a limit test design and did not assess the stomach histopathologically. Thus, the short-term oral toxicity study in the dog was used as a surrogate since dogs were the most sensitive species for the manifestation of toxicity from the oral route. A NOAEL of 34 mg/kg bw/d from the 90-day dietary toxicity study in dogs was selected. At the LOAEL of 162 mg/kg bw/day, an increased incidence of red discolouration or red areas in the gastric mucosa of the stomach in both sexes as well as increased incidences of glandular cell degeneration, round cell infiltrates and foveolar hyperplasia in the stomach of the female animals were noted. For the inhalation component, a NOAEC of 0.18 mg/L (equivalent to 48 mg/kg bw/day) from the 28-day inhalation toxicity study in rats was selected. At the LOAEC of 0.5 mg/L (equivalent to 133 mg/kg bw/day), increased and/or hypertrophic mucus neck cells in the stomach was observed in both sexes. The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.2 Non-occupational exposure and risk assessment

Domestic-class products containing flucarbazone are not registered in Canada; therefore, residential handler exposure is not anticipated. Commercial-class products containing this active ingredient are not expected to be used in residential settings. Therefore, postapplication exposure to flucarbazone residues following commercial applications in residential settings is not anticipated.

There is, however, a potential for non-occupational and bystander exposure to spray drift during commercial applications. As such, a standard best practise label statement to minimize spray drift is proposed on all end-use product labels (Appendix VIII).

3.4.3 Occupational exposure and risk assessment

3.4.3.1 Mixer/loader/applicator exposure and risk assessment

For workers mixing/loading and applying flucarbazone, exposure is expected to occur via the dermal and inhalation routes and to be of a short-term duration.

The following exposure scenarios were assessed based on the currently registered use pattern:

- Open mixing/loading of dry formulation and applying as a spray using groundboom equipment.
- Mixing/loading of dry formulation using water-soluble packets (WSP), and applying as a spray using groundboom equipment.
- Open mixing/loading of liquid formulation and application as a spray using groundboom equipment.
- Open mixing/loading of liquid formulation and application using aerial equipment.

In the absence of chemical-specific data for flucarbazone, exposure of workers mixing/loading and applying flucarbazone was assessed using exposure data from the Agricultural Handlers Exposure Task Force (AHETF) or the Pesticide Handlers Exposure Database (PHED). Workers were assumed to be wearing a long-sleeved shirt, long pants, and chemical-resistant gloves. Additional assumptions included default area treated per day (ATPD) values, the maximum registered application rates, average worker body weight of 80 kg, and 100% dermal absorption.

The risk assessment for a mixer/loader and applicator is presented in Appendix V, Tables 1 and 2. The estimated dermal, inhalation, and combined (dermal plus inhalation) MOEs are above the target MOE (100) for all assessed scenarios.

On this basis, risks to mixers/loaders and applicators using ground or aerial equipment are considered to be acceptable when wearing a long-sleeved shirt, long pants, and chemical resistant gloves, socks and shoes. The proposed label amendment to reflect the clothing and PPE requirements for the mixer, loader and applicator are listed in Appendix VIII.

3.4.3.2 Postapplication exposure and risk assessment

There is a potential for postapplication exposure of workers to flucarbazone residues following post-emergence application of flucarbazone.

Exposure would be predominantly dermal for workers performing postapplication activities in crops following spray application. Based on the vapour pressure of flucarbazone ($<1 \times 10^{-6}$ mPa at 20°C) inhalation exposure would be low, provided the minimum restricted-entry interval (REI) of 12 hours is followed. Currently, not all end-use product labels specify a 12-hour REI.

For workers entering a treated site, REI are calculated to determine the minimum length of time required before workers can enter after application. The REI is the duration of time that must elapse in order to allow residues to decline to a level where risks are considered to be acceptable for postapplication worker activities (that is, performance of a specific activity that results in exposures at or above the target MOE).

Dermal exposure of workers entering treated sites was estimated using activity-specific transfer coefficient (TC) and default dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant, which is a measurement of pesticide residue on foliage that can be transferred to human skin and clothing. No chemical-specific DFR data was available for flucarbazone; therefore, the risk assessment was based on assumptions; DFR of 25% of the application rate on the day of application and 10% of dissipation per day. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers. The activity-specific TC from the Agricultural Re-Entry Task Force (ARTF) was used for this risk assessment. Additional assumptions included an 8-hour workday, an average worker body weight of 80 kg, and 100% dermal absorption. Toxicology reference values used in the assessment are summarized in Appendix III. The risk assessment for workers conducting postapplication activities is summarized in Appendix VI. The calculated MOEs (≥4557) were above the target MOE of 100 and risks were shown to be acceptable for all postapplication activities at the minimum REI. A standard 12-hour REI is proposed to be included on all commercial end-use product labels (Appendix VIII).

3.5 Aggregate exposure and risk assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

For flucarbazone, the aggregate assessment consisted of combining food and drinking water exposure, which is presented in Section 3.2 and is shown to be acceptable.

3.6 Cumulative assessment

Flucarbazone belongs to the triazolone herbicide group. Other Canadian registered triazolone herbicides include carfentrazone, sulfentrazone, thiencarbazone-methyl and propoxycarbazone-sodium. The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for flucarbazone.

Screening examination of the propoxycarbazone-sodium toxicity database revealed that it also produces gastric/forestomach irritation in rats that are similar to those observed in the flucarbazone toxicity database. The PMRA also gave consideration to the recently completed USEPA initial screening analysis of toxicological profiles of triazolones to consider whether a candidate common mechanism group (CMG) can be established. These chemicals were classified in three different subgroups based on similarities in their toxicological profiles and for further screening analysis to determine if a CMG could be determined. Based on common potential effects in thyroid and liver, the USEPA placed flucarbazone and amicarbazone in a subgroup called “triazolone-amides” for further screening analysis.

Overall, there were no mode of action data to establish a common mechanism of toxicity between flucarbazone and amicarbazone or between flucarbazone and propoxycarbazone-sodium. The USEPA also recently published an interim registration review decision for nine acetolactate synthase (ALS) inhibiting herbicides, which included flucarbazone. However, this document did not identify any information that could be used for a cumulative risk assessment on the basis of this chemical grouping.

Therefore, for the current re-evaluation, the PMRA did not identify information indicating that flucarbazone shares a common mechanism of toxicity with other pest control products in this class. In turn, a cumulative risk assessment is not being conducted at this time. The cumulative risk assessment of this chemical class will be revisited when the re-evaluation of the other chemicals in this class are completed.

3.7 Health incident reports

As of 6 May 2021, no human or domestic animal incident reports involving flucarbazone have been submitted to the PMRA.

4.0 Environmental assessment

A summary of environmental fate and behaviour of flucarbazone and its transformation products is presented in Appendix VII, Table 1.

4.1 Fate and behaviour in the environment

In soil, flucarbazone is slightly to moderately persistent in aerobic soil (half-lives of 11–93 days), breaking down primarily through microbial processes to form four major transformation products: flucarbazone sulfonamide (41–84.7% AR), flucarbazone sulfonic acid (11% AR), *O*-desmethyl flucarbazone (15% AR) and NMT (14.4% AR).

Based on laboratory studies, the criteria of Cohen et. al. and the Groundwater Ubiquity Score (GUS), flucarbazone and the major transformation products flucarbazone sulfonamide, NODT, and flucarbazone sulfonic acid are expected to be moderately mobile to very highly mobile in soil, depending on soil type. Despite the fact that field studies did not detect flucarbazone and its transformation products below the 30 cm soil depth and Canadian water monitoring data indicates flucarbazone is rarely detected in groundwater, laboratory studies (adsorption, leaching), a lysimeter study and the physical/chemical properties of flucarbazone, flucarbazone sulfonamide and flucarbazone sulfonic acid indicate they have the potential to leach. A statement indicating potential for leaching to groundwater is proposed for product labels.

At the time of the initial registration of flucarbazone (REG2000-09), half-lives in aerobic aquatic systems were based on studies that had been conducted without using sediment in the test system. For the re-evaluation, additional data were available for aquatic test systems that included sediment. These data show that flucarbazone breaks down more quickly in aerobic aquatic systems than previously reported (half-lives of 71–405 days). Thus flucarbazone can be considered as moderately persistent to persistent in aerobic aquatic systems. Under anaerobic conditions, flucarbazone is considered moderately persistent (half-lives of 66 and 104 days).

Flucarbazone-sulfonamide was found to be the major transformation product in both aerobic and anaerobic test systems. NMT was also found to be a major transformation product under anaerobic conditions. Under both aerobic and anaerobic conditions, flucarbazone is broken down by microbes.

Flucarbazone is non-volatile (vapour pressure at 20°C $<1 \times 10^{-9}$ Pa) and is not expected to volatilise from moist soil or water surfaces (Henry's law Constant (1/H) of 2.48×10^{14}).

Flucarbazone is not expected to bioconcentrate/bioaccumulate in organisms (Log K_{ow} of -1.84 at pH 7).

4.2 Environmental risk characterization

A summary of ecotoxicity data for flucarbazone is presented in Appendix VII, Table 2.

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air.

The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient is calculated by dividing the exposure estimate by an appropriate toxicity value (risk quotient = exposure/toxicity), and the risk quotient is then compared to the level of concern. If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints.

Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Where possible the analysis of toxicity data also includes the determination of the hazardous concentration to five percent of species (HC_5) from species sensitivity distributions (SSDs) or determination of the most sensitive endpoint in each taxonomic group and category. The HC_5 is

calculated for acute and chronic data sets using the LC_{50}/EC_{50} values and NOEC values as appropriate (EC_{25} was also used for terrestrial plants when no other data was available). The HC_5 is the concentration which is assumed to be protective for 95% of species of the assessed taxonomic group or assemblage as related to the assessment endpoint and ecological protection goal. At an EEC equal to the HC_5, 95% of all species (within each taxonomic group) are not expected to be exposed to concentrations exceeding their threshold toxicity value (for example, LC_{50}, NOEC).

The software program ETX 2.0 was used with a log-logistic model to generate SSDs where sufficient toxicity endpoints were available for different taxa, using all available relevant information on toxicity. This reduces the uncertainty in risk estimates and provides endpoints that are scientifically robust as compared to single species toxicity test endpoints, as well as returning endpoints that are more ecologically relevant as compared to relying on the most sensitive species available. Median HC_5 values are reported for SSDs and where possible are used to determine risk and mitigation measures. The variability in the data sets is indicated by the upper and lower bound HC_5 estimates and the confidence limit of the fraction of species affected (FA), which indicates the minimum and maximum percent of species that could be affected when exposed to the HC_5 concentration.

The environmental risk assessment was conducted based on the maximum annual application rate for both groundboom and aerial application methods, using either medium or coarse ASABE spray quality where applicable.

4.2.1 Risks to non-target organisms

There were no exceedances identified at the screening level for earthworms, honeybees, birds, mammals, freshwater invertebrates, cold and warm water fish, amphibians, marine fish and invertebrates, or freshwater aquatic plants and algae or marine algae (Appendix VII, Table 3). Potential risks were identified at the screening level for terrestrial plants and aquatic vascular plants.

Risks to non-target terrestrial plants were further characterized by considering spray drift. The level of concern for terrestrial vascular plants was exceeded for both aerial application (risk quotients 3.3 –5.9) and groundboom application methods (1.2–1.5) (Appendix VII, Table 4). To protect non-target terrestrial vascular plants, spray buffer zones are required (Appendix VIII).

Risks to aquatic vascular plants were further characterized by considering potential exposure from spray drift and runoff (Appendix VII, Table 5). The level of concern was exceeded for spray drift (risk quotients 0.5–3.1) and runoff (risk quotient =18.2). To protect aquatic vascular plants from spray drift at the time of application, spray buffer zones are required (Appendix VIII). Risk to aquatic plants from exposure to flucarbazone in runoff is based on conservative exposure modelling estimates. Although Canadian surface water monitoring data was not available, concentrations of flucarbazone in surface runoff are expected to be lower than predicted by modelling. Risks associated with runoff are considered to be acceptable when precautionary label statements are followed to reduce runoff from treated areas.

4.3 Environmental incident reports

Canadian incident reports

One minor environmental incident was reported to the PMRA in which an unspecified amount of Estaprop (Reg. 29660; dichlorprop and 2,4-D) and Everest Solupak 75 DF (Reg. No. 26448; containing flucarbazone) was applied to an outdoor agricultural site followed by leaf curling being observed on trees (mostly maple trees) and caragana shrubs approximately 800 m from the application site. It was determined that flucarbazone was unlikely to have caused this incident.

United States environmental incidents

The United States EIIS (Ecological Incident Information System) database was queried for environmental incidents involving flucarbazone that occurred in the United States. As of 2012, there were 23 incidents involving flucarbazone. All flucarbazone environmental incidents involved reports of plant damage (22) with the exception of 1 report which involved stunted plant growth. All of these incidents were assigned the certainty index of possible or higher. The plant species involved were mostly wheat (17) with the remainder being identified as potato (2) or corn (3). Two incidents indicated the route of exposure was due to carryover, although the type of use was undetermined in these incidents.

Otherwise the route of exposure was reported as direct treatment. In all cases where the application method was reported (16), broadcast application was used. Current labels includes label statements related to crop injury following application. No further mitigation measures are required.

4.4 Toxic Substances Management Policy considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[3] the assessment of flucarbazone against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. Health Canada has reached the conclusions that:

Flucarbazone does not meet all Track 1 criteria, and is not considered a Track 1 substance (Refer to Appendix VII, Table 6).

Flucarbazone does not form any transformation products that meet all Track 1 criteria.

4.4.1 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[4] The list is

[3] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[4] SI/2005-114, last amended on June 24, 2020. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

used as described in the Health Canada's Science Policy Note SPN2020-01[5] and is based on existing policies and regulations including the Toxic Substances Management Policy[Error! Bookmark not defined.] and Formulants Policy,[6] and taking into consideration the Ozone-depleting Substances and Halocarbon Alternatives Regulations under the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol). Health Canada has reached the following conclusions:

Flucarbazone and its end-use products do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[6]

5.0 Value assessment

Flucarbazone is an important weed management tool for Western Canadian wheat growers.

As a "universal" tank-mix partner, flucarbazone can be tank mixed with almost all broadleaf herbicides for use on wheat (currently up to 35 broadleaf herbicides) to broaden weed control spectrum. This provides growers greater flexibility to choose a weed control program that is based on their specific needs.

Flucarbazone is a tool to manage resistant weed biotypes including wild oat biotypes which have developed resistance to ACCase (Group 1) and triallate (Group 8) herbicides and green foxtail biotypes resistant to ACCase (Group 1) and dinitroaniline (Group 3) herbicides. These herbicide resistant wild oats and green foxtail populations are increasingly becoming issues to wheat growers.

[5] PMRA's Science Policy Note SPN2020-01, Policy on the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under paragraph 43(5)(b) of the *Pest Control Products Act*

[6] DIR2006-02, *Formulants Policy and Implementation Guidance Document*

List of abbreviations

↑	Increased
↓	Decreased
µg	Microgram
♀	Female
♂	Male
14C	carbon-14
a.e.	acid equivalents
a.i.	active ingredient
Abs	Absolute
AD	administered dose
ADI	acceptable daily intake
AFC	antibody forming cell
AHETF	Agricultural Handlers Exposure Task Force
ALD	aldrin epoxidase
ALP	alkaline phosphatase
ALP	alkaline phosphatase
ALS	acetolactate synthase
AR	applied radioactivity
ARfD	acute reference dose
ARTF	Agricultural Re-Entry Task Force
ASABE	American Society of Agricultural and Biological Engineers
atm	atmospheres
ATPD	area treated per day
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Society
CD	classification determinant or cluster of differentiation
CDC	United States Centers for Disease Control and Prevention
CFIA	Canadian Food Inspection Agency
cm	Centimeters
cm^2	square centimeter
Cmax	maximum concentration
CMG	common mechanism group
ConA	concavalin A
CYP	cytochrome P
d	day(s)
DA	dermal absorption
DAF	dermal absorption factor
DEEM	Dietary Exposure Evaluation Model
DFR	dislodgeable foliar residue

DNA	deoxyribonucleic acid
DT_{50}	dissipation time to 50%
EC_{50}	effective concentration to 50%
ECOD	7-ethoxycoumarin deethylase
EDE	estimated daily exposure
EEC	estimated environmental concentration
EFED	Environmental Fate and Effects Division (USEPA)
EFSA	European Food Safety Authority
EH	epoxide hydrolase
EROD	7-ethoxyresorufin O-deethylase
F1	first generation
F2	second generation
FACS	fluorescence activated cell sorter
fc	food consumption
FCID™	Food Commodity Intake Database™
fe	food efficiency
FOB	functional observational battery
g	gram(s)
GC	gas chromatograph
GD	gestation day
GI	Gastrointestinal
GST	glutathione S-transferase
h	hour(s)
ha	Hectare
HPLC	high performance liquid chromatography
hr(s)	hour(s)
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-1α	interleukin 1 alpha
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K	Henry's law constant
*K*d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	litre(s)
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD_{50}	dose estimated to be lethal to 50% of the test population
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
LOD	limit of detection

LOEC	lowest observable effect concentration
LOEL	lowest observable dose level
LOQ	limit of quantitation
LPS	lipopolysaccharide
M/L	mixer/loader
MAS	maximum average score for 24, 48 and 72 hours
mg	milligram(s)
min	minute(s)
MIS	maximum irritation score
mL	millilitre(s)
mm Hg	millimetre mercury
MOE	margin of exposure
mol	moles
mPa	millipascal
MRL	maximum residue limit
MTD	maximum tolerated dose
NCHS	National Center for Health Statistics
N-DEM	N-demethylase
NHANES	National Health and Nutrition Examination Survey
NK	natural killer
nm	nanometre
NMRI	Naval Medical Research Institute
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NTP	National Toxicology Program
OC	organic carbon
O-DEM	O-demethylase
OECD	Organisation for Economic Co-operation and Development
OM	organic matter
ORETF	Outdoor Residential Exposure Task Force
P	parental generation
PCPA	*Pest Control Product Act*
PDP	Pesticide Data Program
pH	log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
p*K*a	log10 acid dissociation constant
PMA	phorbol 12-myristate 13-acetate
PMRA	Pest Management Regulatory Agency
PND	postnatal day
POD	point of departure
ppb	parts per billion

PPE	personal protective equipment
ppm	parts per million
PWC	Pesticide Water Calculator model
q_1*	cancer slope factor
REI	Restricted-entry interval
Rel	Relative
SMILES	Simplified Molecular Input Line Entry System (line notation describing structure of chemical species)
SRBC	sheep red blood cells
t1/2	first-order half-life
T3	triiodothyronine
T4	thyroxine
TBC	thyroxine binding capacity
TC	transfer coefficient
t.p.	transformation product
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TSMP	Toxic Substance Management Policy
UDPGT	uridine diphosphate glucuronyltransferase
UDS	unscheduled DNA synthesis
UE	Unit exposure
USEPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
UV	Ultraviolet
vp	vapour pressure
wk	week(s)
WSP	water-soluble packets
wt	Weight
WWEIA	What We Eat in America

Appendix I Registered products containing flucarbazone in Canada

Table 1 Products containing flucarbazone subject to proposed label amendments[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
26447	Commercial	Arysta LifeScience North America, LLC	Everest 70 WDG Herbicide	Wettable granules	66%
26448			Everest Solupak 70 DF	Wettable granules in water-soluble packets	66%
29500			Pre-Pare Herbicide	Wettable granules	66%
30342			Everest 2.0 Herbicide	Suspension	397.33 g/L
30580			ARY 0548-019 Herbicide		36.3 g/L (+ 200 g/L fluroxypyr)
30663			Inferno Duo	Wettable granules	45% (+ 23.9% tribenuron methyl)
32602			Everest 3.0 Herbicide	Suspension	200 g/L
33258			Everest 3.0 AG Herbicide	Suspension	200 g/L
33273			Inferno Trio Herbicide	Emulsifiable Concentrate or Emulsion	141 g/L (+50 g/L florasulam + 175 g/L carfentrazone-ehtyl)
33372			Batalium Suspension Concentrate Herbicide	Suspension	20.4 g/L (+ 241 g/L MCPA ester + 90.5 g/L fluroxypyr + 241 g/L bromoxynil)
33370		New Agco Inc.	Mpower Himalaya Herbicide	Wettable granules	66%
29558		Syngenta Canada Inc.	Sierra 70 WDG Herbicide	Wettable granules	66%
30430			Sierra® 2.0 Herbicide	Suspension	397.33 g/L
32941			Sierra® 3.0 Herbicide	Suspension	200 g/L
33538			Sierra® 3.0 AG Herbicide	Suspension	200 g/L

26446	Technical Grade Active Ingredient	Arysta LifeScience North America, LLC	Everest Technical Herbicide	Solid	89.20%
33333		New Agco Inc.	Newagco Flucarbazone Technical	Solid	93.20%
34110		Albaugh LLC	Flucarbazone Technical Herbicide	Solid	91.2%

[1] as of 7 January 2021, excluding discontinued products or products with a submission for discontinuation.

Appendix II Registered uses

Table 1 Registered commercial class uses of flucarbazone in Canada[1, 2]

Use Site Category	Sites[3]	Weeds	Application Method and Equipment	Maximum Application Rate (g a.i./ha)	
				Single	Cumulative Per Year
13 – Terrestrial Feed crops	Spring wheat (hard red spring, Canada Prairie spring, soft white spring and extra strong (utility) wheat) and durum wheat Alberta, Manitoba, Saskatchewan, and Interior of British Columbia (including Peace River region of British Columbia only)	Annual grass and broadleaf weeds	Ground or aerial	9.6–28.8	28.8
14 – Terrestrial Food Crops	Winter wheat Alberta, Manitoba, Saskatchewan, and Interior of British Columbia (including Peace River region of British Columbia only)	Annual grass and broadleaf weeds	Ground or aerial	14.3–28.8	28.8

1. as of 7 January 2021. Uses from discontinued products or products with a submission for discontinuation are excluded.
2. The maximum number of applications is once per year. Note that the maximum number of applications per year was not stated on registered end use product labels but was interpreted as such by PMRA based on the label instructions for each end use product.
3. Sites are listed either as stated on the label or as interpreted by the PMRA so as to achieve consistency.

Appendix III Toxicological information for health risk assessment

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted.

Table 1 Toxicity profile of technical flucarbazone

Study type/ Animal/PMRA#	Study results
Toxicokinetic Studies	
Toxicokinetics – single dose, and repeated dose studies Wistar Rats PMRA# 1180196	Studies of blood kinetics, bile/urine/feces/tissue residue levels, enterohepatic recirculation, and metabolite identification and isolation were conducted with phenyl-UL-^{14}C-labelled flucarbazone-sodium. Single low (5/sex) and high (5♂) dose experiments included dose levels of 5-17.5 and 400 mg/kg bw, respectively. Repeated dose experiment included 14 days of unlabeled flucarbazone-sodium followed by labelled dose levels of ~18 mg/kg bw/day (5♂). The percent AD was determined in the bile as well as in the plasma, expired air, urine and feces. **Rate and extent of absorption and excretion**: Following a single or repeat oral dose, [phenyl-UL-^{14}C] flucarbazone-sodium was rapidly absorbed, with plasma concentrations reaching a maximum within 30 minutes. The low biliary and urinary excretion of [phenyl-UL-^{14}C] flucarbazone-sodium suggests that oral absorption was low (approximately 25–30% at the low dose level and 15% at the high dose level). Flucarbazone-sodium residues were rapidly excreted, with 84–95% of the AD being excreted within 24 hours. Fecal excretion (64–78% of the AD) was greater than urinary excretion (15–30%). Urinary excretion was lower in the high dose experiment (15% of the AD) than in the low dose (24–30%). Biliary excretion accounted for 1–5% (average 2%) of the AD. Less than 1% of the AD was excreted in expired air. There were no sex-related differences in the absorption, distribution, metabolism, or excretion of flucarbazone-sodium. **Distribution and target organ(s)**: The highest tissue residues were found in the liver. However, less than 1% of the AD remained in the carcass and tissues at necropsy (72 or 96 hours post-dosing). The low mean recovery of radioactivity levels in the tissues and carcass at necropsy indicate a lack of flucarbazone-sodium tissue retention. Approximately 89% of the AD was excreted in the urine and faeces as the unchanged flucarbazone-sodium. No other residue present in the faeces or urine comprised greater than 1% of the AD.
Toxicokinetics – single dose Wistar Rats PMRA# 1180208	Studies of blood kinetics, bile/urine/faeces/tissue residue levels, and metabolite identification and isolation were conducted with single low dose levels of 5–18 mg/kg bw of triazolinone-3-^{14}C-labelled flucarbazone-sodium. **Rate and extent of absorption and excretion**: Following a single oral dose, [triazolinone-3-^{14}C] flucarbazone-sodium was rapidly absorbed in ♂ rats with maximal plasma concentrations being achieved within 15–30 minutes. The low urinary excretion (approximately 27% of AD) suggest that absorption was low. The major route of elimination was via the faeces, with approximately 70% of the AD (majority of which was unchanged flucarbazone-sodium). The majority of the radioactivity was eliminated via the faeces and urine within 24 and 6–12 hours, respectively. The total recovery was approximately 97% of the AD; the majority of this was eliminated within 24 hours (95% of the AD).

Study type/ Animal/PMRA#	Study results
	Distribution and target organ(s): The highest tissue residues were observed in the liver. The mean recovery of radioactivity in the tissues and carcass at necropsy was less than 1% of the AD indicating that the potential for tissue retention was low. The major component in both the urine and fecal extracts was identified as the unchanged flucarbazone-sodium (94% of the AD). Other metabolites identified in the excreta included urazole, methylurethane, N-methyltriazolinone, O-methyltriazolinone, and N,O-dimethyltriazolinone. Each of these metabolites represented less than 1% of the AD.
Toxicokinetics for plant metabolite – single dose Flucarbazone-sodium sulfonamide lactate Wistar Rats PMRA# 1180215	Studies of tissue residue levels, metabolite identification and isolation, and urine/faeces excretion were conducted with single low dose levels of ~5 mg/kg bw of phenyl-UL-^{14}C-labelled flucarbazone-sodium sulfonamide lactate (plant metabolite of flucarbazone-sodium). **Rate and extent of absorption and excretion**: The rapid excretion of [phenyl-UL-^{14}C] flucarbazone-sodium sulfonamide lactate residues in the faeces and urine (99% of AD after 24 hrs) suggest that absorption of [phenyl-UL-^{14}C] flucarbazone-sodium sulfonamide lactate is rapid. The fecal excretion was 65% of the AD. The urinary excretion rate was 35% of the AD. Unchanged flucarbazone-sodium sulfonamide lactate in faecal extracts accounted for 65% of the AD. On the basis of the radioactivity detected in the urine, approximately 35% of the AD was absorbed. **Metabolism**: Flucarbazone-sodium sulfonamide lactate was the major residue identified in both the urine (22% of the AD) and feces (65% of the AD). The metabolites identified in the urine were sulfonamide (10% of the AD) and sulfonamide acetate (3% of the AD). No metabolite was identified in the feces. **Distribution and target organ(s)**: Less than 1% of the AD remained in the carcass and tissues at necropsy (at 72 hours) indicating that the potential for tissue retention was low.
Toxicokinetics for plant metabolite – single dose MKH 6562 sulfonamide alanine Wistar Rats PMRA# 1180214	Studies of tissue residue levels, metabolite identification and isolation, and urine/faeces excretion levels were conducted with single low dose levels of ~5 mg/kg bw of phenyl-UL-^{14}C-labelled flucarbazone-sodium sulfonamide alanine (plant metabolite of flucarbazone-sodium). Approximately 70% of the AD was absorbed based on the urinary excretion data and 98% of the AD was recovered in urine and fecal extracts. Unchanged flucarbazone-sodium sulfonamide alanine accounted for 17% of the AD. Several metabolites were also isolated, but were not identified. Less than 1% of the AD was recovered in the carcass, tissues, expired air, and cage wash. Highest residue level was in the liver 96 hours post-dosing.
Acute Toxicity Studies	
Acute oral toxicity (gavage) Wistar rats PMRA#: 1179287	LD_{50} > 5000 mg/kg bw Clinical observations included moist anus, lightly coloured and mucoid faeces. Resolved by day 4. **Low acute toxicity**
Acute dermal toxicity Wistar rats PMRA# 1179288	LD_{50} > 5000 mg/kg bw **Low acute toxicity**

Study type/ Animal/PMRA#	Study results
Acute inhalation toxicity (nose-only) Wistar rats PMRA# 1179289	LC_{50} > 5.13 mg/L Clinical observations included ungroomed coat, piloerection, ↓ motility, and red encrustation of nose. Resolved by day 6. **Low acute toxicity**
Skin irritation New Zealand White rabbits PMRA# 1179290	MIS and MAS (at 24, 48, and 72 hours) = 0/8 **Non-irritating**
Eye irritation New Zealand White rabbits PMRA# 1179290	MIS = 5.0/110 at 1 hour MAS (at 24, 48, and 72 hours) = 1.7/110 **Minimally irritating**
Dermal sensitization (Maximization test) Guinea pigs PMRA# 1179291	**Negative**
Acute oral toxicity (gavage) Trifluoromethoxy sulfonamide (animal and plant metabolite of MKH 6562) Wistar rats PMRA# 1180148	LD_{50} > 2000 mg/kg bw **Low acute toxicity**
Acute oral toxicity (gavage) Flucarbazone-sodium lactate conjugate (plant metabolite of flucarbazone-sodium) Wistar rats PMRA# 1179294	LD_{50} > 5000 mg/kg bw **Low acute toxicity**
Acute oral toxicity (gavage) Flucarbazone-sodium sulfonamide alanine (plant	**LD_{50} > 5000 mg/kg bw** Clinical signs included lightly discoloured feces observed in all animals, first apparent 2 days after administration, completely resolved by day 7. **Low acute toxicity**

Study type/ Animal/PMRA#	Study results
metabolite of flucarbazone-sodium) Wistar rats PMRA# 1179295	
Acute oral toxicity (gavage) Flucarbazone-sodium sulfonic acid sodium salt (animal, plant, and soil metabolite of flucarbazone-sodium) Wistar rats PMRA# 1190314	**LD_{50} > 5000 mg/kg bw** **Low acute toxicity**
Acute oral toxicity (gavage) Non-guideline *O*-desmethyl flucarbazone-sodium (a soil metabolite of flucarbazone-sodium) Wistar rats PMRA# 1190316	**LD_{50} > 2500 and < 5000 mg/kg bw** At 2500 mg/kg bw, there were no deaths. At 5000 mg/kg bw, 3/5 ♂ and 5/5 ♀ died. Clinical signs included laboured breathing, uncoordinated gait, piloerection, and narrow palpebral fissures were observed in both sexes at 2500 and 5000 mg/kg bw. These clinical signs were observed within an hour of dosing and lasted up to day 11. **Low acute toxicity**
Short-Term Toxicity Studies	
28-day oral toxicity (diet) – Non-guideline (dose-range finding) B6C3F1 mice PMRA# 1180154	Supplemental There were no adverse treatment-related findings in either sex up to and including doses exceeding the limit dose.
90-day oral toxicity (diet) B6C3F1 mice PMRA# 1179296, 1180149	NOAEL = 2083/3051 mg/kg bw/day (♂/♀) There were no adverse treatment-related findings.
28-day oral toxicity (diet) Wistar rats PMRA# 1179298	NOAEL = 27/25 mg/kg bw/day (♂/♀) **≥ 27/25 mg/kg bw/day**: ↓ splenic cell counts (♂); ↑ discoloured (white) faeces (♀) (non-adverse) **≥ 266/251 mg/kg bw/day**: ↓ IgA titer (♂/♀); ↑ macrophage activation in spleen (♀)

Study type/ Animal/PMRA#	Study results
	1134/1150 mg/kg bw/day: ↓ surface markers for T lymphocytes (CD45) and B cells in lymph nodes (♂/♀); ↑ macrophage activation in spleen (PMA stimulation), slight ↓ macrophage activity in lymph node, slight ↓ lymph node cell count, ↑ water consumption, ↑ discoloured (white) feces (♂) The following immunological investigation were conducted: • FACS-analysis to determine sub-populations of spleen cells and lymph node cells • Macrophage activity after PMA stimulation in spleen and lymph node cells • Responsiveness of spleen and lymph node cells to stimulation with mitogen ConA or LPS was determined • Antibody (IgG, IgM, and IgA) titers in sera were determined
90-day oral toxicity (diet) with 5-week recovery period Wistar rats PMRA# 1179297, 1180150	NOAEL = 74/102 mg/kg bw/d (♂/♀) **≥ 18/21 mg/kg bw/day**: ↓ spleen wt (♂) (non-adverse) **≥ 287/358 mg/kg bw/day**: ↓ macrophage activity after PMA stimulation in mesenteric lymph cells (♂/♀); ↑ T-cell marker CD2 and T-cell stimulation ConA in lymph node (♂); ↓ markers for B-cells (PanB) in the lymph node (♀) **1669/2314 mg/kg bw/day**: ↑ discoloured feces, ↑ food and water consumption, ↑ vacuolation of the fore-stomach squamous epithelium (♂/♀); ↑ cells positive for markers for T lymphocytes (CD4/CD45^{low}), antigen-presenting cells (IL-1α), and T-cell (CD2) in spleen cells, ↓ cells positive for markers for B-cells and lymphocytes (PanB and CD4/CD45^{low}) in lymph node cells, ↓ serum antibody-titer of the subclasses IgA and IgG, ↓ bone marrow cell count (♂); ↓ bw, ↑ cells positive for markers for T-lymphocytes (CD4/CD45^{low}) in spleens, ↑ B-cell/macrophage stimulation (LPS) in lymph nodes (♀) Immunological changes appeared to be reversible; only minimal findings were observed at the end of the recovery period in the satellite high dose and control rats. The following immunological investigation were conducted: • FACS-analysis to determine sub-populations of spleen cells and lymph node cells • Macrophage activity after PMA stimulation in spleen and lymph node cells • Responsiveness of spleen and lymph node cells to stimulation with mitogen ConA or LPS was determined • Antibody (IgG, IgM, and IgA) titers in sera were determined
28-day oral toxicity (diet) – Non-guideline (dose-range finding) Beagle dogs PMRA# 1179300, 1191197	Supplemental **1614/1319 mg/kg bw/day**: ↓ bwg and fc, ↓ T4, induction of microsomal liver enzymes Phases I and II, "cytoplasmic changes" in centrilobular cells of liver (♂/♀)
90-day oral toxicity (diet) Beagle dogs PMRA# 1180157 1179307	NOAEL= 34/35 mg/kg bw/day (♂/♀) **≥ 34/35 mg/kg bw/day**: induction of microsomal liver enzymes Phases I and II (↑ N-DEM, ↑ CYP450, ↑ ECOD, ↑ ALD, ↑ EH, ↑ GST, ↑ UDPGT), ↓ T4 (secondary to liver enzyme induction; non-adverse) (♂/♀) **≥ 162/170 mg/kg bw/day**: ↑ eosinophilic cytoplasmic changes in the liver, ↑ gross

Study type/ Animal/PMRA#	Study results
	pathological findings in the stomach (red discolouration or red areas in the gastric mucosa) (♂/♀); ↑ glandular cell degeneration in the stomach, ↑ round cell infiltrates in the stomach, ↑ foveolar hyperplasia in the stomach (♀) **1674/1750 mg/kg bw/day**: ↓ fc, ↓ serum protein, ↓ albumen, ↑ ALP, ↑ vacuolation of surface epithelium of the stomach, ↑ slight vacuolation of inner cortex of adrenals, ↑ slight lipofuscin storage in proximal tubular epithelia of kidneys, ↑ condensed and homogenous cytoplasmic structure in the liver (♂/♀); ↑ liver triglycerides level, ↑ liver wt, ↑ adrenal wt, ↑ glandular cell degeneration in the stomach, ↑ round cell infiltrates in the stomach, ↑ foveolar hyperplasia in the stomach (♂) There were no treatment-related effects on TBC or T3 levels in either sex.
12-month oral toxicity (diet) Beagle dogs PMRA# 1180151, 1180152, 1180153	NOAEL= 36/37 mg/kg bw/day (♂/♀) **≥ 36/37 mg/kg bw/day**: ↓ bwg (non-adverse) (♂/♀) **183/187 mg/kg bw/day**: ↓ bw, ↑ N-DEM, ↓ T4 levels (♂/♀); ↑ liver wt (♀) N-DEM levels were elevated with no change in the O-DEM levels or triglyceride levels or CYP450 content. No treatment-related effects were noted on the activities of the CYP450 dependent monooxygenases (ECOD, EROD, and ALD), EH and the conjugation enzymes (GST, and UDPGT). There were no treatment-related effects on TBC, TSH or T3 levels in either sex.
28-day dermal toxicity (limit test) Wistar rats PMRA# 1179299	NOAEL (systemic) ≥ 1000 mg/kg bw/day There were no treatment-related systemic findings in either sex. **1000 mg/kg bw/day**: ↑ skin-fold thickness (♂/♀); ↑ minimal to slight acanthosis characterized by thickening of the stratum spinosum and corneum (♂) Limited histopathology was conducted. Spleen was examined histopathologically. Congestion in spleen was noted in all animals except one control ♂ animal. Stomach was not examined.
28-day inhalation toxicity (nose-only) Wistar rats PMRA# 2801451	NOAEC = 0.03 mg/L (NOAEL approximately equivalent to 8.0/8.7 mg/kg bw/day in ♂/♀) **≥ 0.03 mg/L**: ↑ eosinophilic globules in the nasal cavity (non-adverse) (♀) **≥ 0.18 mg/L**: ↑ squamous cell metaplasia of the larynx, ↑ focal inflammation infiltrates in the larynx (♂/♀); eosinophilic globules in the nasal cavity (♂); ↑ goblet cell hyperplasia in the nasal cavity (♀) **0.5 mg/L:** ↑ increased/hypertrophic mucous neck cells in the stomach (♂/♀); ↑ goblet cell hyperplasia in the nasal cavity (♂) Examination of N-DEM, O-DEM, P450 and triglycerides did not reveal any treatment-related effects. There were no treatment-related histopathological findings in spleen or thymus

Study type/ Animal/PMRA#	Study results
Chronic Toxicity/Oncogenicity Studies	
18-month oncogenicity (diet) B6C3F1 mice PMRA# 1180169, 1180174, 1180185, 1180186, 1191196, 1191198	NOAEL = 275/459 mg/kg bw/day (♂/♀) **2066/3212 mg/kg bw/d**: ↓ bw, ↑ fc (♂/♀) **No evidence of oncogenicity**
24-month chronic toxicity/oncogenicity (diet) Wistar rats PMRA# 1180158, 1180166, 1180167, 1180168, 1191199	NOAEL = 125 mg/kg bw/day **1000 mg/kg bw/day**: ↑ fc, ↑ thickened mucosa of the glandular stomach (terminal necropsy) (♂/♀); slight ↑ incidence of inflammatory infiltrates in the stomach (interim necropsy), immunotoxicological findings observed at interim (but not terminal) necropsy: ↓ # of splenic T-helper cells (CD4, $CD45^{low, high}$), ↓ lymphocytes (CD45), ↓ T-cells (CD2, CD5, CD8), ↓ interleukin-2 receptor expressing cells (CD25), and ↑ serum IgM titers, immunotoxicological findings observed in both interim and terminal necropsy: ↓ response to mitogen stimulation in splenic cells and ↓ serum IgG titers (♂); ↑ mild vacuolation of the fore-stomach epithelium (terminal necropsy), ↓ bw, ↓ bwg (♀) **No evidence of oncogenicity** The following immunological investigation were conducted: • FACS-analysis to determine sub-populations of spleen cells and lymph node cells • Macrophage activity after PMA stimulation in spleen and lymph node cells • Responsiveness of spleen and lymph node cells to stimulation with mitogen ConA or LPS was determined • Antibody (IgG, IgM, and IgA) titers in sera were determined
Developmental/Reproductive Toxicity Studies	
2-generation reproductive toxicity (diet) Wistar rats PMRA# 1180187, 1180189, 1180190,	**Parental Toxicity** NOAEL = 287/340 mg/kg bw/day (♂/♀) **≥ 287/340 mg/kg bw/day**: ↑ incidence of cecal enlargement (F1♀) (non-adverse) **800/991 mg/kg bw/day** (dose level was adjusted from 2242/3130 mg/kg bw/day after week 5 premating): ↑ incidences of clinical signs of toxicity (water intake, discoloured faeces, and diarrhea in both generations), ↓ bw, ↓ bwg, ↑ fc during wk 1-5 period in P generation only (♂/♀); ↓ liver wt (P and F1) (♂); ↑ incidence of severe cecal enlargement (F1♀) **Offspring Toxicity** NOAEL = 340 mg/kg bw/day Histopathology was not conducted in pups **991 mg/kg bw/day:** ↓ pup bw (PND 21), ↓ litter wt, ↑ incidences of marbled liver surface (F1 and F2 pups), air-filled stomach (F1 pups) (♂/♀); ↓ rel. liver wt (F2♂) **Reproductive Toxicity** NOAEL = 800/991 mg/kg bw/day (♂/♀) No adverse treatment-related effects on reproductive parameters

Study type/ Animal/PMRA#	Study results
	991 mg/kg bw/day: ↓ uterus wt (P and F1) (♀)(non-adverse) **No evidence of sensitivity of the young**
Developmental toxicity (gavage) Sprague-Dawley rats PMRA# 1179318, 1179320, 1179321, 1180191, 1180193	**Maternal toxicity** NOAEL ≥ 1000 mg/kg bw/day No treatment-related effects **Developmental toxicity** NOAEL ≥ 1000 mg/kg bw/day No treatment-related effects **No evidence of treatment-related malformations or sensitivity of the young**
Developmental toxicity (gavage) Himalayan Rabbits PMRA# 1179322, 1179323, 1180194,	**Maternal toxicity** NOAEL = 100 mg/kg bw/day **≥ 300 mg/kg bw/day:** ↓ bw loss (observed immediately post-dosing), ↓ fc, ↑ incidence and frequency of clinical signs of toxicity (alopecia, cold ears, reduced feces, soft faeces, discoloured urine, light coloured feces), ↓ gravid uterine wt **≥ 500 mg/kg bw/day:** ↑ incidence and frequency of other clinical signs of toxicity (diarrhea, vaginal and anal prolapse) ↑ cecal enlargement, ↑ cytoplasmic changes and fatty change in the liver **1000 mg/kg bw/day:** One treatment-related mortality, ↓ bw, ↓ placental wt, ↑ incidence of coarse grained and light discoloured placentas, ↑ number of abortions occurring late in gestation, ↑ gross pathological changes (enlarged, discoloured areas, and contents gaseous) in the liver and GI tract, ↑ vacuolation of the hepatocytes **Developmental toxicity** NOAEL = 100 mg/kg bw/day **≥ 300 mg/kg bw/day:** ↓ fetal bw **≥ 500 mg/kg bw/day:** ↑ incidence of incomplete skeletal ossification at the following sites: medial phalanx digits and toes (5th right and left), metacarpals (1st right and left), calcaneus (bilateral), 6th sternebrae, caudal vertebral bodies (10th and 13th), frontal bone (bilateral) **1000 mg/kg bw/day:** ↑ number of abortions occurring late in gestation **No evidence of treatment-related malformations or sensitivity of the young**

Study type/ Animal/PMRA#	Study results
Genotoxicity Studies	
Bacterial Reverse Mutation Assay Salmonella typhimurium (TA98, TA100, TA1535 and TA 1537) PMRA# 1179324	Negative ± metabolic activation Tested up to a limit concentration
In Vitro Mammalian Clastogenicity Chinese hamster V79 cells PMRA# 1179326	Negative ± metabolic activation Tested up to a limit concentration
Mammalian chromosomal aberration (in vitro) Chinese hamster V79 cells PMRA# 1179325	Negative ± metabolic activation Tested up to a limit concentration
Micronucleus assay (in vivo) NMRI Mice PMRA# 1179308	Negative Tested up to limit dose
UDS in vitro Rat primary hepatocytes PMRA# 1179309	Negative Tested up to a limit concentration
Bacterial Reverse Mutation Assay Salmonella typhimurium (TA98, TA100, TA102, TA1535, and TA 1537) MKH 6562 sulfonic acid sodium salt (a major plant and soil metabolite of MKH 6562) PMRA# 1190317	Negative ± metabolic activation Tested up to a limit concentration

Study type/ Animal/PMRA#	Study results
Neurotoxicity Studies	
Acute oral neurotoxicity (gavage) Fischer rats PMRA# 1180175	NOAEL = 500 mg/kg bw **2000 mg/kg bw:** ↓ motor activity on day of dosing, ↓ locomotor activity on day of dosing, ↓ level of activity in open field assessed during FOB (♂/♀); ↑ perineal staining (♂) **No evidence of selective neurotoxicity**
90-day oral neurotoxicity (diet) Fischer rats PMRA# 1180176	NOAEL = 147/174 mg/kg bw/day (♂/♀) **1482/1736 mg/kg bw/day:** ↓ bw, ↓ bwg (♂/♀); ↓ fc (♂) **No evidence of neurotoxicity**
Immunotoxicity Studies	
28-day oral immunotoxicity (diet) ♀ Wistar rats PMRA# 1190319	NOAEL ≥ 966 mg/kg bw/day A splenic AFC assay was used to determine the response to antigen administration (T cell-dependent, sRBC) No treatment-related findings were noted in the AFC assay based on lack of dose-related trends or patterns, however, the antibody-forming cell response data were highly variable **≥ 134 mg/kg bw/day:** ↓ bwg (non-adverse) **966 mg/kg bw/day**: ↓ spleen wt, ↓ spleen cells (non-adverse)
28-day oral immunotoxicity (diet) ♂ Wistar rats PMRA# 1190318	NOAEL = 157 mg/kg bw/day A splenic AFC assay was used to determine the response to antigen administration (T cell-dependent, sRBC) **≥ 157 mg/kg bw/day:** ↓ bwg, ↓ IgM AFC/10^6 spleen cells (non-adverse) **1116 mg/kg bw/day:** ↓ bw, ↓ IgM AFC/spleen cells (10^3), ↓ spleen cells **Evidence of immune dysregulation at limit dose**
28-day oral immunotoxicity (diet) ♀ Wistar rats PMRA# 1190321	NOAEL ≥ 1131 mg/kg bw/day Assays investigating enumeration of total spleen cells, total T and B cell populations and T-cell subsets (CD4+ and CD8+), a spleen cell proliferation assay (anti-CD3 mediated T cell proliferation) and NK assay (YAC-1 target cell cytotoxic activity of NK cell) were conducted. Treatment did not influence splenic cell population as indicated by spleen cell, B cell, total T cell, T helper cell, or T suppressor/cytotoxic cell numbers. No treatment-related findings were noted in the anti-CD3 T-cell proliferation assay in both the stimulated and unstimulated spleen cell cultures or in the NK cell assay. **≥ 167 mg/kg bw/day**: ↑ liver wt (non-adverse) **1131 mg/kg bw/day**: ↓ spleen wt (non-adverse)

Study type/ Animal/PMRA#	Study results
28-day oral immunotoxicity (diet) ♂ Wistar rats PMRA# 1190320	NOAEL = 177 mg/kg bw/day Assays investigating enumeration of total spleen cells, total T and B cell populations and T-cell subsets (CD4+ and CD8+), a spleen cell proliferation assay (anti-CD3 mediated T cell proliferation) and NK assay (YAC-1 target cell cytotoxic activity of NK cell) were conducted. **≥ 18 mg/kg bw/day**: ↓ bwg (non-adverse) **1222 mg/kg bw/day:** ↓ bw, ↓ spleen wt, ↓ spleen cells, ↓ B lymphocytes (CD45+), ↓ T helper cells (CD4+/CD5+) **Evidence of immune dysregulation at limit dose**
28-day oral immunotoxicity (diet) – Non-guideline Wistar rats PMRA# 1179311	Supplemental No treatment-related findings in the AFC assay based on lack of dose-related trends or patterns. **≥ 612 mg/kg bw/day**: ↑ discoloured feces (♀) **2205 mg/kg bw/day:** ↑ discoloured feces, ↓ bwg (♂)

Table 2 Toxicology reference values for use in health risk assessment for flucarbazone

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or target MOE[1]
Acute dietary (all populations	Developmental toxicity study in rabbits	Maternal toxicity NOAEL = 100 mg/kg bw/day Increased incidences of clinical signs of toxicity, decreased food consumption and body weight loss observed within the first few days of dosing	100
	ARfD = 1.0 mg/kg bw		
Repeated dietary (all populations)	12-month dietary toxicity study in dogs	NOAEL = 36 mg/kg bw/day Decreased body weight and body weight gain	100
	ADI = 0.4 mg/kg bw/day		
Short-term inhalation	28-day inhalation toxicity study in rats	NOAEC = 0.03 mg/L (approximately equivalent to NOAEL = 8.0 mg/kg bw/day) Increased incidences of eosinophilic globules in the nasal cavity, and squamous metaplasia and focal inflammation infiltration in the larynx as well as increased goblet cell hyperplasia in the nasal cavity in females	100
Short-term dermal[2]	Co-critical studies: 90-day and 12-month dietary toxicity studies in dogs	NOAEL = 36 mg/kg bw/day Increased incidence of red discolouration or red areas in the gastric mucosa of the stomach in both sexes as well as increased incidences of glandular cell degeneration, round cell infiltrates and foveolar	100

Exposure Scenario	Study	Point of Departure and Endpoint	CAF or target MOE[1]
		hyperplasia in the stomach of the female animals	
Combined short-term dermal[2] and inhalation	Dermal: 90-day dietary toxicity study in dogs Inhalation: 28-day inhalation toxicity study in rats	Common endpoint: Treatment-related pathological findings in the stomach Dermal NOAEL = 34 mg/kg bw/day Inhalation NOAEC = 0.18 mg/L (approximately equivalent NOAEL to 48 mg/kg bw/day)	Dermal: 100 Inhalation: 100
Cancer	No evidence of oncogenicity		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 100% was used in a route-to-route extrapolation

Appendix IV Dietary exposure and risk estimates

Table 1 Summary of dietary exposure and risk from flucarbazone

Population Subgroup	MRL/Tolerance-level							
	Acute Dietary (95th percentile)[1]				Chronic Dietary[2]			
	Food Only		Food + Water		Food Only		Food + Water	
	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ADI	Exposure (mg/kg/day)	%ADI
General Population	0.000211	0.02	0.002173	0.22	0.000073	0.0	0.000861	0.2
All Infants (<1 year old)	0.000370	0.04	0.007153	0.72	0.000079	0.0	0.003022	0.8
Children 1–2 years old	0.000593	0.06	0.003326	0.33	0.000309	0.1	0.001393	0.3
Children 3–5 years old	0.000385	0.04	0.002589	0.26	0.000204	0.1	0.001085	0.3
Children 6–12 years old	0.000255	0.03	0.002001	0.20	0.000123	0.0	0.000778	0.2
Youth 13–19 years old	0.000148	0.01	0.001828	0.18	0.000067	0.0	0.000622	0.2
Adults 20–49 years old	0.000109	0.01	0.002098	0.21	0.000053	0.0	0.000836	0.2
Adults 50–99 years old	0.000094	0.01	0.001833	0.18	0.000048	0.0	0.000809	0.2
Females 13–49 years old	0.000107	0.01	0.002114	0.21	0.000051	0.0	0.000820	0.2

[1]Acute Reference Dose (ARfD) of 1 mg/kg bw applies to the general population and all population subgroups.
[2]Acceptable Daily Intake (ADI) of 0.4 mg/kg bw/day applies to the general population and all population subgroups.

Food residue chemistry summary

Flucarbazone is an acetolactate synthase (ALS) or acetohydroxy acid synthase (AHAS) inhibiting herbicide. ALS and AHAS are key enzymes in the pathway of biosynthesis of the branched-chain amino acids isoleucine, leucine, and valine; their inhibition results in plant death. The currently registered food use of flucarbazone in Canada is grass and broadleaf weed control in winter wheat, spring wheat and durum wheat at a maximum rate of 30 g a.i./ha per growing season with a preharvest interval (PHI) of 80 days. Grazing treated fields or using treated green crop for feed is prohibited but wheat grain or straw harvested from treated fields may be fed to livestock. Treatment of wheat underseeded to legumes is not allowed. A plantback interval (PBI) of 11 months has been established for specific crops in zones with specific soil characteristics.

The first dietary risk assessment for flucarbazone was conducted under PMRA-USEPA Joint Review in support of the Regulatory Note (REG) document REG2000-09, *Flucarbazone-sodium*, published on 25 September 2000 for a temporary registration on spring wheat, pending submission of additional data (in other words, analytical method for residues in animal commodities and freezer storage stability data) for a full registration. Following submission and review of the requested data, a full registration (and addition of durum wheat on the label) was granted in 2009 after consultation under the Proposed Registration Decision (PRD) document PRD2008-13, *Flucarbazone-sodium*, published on 18 July 2008. The Registration Decision document RD2009-02, *Flucarbazone-sodium* was published on 1 April 2009. Winter wheat was added on the label in 2014, supported by the existing (same) data previously submitted for the registration of spring and durum wheat. MRLs were established for residues of flucarbazone in/on wheat grain, eggs, meat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep at the limit of quantitation (LOQ) of 0.01 ppm; in milk at 0.0025 ppm (LOQ); and in liver of cattle, goats, hogs, horses and sheep at 0.05 ppm.

The residue chemistry database for flucarbazone is complete and up-to-date for the registered uses (in other words, grass and broadleaf weed control in wheat). The residue definition (RD) was first determined by the PMRA-USEPA Joint Review (REG2000-09) to be the sum of flucarbazone and the metabolite *N*-desmethyl flucarbazone, calculated as the stoichiometric equivalent of flucarbazone, in plant commodities and only flucarbazone in animal commodities, for enforcement and dietary risk assessment. Later on, taking into account that the metabolite *N*-desmethyl flucarbazone was only found in animal feedstuffs and not in edible plant commodities, the PMRA revised the residue definition to exclude the metabolite. The rationale for excluding the metabolite was based on the following: the wheat metabolism study indicated that no residues of flucarbazone were identified in grain, but *N*-desmethyl residues accounted for up to 22% of the total radioactive residues (TRRs). However, supervised residue trials indicated that residues of parent flucarbazone and *N*-desmethyl were <0.01 ppm (<LOQ) in grain, even at exaggerated rates. Residues of the metabolite *N*-desmethyl were found to be detectable only in wheat feedstuffs (forage, hay and straw).

The Canadian residue definition is therefore flucarbazone per se for both plant and animal commodities, for enforcement and dietary risk assessment [see PRD2008-13]. The USEPA did not follow this path and maintained the previous PMRA-USEPA Joint Review residue definition. There are no JMPR evaluations and no Codex MRLs established for residues of flucarbazone. Flucarbazone is not approved for use in European Union countries.

The RD in drinking water (for risk assessment) is proposed to be expressed as the combined residue of flucarbazone (development code name: MKH 6562) and five of its transformation products: MKH 6562 sulfonamide; MKH 6562 sulfonic acid; *O*-desmethyl MKH 6562; N,O-dimethyl triazolinone (NODT) and *N*-methyl triazolinone (NMT). Inclusion of these transformation products in the RD is due to their concentration levels in environmental media (soil and/or water) and their predicted mobility based on water solubility and/or detections in terrestrial field dissipation studies. Concerning MKH 6562 sulfonamide, in addition to preceding reasons, its inclusion in the RD is also due to the evidence of its existence via multiple transformation pathways. Based on lack or limited availability of toxicity data, all these transformation products are assumed to be of equal toxicity to the unchanged (parent) flucarbazone.

Adequately validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical methods were provided in previous petitions for both data gathering and enforcement of flucarbazone residues in plant and animal commodities with LOQs of 0.01 ppm for plant matrices and animal tissues and 0.0025 ppm for milk. Flucarbazone residues in foods (other than cereals) are monitored by the CFIA monitoring program but not by the USDA PDP, except in heavy cream. All samples in the 2008–2017 CFIA monitoring data and in the 2009–2018 PDP data (for heavy cream) were practically non-detects.

Appendix V Mixer/loader/applicator exposure and risk assessment

Table 1 Dermal, inhalation or combined (dermal plus inhalation) exposure and risk assessment for mixer/loader/applicators (M/L/A) using groundboom equipment

Crop	M/L UE (µg/kg a.i.)		Applicator UE (µg kg a.i.)		Maximum AR[a] (kg a.i./ha)	ATPD[b] (ha)	Dermal exposure (mg/kg bw/day)[c]	Dermal MOE [d]	Inhalation exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Combined MOE[g]
	Dermal	Inhalation	Dermal	Inhalation							
Spring wheat and/or excluding Durum wheat; Winter wheat	Open mixing/loading dry flowable and open cab groundboom liquids application (AHETF); PPE: long sleeved-shirt and long pants, chemical-resistant gloves										
	84.14	21.8	25.40	1.68	0.0284	360	0.0140	2571	0.0030	2667	2109
	Mixing/loading water-soluble packets (PHED) and open cab groundboom liquids application (AHETF); PPE: long sleeved-shirt and long pants, chemical-resistant gloves										
	21.61	0.18	25.40	1.68	0.0284	360	0.0060	6000	0.0002	40,000	5536
	Open mixing/loading liquid and open cab groundboom liquids application (AHETF); PPE: long sleeved-shirt and long pants, chemical-resistant gloves										
	58.50	0.63	25.40	1.68	0.0288	360	0.0109	3303	0.0003	26,667	3060

AR = application rate; ATPD = area treated per day; MOE = Margin of Exposure; UE = Unit Exposure.

[a] Maximum AR (kg a.i./ha) as per current product labels

[b] ATPD (ha) – area treated per day (default values)

[c] Dermal exposure (mg/kg bw/day) = Dermal unit exposure (µg/kg a.i.) × CF (1 mg/1000 µg) × ATPD (ha) × Maximum AR (kg a.i./ha) × 100% dermal absorption / average worker body weight (80 kg)

[d] Based on a short-term dermal NOAEL of 36 mg/kg bw/day; target MOE of 100 (Appendix III)

[e] Inhalation exposure (mg/kg bw/day) = Inhalation unit exposure (µg/kg a.i.) × CF (1 mg/1000 µg) × ATPD (ha) × Maximum AR (kg a.i./ha) / average worker body weight (80 kg)

[f] Based on a short-term inhalation NOAEL of 8 mg/kg bw/day; target MOE of 100 (Appendix III),

[g] Based on a combined dermal NOAEL of 34 mg/kg bw/day and inhalation NOAEL of 48 mg/kg bw/day, target MOE of 100 (Appendix III), and the combined MOE = 1/ ((1/MOE-dermal)+(1/MOE-inhalation)).

Table 2 Dermal, inhalation and combined (dermal plus inhalation) exposure and risk assessment for mixer/loader and applicators (M/L/A) using aerial equipment

Crop	M/L UE (µg/kg a.i.)		Applicator UE (µg kg a.i.)		Maximum AR[a] (kg a.i./ha)	ATPD [b] (ha)	Dermal exposure (mg/kg bw/day) [c]	Dermal MOE [d]	Inhalation exposure[e] (mg/kg bw/day)	Inhalation MOE[f]	Combined MOE[g]
	Dermal	Inhalation	Dermal	Inhalation							
Wheat Spring and Durum; Wheat winter	Open mixing/loading liquid (AHETF); PPE: a long sleeved-shirt and long pants, chemical-resistant gloves;										
	58.50	0.63	-	-	0.0288	400	0.0084	4286	0.000091	87,912	4017
	Closed cockpit aerial liquid application (AHETF); PPE: a long sleeved-shirt and long pants, chemical-resistant gloves*;										
	-	-	2.67	0.00969	0.0288	400	0.0004	90,000	0.0000014	>100,000	84,790

AR = application rate; ATPD = area treated per day; MOE = Margin of Exposure; UE = Unit Exposure. * Chemical-resistant gloves only worn to perform activities outside of the cockpit.

[a] Maximum AR (kg a.i./ha), as per current product labels,
[b] ATPD (ha) – area treated per day. (default values).
[c] Dermal exposure (mg/kg bw/day) = Dermal unit exposure (µg/kg a.i.) × CF (1 mg/1000 µg) × ATPD (ha) × Maximum AR (kg a.i./ha) × 100% dermal absorption / average worker body weight (80 kg).
[d] Based on a short-term dermal NOAEL of 36 mg/kg bw/day; target MOE of 100 (Appendix III)
[e] Inhalation exposure (mg/kg bw/day) = Inhalation unit exposure (µg/kg a.i.) × CF (1 mg/1000 µg) × ATPD (ha) × Maximum AR (kg a.i./ha) / average worker body weight (80 kg).
[f] Based on a short-term inhalation NOAEL of 8 mg/kg bw/day; target MOE of 100 (Appendix III),
[g] Based on a combined dermal NOAEL of 34 mg/kg bw/day and inhalation NOAEL of 48 mg/kg bw/day, target MOE of 100 (Appendix III), and the combined MOE = 1/((1/MOE-dermal) + (1/MOE-inhalation)).

Appendix VI Postapplication workers exposure and risk assessment

Crop	Use directions [a]		Peak DFR[b] (µg a.i./cm^2)	Activity	TC [c] (cm^2/hr)	Dermal Exposure [d] (mg/kg bw/day)	MOE [e]	REI (hours)
	Maximum AR (µg a.i./ha)	No. of applications						
Spring wheat, Durum wheat and Winter wheat,	0.288	1	0.072	Scouting	1100	0.0079	4557	12
	0.288	1	0.072	Weeding, hand	70	0.0005	72,000	12

AR = application rate; DFR = dislodgeable foliar residue; TC = transferable residues; MOE = margin of exposure; REI = Restricted-entry interval.

[a] Use directions as per current product labels

[b] Peak DFR (µg a.i./cm^2) – calculated assuming 25% residue deposition residue following the application at the indicated application rate

[c] TC (cm^2/hr) –TC value for a given crop (ARTF, 2019)

[d] Dermal Exposure (mg/kg bw/day) = TC (cm^2/hr) × DFR (µg a.i./cm^2) × CF (1 mg/1000 µg) × DAF (100%) × 8 hours/day / average worker body weight (80kg)

[e] Based on the short term dermal, NOAEL of 36 mg/kg bw/day/ daily dermal exposure (mg/kg bw/day); target MOE of 100.

Appendix VII Fate and behaviour in the environment

Table 1 Summary of fate and behaviour of flucarbazone and transformation products in terrestrial and aquatic environments

Study Type	Endpoint	Endpoint Value	Comments
Hydrolysis (PMRA# 1179373)	Half-life	pH 5: 525 d pH 7: 521 d pH 9: 753 d	Minor transformation product: Flucarbazone sulfonamide acid maximum of 4.2%, 3.9% and 4.0% of the applied radioactivity at pH 5, pH 7 and pH 9, respectively, all at 30 days (end of test) Not an important route of transformation at environmentally relevant pH
Phototransformation in water (PMRA# 1179328) (PMRA# 1179329)	Half-life	82.4 d	PMRA# 1179328 – half-life calculated based on maximum irradiation for June in Edmonton, Alberta One major transformation product: Flucarbazone sulfonamide max 22.6% AR at 30 days (end of test) PMRA# 1179329 is a supplemental, laboratory UV-VIS absorbance study that demonstrates no absorbance by flucarbazone in various buffer solutions (pH 5, 7 and 9) at wavelengths >286 nm May be an important route of transformation
Phototransformation on soil (PMRA# 1179374)	Half-life	287 d	Half-life calculated based on maximum global irradiation for June in Edmonton, Alberta Not an important route of transformation Not an important route of transformation.
Phototransformation in air	Half-life	1.8 d (21 hr)	AopWin v1.92 estimate based on overall OH radical rate constant of 5.9847 E-12 cm^3/molecule-sec
Aerobic biotransformation in water/sediment Phenyl label (PMRA# 3139544)	DT_{50} DT_{90}	Brandywine Creek DT_{50} = 75.6 d DT_{90}= 251 d Choptank River DT_{50} = 335 d DT_{90} = 1112 d	Brandywine Creek: Major transformation product Flucarbazone sulfonamide 31.8.9% AR (Day 100) Choptank River: Major transformation product Flucarbazone sulfonamide 9.7% AR (Day 100)

Study Type	Endpoint	Endpoint Value	Comments
			Moderately persistent to persistent, depending on aquatic system May be an important route of transformation
Anaerobic biotransformation in water/sediment Phenyl label (PMRA# 1180203) Phenyl label (PMRA# 1179335)	DT_{50}	PMRA# 1180203 DT_{50} = 104 d (DFOP) PMRA 1179335 DT_{50} = 73 d (SFO)	PMRA# 1180203 – **study conducted at 5°C**: Major transformation product Flucarbazone sulfonamide 49.0% AR (Day 275) -excess of glucose added to test systems (~500-fold greater than oxygen concentration) PMRA# 1179335 – **study conducted at 20°C**: Major transformation product Flucarbazone sulfonamide 88.8%AR (Day 367) -Excess of glucose added to test systems (~500-fold greater than oxygen concentration) Moderately persistent. May be an important route of transformation but glucose enriched test systems may not reflect naturally occurring anaerobic environments.
Aerobic biotransformation in soil Phenyl label (2734406) Phenyl label (PMRA# 1179331) Phenyl label (PMRA# 1179330) Triazolinone label (PMRA# 1180202)	DT_{50}	PMRA# 2734406 Sandy clay loam DT_{50} = 11.4 d (IORE) clay loam DT_{50} = 12.1 d (SFO) PMRA 1179331 Sandy loam DT_{50} = 92.5 (DFOP) PMRA# 1179330 Sandy loam DT_{50} = 25.1 d (IORE) PMRA# 1180202 Sandy loam DT_{50} = 29.6 d (SFO)	PMRA# 2734406: Major transformation product Flucarbazone sulfonamide max 84.7% AR (Day 123) PMRA# 1179331: Major transformation product Flucarbazone sulfonamide max 41% AR (Day 366) PMRA# 1179330: Two major transformation products - Flucarbazone sulfonamide 69% AR and Flucarbazone sulfonic acid 11% AR (Day 272) PMRA# 1180202: Two major transformation products *O*-desmethyl Flucarbazone at 15% AR NMT at 14.4% AR (Day 60) Slightly to moderately persistent Important route of transformation.

Study Type	Endpoint	Endpoint Value	Comments
Adsorption/Desorption Parent (PMRA# 1179337) N,O-dimethyltriazolinone (PMRA# 118020) NMT (PMRA# 1180204) Flucarbazone Sulfonamide (PMRA# 1180210) N,O-Dimethyltriazolinone (PMRA# 1180210) NMT (1180210) Flucarbazone Sulfonamide (PMRA# 1180206) Flucarbazone Sulfonic acid (PMRA# 1180207)	K_{oc}	Sandy loam = 10 Silty loam = 18 Sandy clay loam = 14 Silt clay loam = 10 Sand = 15 Loamy sand = 27 Loam = 33 Loam = 24 Sandy loam = 25 Loamy sand = 1202 Loam = 580 Loam = 2756 Sandy loam = 574 Sandy loam soil: Flucarbazone Sulfonamide = 13 N,O-Dimethyltriazolinone = 8 NMT = 242 Sand: NMT = 4 Loamy sand = 37 Loam = 49 Loam = 37 Sandy loam = 39 N/A	Parent: Very high mobility N,O-dimethyltriazolinone: Very high mobility NMT: low mobility Sandy loam soil: Flucarbazone Sulfonamide: Very high mobility N,O-Dimethyltriazolinone: Very high mobility NMT: moderate mobility Sand: NMT: Very high mobility Flucarbazone: Very high mobility K_{oc} values could not be calculated as <1% applied test substance was adsorbed to soils used (loamy sand, loam, sandy loam) Adsorption processes not expected to contribute to dissipation in the environment
Aged soil leaching (PMRA# 2347640)	K_{oc}	Parent: 10 Flucarbazone sulfonamide: 36 Flucarbazone sulfonic acid: no adsorption to soil	Adsorption processes not expected to contribute to dissipation in the environment
Outdoor lysimeter (PMRA# 1179341)	N/A	Maximum residues in soil (0–23 cm depths) and	Flucarbazone reached maximum of 16.9% AR at 10–23 cm soil depth (30

Study Type	Endpoint	Endpoint Value	Comments
		cumulative residues in leachate: **Soil** Parent: 32.9% AR (30 d); 13.4% AR (91 d) 9.1% AR (180 d) Flucarbazone sulfonamide: 27.4%,AR (30 d); 20.2% AR (91 d) 19.1% AR (180 d) Flucarbazone sulfonic acid: 2.7% AR (30 d); 4.0% AR (91 d) 5.7% AR (180 d) **Leachate** Parent: 17.0% AR (30 d); 24.5% AR (91 d) 26.5% AR (180 d) **Cumulative total: 68.0% AR** Flucarbazone sulfonamide: 2.8% AR (30 d); 6.0% AR (91 d) 7.2% AR (180 d) **Cumulative total: 15.9% AR** Flucarbazone sulfonic acid: 1.3% AR (30 d); 4.9% AR (91 d) 7.3% AR (180 d) **Cumulative total: 13.6% AR**	DAT) Flucarbazone sulfonamide reached maximum of 12.7% AR at 10–23 cm soil depth (30 DAT) Flucarbazone sulfonic acid reached maximum of 2.33% AR at 10–23 cm soil depth (180 DAT) Flucarbazone and transformation products, flucarbazone sulfonamide and flucarbazone sulfonic acid, can be expected to migrate to groundwater
Volatilization	Henry's law Constant (atm m^3/mol at 20ºC)	2.48E+14	Flucarbazone is not expected to be volatile from water and moist surfaces Volatilization not expected to contribute to dissipation in the environment
Terrestrial Field Dissipation **Soil** Lacombe, Alberta (PMRA# 1180128)	DT_{50}	13–14 d	Lacombe, Alberta: bare loam soil Major transformation products Flucarbazone sulfonamide: 22% AR

Study Type	Endpoint	Endpoint Value	Comments
			(59 DAT) and 24% AR (332 DAT) 18% AR at end of study (505 DAT) O-desmethyl Flucarbazone: 28% AR (28 DAT) <LOD (59 DAT) Flucarbazone sulfonic acid (detected only in one sample at 4% AR in surface layer Low potential to carryover
---------- Outlook, Saskatchewan (PMRA# 1180129)		---------- 17–19 d	---------- Outlook, Saskatchewan, bare clay loam soil major transformation products Flucarbazone sulfonamide: 17% AR (28 DAT) and 15% AR (138 DAT) 5% AR at end of study (505 DAT) O-desmethyl Flucarbazone: 10% AR (1 DAT) <LOD (28 DAT) Flucarbazone sulfonic acid (detected only in one sample at 7% AR in surface layer NODT detected in 1 sample 3% AR (10 DAT) Low potential to carryover
---------- Saskatoon, Saskatchewan (PMRA# 1180130)		---------- 16–31 d	---------- Saskatoon, Saskatchewan, bare clay loam soil Major transformation products Flucarbazone sulfonamide: 14.5% AR (402 DAT) and 13% AR (28 DAT) 5% AR at end of study (505 DAT) O-desmethyl Flucarbazone: 13% AR (3 DAT) 10% AR (3 DAT) <LOD (61 DAT) Flucarbazone sulfonic acid 9% AR (91DAT) in surface layer and 7% AR (505 DAT) NODT detected in 1 sample 1% AR (10 DAT)

Study Type	Endpoint	Endpoint Value	Comments
---------- Northwood, North Dakota (PMRA# 1180131)		---------- 26 d	Low potential to carryover ---------- Northwood, North Dakota bare loam soil Major transformation products Flucarbazone sulfonamide: 28% AR (28 DAT) 4% AR at end of study (367 DAT) O-desmethyl Flucarbazone: 7% AR (28 DAT) <LOD at end of study (367 DAT) Flucarbazone sulfonic acid 3.4% AR (63 DAT) in <LOD at end of study (367 DAT) Low potential to carryover
---------- Ephrata, Washington (PMRA# 1180132)		---------- 15 d	---------- Ephrata, Washington bare loamy sand Major transformation products Flucarbazone sulfonamide: 6.7%AR (14DAT) <LOD at end of study (456 DAT) Low potential to carryover
Bioaccumulation (PMRA# 2897123)	log K_{ow}	Log K_{ow} for free acid: -2.85 (unbuffered), -1.88 (pH 9), -1.84 (pH 7), -0.89 (pH 4)	Limited potential for bioaccumulation

Table 2 Summary of terrestrial and aquatic toxicity data for flucarbazone and transformation products

PMRA#	Species	Type of test	Toxicity endpoint*	Comments
Terrestrial Organisms				
1179342	Earthworm	acute	945 mg a.e./kg soil	No adverse effects reported
1180225	Earthworm	acute	>1000 mg NMT/kg soil	weight gain was affected by NMT (*N*-methyltriazolinone) at concentrations >32 mg NMT/kg soil)
1180237	Honey bee (*Apis mellifera*)	48 hr Acute contact	LD_{50} >189 µg a.e./bee	not toxic
1180237	Honey bee (*Apis mellifera*)	48-hr Acute Oral	LD_{50} >420.5 µg a.e./bee	not toxic
1179347	Bobwhite quail (*Colinus virginianus*)	Acute oral	LD_{50} >1890 mg a.e./kg bw/day	practically non-toxic
1179348 1180255	Bobwhite quail (*Colinus virginianus*)	Acute dietary	LC_{50} > 4646 mg a.i./kg diet >1065.9 mg a.e./kg bw/day	Practically non-toxic
1180258	Bobwhite quail (*Colinus virginianus*)	Reproductive	NOEC = 1311 mg a.i./kg diet	No adverse effects reported
1179350 1180256	Mallard duck (*Anas platyrhynchos*)	Acute dietary	LC_{50} > 4969 mg a.i./kg diet	Practically non-toxic
1180257	Mallard duck (*Anas platyrhynchos*)	Reproductive	NOEC = 223 mg a.i./kg diet NOEL = 20.6 mg a.e./kg bw/day	NOEC based on reproductive performance and reduction in adult body weight
2703322	Rat	Acute oral	>4725 mg a.e./kg bw	Practically non-toxic
2703322	Rat	Reproductive	NOAEC = 3780 mg a.e./kg bw/day NOAEL = 548.6 mg a.e/kg bw/day LOAEL = 2950mg a.e./kg bw/day	NOAEL based offspring toxicity LOAEL (2-gen reproductive endpoint) based on weight reduction in off-spring (male and female F1 pups)
1180134	Terrestrial plants	Seedling emergence	EC_{25} (dry weight) = 0.30 g a.e./ha	Canola

PMRA#	Species	Type of test	Toxicity endpoint*	Comments
1180134	Terrestrial plants	Vegetative vigour	EC_{25} (dry weight) = 0.39 g a.i./ha	Onion
3139545	Terrestrial plants Flucarbazone sulfonamide (a metabolite of flucarbazone 6562) on Lentil, Oat, and Sugarbeet.	Seedling emergence	EC>0.3 g t.p./ha	Flucarbazone sulfonamide is a major transformation product 3 test species: Lentil, Oat, and Sugarbeet
3139545	Terrestrial plants Flucarbazone sulfonamide (a metabolite of flucarbazone 6562) on Lentil, Oat, and Sugarbeet.	Vegetative vigour	EC>0.3 g t.p./ha	Flucarbazone sulfonamide is a major transformation product 3 test species: Lentil, Oat, and Sugarbeet
1180135	Terrestrial plants: Supplemental Data for Report Number 108315: Tier 2 Seedling Emergence and Vegetative Vigor: Nontarget Phytotoxicity Study Using FLUCARBAZONE 6562 70% WG	Seedling emergence/Vegetative vigour	EC_{25} (dry weight) = 0.30 g a.i./ha	
Aquatic Organisms – Freshwater				
1179343	*Daphnia magna*	48-hr Acute	LC_{50} > 109 mg a.i./L	Practically non-toxic
1179344	*Daphnia magna*	21-d Chronic	NOEC = 114.6 mg a.i./L	No adverse effects reported
1179345	Rainbow trout (*Oncorhynchus mykiss*)	96-hr Acute	96hr LC_{50} > 96.7 mg a.i./L	Practically non-toxic
1179346	Bluegill sunfish	96-hr Acute	LC_{50} > 99.3 mg a.i./L	Practically non-toxic
1180248	Rainbow trout (*Oncorhynchus mykiss*)	97-d Early Life Cycle	NOEC = 2.75 mg a.i./L	NOEC is based on scoliosis or kyphoscoliosis on off-spring
1179354	Duckweed (*Lemna gibba*)	14-day static renewal	EC_{25} = 0.0094 mg a.e./L EC_{50} = 0.0123 mg a.e./L	based on biomass

PMRA#	Species	Type of test	Toxicity endpoint*	Comments
1179355	Duckweed (*Lemna gibba*)	7-day – spray application of 70 WG (68% a.i.)	EC_5 = 1.12E-05 mg a.e./L (90 mg a.e./ha) EC_{25} = 6.63E-05 mg a.e./L (530 mg a.e./ha) EC_{50} = 2.2E-04 mg a.e./L (1760 mg a.e./ha)	Based on frond dry weight
3139548	Duckweed (Lemna gibba) Flucarbazone Sulfonamide	7-day static renewal	EC_{25} > 4.58 mg t.p./L EC_{50} > 4.58 mg t.p./L	Flucarbazone sulfonamide is a major transformation product
1179351	Freshwater Green Alga, (*Selenastrum capricornutum*)	96-hr	EC_{50} = 6.4 mg a.i./L EC_{25} = 3.8 mg a.i./L	Based on cell density (growth inhibition)
1179352	Freshwater Cyanobacteria (*Anabaena flos-aquae*)	96-hr	EC_{50} = 12 mg a.i./L EC_{25} = 9.1 mg a.i./L	Based on biomass
1179353	Freshwater Diatom (*Navicula pelliculosa*)	96-hr	EC_{50} > 115 mg a.i./L EC_{25} > 115 mg a.i./L	Based on growth inhibition (cell density)
Aquatic Organisms – Marine				
1180259	Saltwater Diatom (*Skeletonema costatum*)	96-hr Acute	EC_{50} > 89.2 mg a.i./L EC_{25} > 89.2 mg a.i./L	Based on growth inhibition (cell density)
3139550	Sheepshead minnow (*Cyprinodon variegatus*)	96-hr Acute	EC_{50} > 141 mg a.e./L	
3139549	Marine invertebrate Saltwater Mysid (*Americamysis bahia*)	96-hr Acute	96-h LC_{50} > 120 mg a.e./L	
3139547	Marine bivalve: Eastern Oyster (*Crassostrea virginica*)	Acute – shell deposition	96-h LC_{50} > 83 mg a.e./L	

* Unless indicated otherwise, endpoints were reported as flucarbazone-sodium, thus were converted to acid equivalents for risk assessment and when endpoints were based on mean measured test concentrations and/or analytical method used would result in conversion to acid form and as such, results were considered to have been reported as flucarbazone and not flucarbazone-sodium, thus no need to convert to acid equivalents and if insufficient information available to determine whether conversion of active ingredient to acid equivalents was required, as such, it was assumed that conversion was required.

Table 3 Screening level risk for non-target organisms

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty factor	EECs	Risk quotient
1179342	Earthworm	acute	945 mg a.e./kg soil	2	472.5 mg a.e./kg soil	0.013 mg a.e./kg soil	0.00003
1180225	Earthworm (conducted with NMT)	Acute	>1000 mg t.p./kg soil	2	>500 mg a.e./kg soil	0.013 mg a.e./kg soil	<0.00003
1180237	Honey bee (*Apis mellifera*)	48 hr Acute contact	>188.5 µg a.e./bee	1	LC_{50} > 188.5 µg a.e./bee	0.067 µg a.e./bee	<0.0004
1180237	Honey bee (*Apis mellifera*)	48-hr Acute Oral	>420.5 µg a.e./bee	1	LC_{50} > 420.5 µg a.e./bee	0.812 µg a.e./bee	<0.0019
1179347	Bobwhite quail (*Colinus virginianus*)	Acute oral	>1890 mg a.e./kg bw/day	10	LD_{50} > 189.0 mg a.e./kg bw/day	EDE (mg a.i./kg bw) Small: 2.30 Med: 1.80 Large: 1.16	 <0.01 <0.01 <0.01
1180257	Mallard duck *(Anas platyrhynchos)*	Reproductive	NOEC = 210 mg a.e./kg diet NOEL = 20.6 mg a.e./kg bw/day	1	NOEL = 20.6 mg a.e./kg bw/day	EDE (mg a.i./kg bw) Small: 2.30 Med: 1.80 Large:1.16	 0.11 0.09 0.06
2703322	Rat	Acute oral	>4725 mg a.e./kg bw	10	LD_{50} > 472.5 mg a.e./kg bw	EDE (mg a.i./kg bw) Small: 1.33 Med: 2.57 Large:1.38	 0 < 0.01 0

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty factor	EECs	Risk quotient
2703322	Rat	Reproductive	3780 mg a.e./kg/diet 548.5 mg a.e./kg bw/day	1	548.5 mg a.e./kg bw/day	EDE (mg a.i./kg bw) Small: 1.32 Med: 2.57 Large: 1.37	 0 0 0
1180134 1180135	Terrestrial plants	Seedling emergence (canola)	EC_{25} = 0.30 g a.e./ha	1	0.30 g a.i./ha	28.35 g a.e./ha	**94.5**
1180134 1180135	Terrestrial plants	Vegetative vigour (oinion)	EC_{25} = 0.39 g a.e./ha	1	0.39 g a.e./ha	28.35 g a.e./ha	**72.7**
3139545	Terrestrial plants Flucarbazone sulfonamide (transformation product)	Seedling emergence (lentil, oat, sugarbeet)	EC_{50} > 0.3 g t.p.ha	1	>0.3 g t.p./ha	28.35 g t.p./ha	**<94.3**
3139545	Terrestrial plants Flucarbazone sulfonamide (transformation product)	Vegetative vigour (lentil, oat, sugarbeet)	EC_{50} > 0.3 g t.p.ha	1	>0.3 g t.p./ha	28.35 g t.p./ha	**<94.3**
1179343	*Daphnia magna*	48-hr Acute	>109 mg a.e./L	10	>10.9 mg a.e./L	0.004 mg a.e./L	<0.0001
1179344	*Daphnia magna*	21-d Chronic	114.6 mg a.e./L	1	114.6 mg a.e./L	0.004 mg a.e./L	0.00003
1179345	Rainbow trout (*Oncorhynchus mykiss*)	96-hr Acute	>96.7 mg a.e./L	10	>9.67 mg a.e./L	0.004 mg a.e./L	<0.0004
1179345	amphibians	96-hr Acute	>96.7 mg a.e./L	10	>9.67 mg a.e./L	0.019 mg a.e./L	<0.002
1179346	Bluegill sunfish	96-hr Acute	>99.3 mg a.e./L	10	>9.93 mg a.e./L	0.004 mg a.e./L	<0.0004
1180248	Rainbow trout *(Oncorhynchus mykiss)*	97-d Early Life Cycle	2.75 mg a.e./L	1	2.75 mg a.e./L	0.004 mg a.e./L	0.0015
1180248	amphibians	chronic	2.75 mg a.e./L	1	2.75 mg a.e./L	0.019 mg a.e./L	0.007

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty factor	EECs	Risk quotient
1179354	Duckweed (*Lemna gibba*)	14-day static renewal	0.012 mg a.e./L	2	0.006 mg a.e./L	0.004 mg a.e./L	0.65
1179355	Duckweed (*Lemna gibba*)	7-day – spray application of 70 WG (68% a.i.)	2.2E-04 mg a.e./L (*1.76 g a.e./ha Application rate)	2	0.00011 mg a.e./L	0.004 mg a.e./L	**36.4**
3139548	Duckweed (*Lemna gibba*) Flucarabazone sulfonamide	7-day static renewal	EC_{50}>4580 4.58 mg t.p./L	2	>2.29 mg t.p./L	0.004 mg a.e./L (assuming 100% conversion of parent to transformation product)	<0.0000
1179351	Freshwater Green Alga, (*Selenastrum capricornutum*)	96-hr	6.4 mg a.e./L	2	3.2 g a.e./ha	0.004 mg a.e./L	0.0013
1179352	Freshwater Cyanobacteria (*Anabaena flos-aquae*)	96-hr	9.1 mg a.e./L	2	4.55 mg a.e./L	0.004 mg a.e./L	0.0009
1179353	Freshwater Diatom (*Navicula pelliculosa*)	96-hr	>115 mg a.e./L	2	>57.5 mg a.e./L	0.004 mg a.e./L	<0.0001
1180259	Saltwater Diatom (*Skeletonema costatum*)	96-hr Acute toxicity	>89.2 mg a.e./L	2	44.6 mg a.e./L	0.004 mg a.e./L	<0.0001

PMRA#	Species	Type of test	Toxicity endpoint	Uncertainty factor	Toxicity endpoint adjusted for uncertainty factor	EECs	Risk quotient
3139550	Marine fish Sheepshead Minnow (*Cyprinodon variegatus*)	96-hr Acute toxicity - flow-through	>141 mg a.e./L	10	>14.1 mg a.e./L	0.004 mg a.e./L	<0.0003
3139549	Saltwater Mysid (*Americamysis bahia*)	96-hr Acute toxicity - flow-through	>120 mg a.e./L	10	>60 mg a.e./L	0.004 mg a.e./L	<0.0001
3139547	Marine bivalve: Eastern Oyster (*Crassostrea virginica*).	96-hr Acute toxicity - flow-through	> 83 mg a.e./L	10	>8.3 mg a.e./L	0.004 mg a.e./L	<0.0001

* As water concentrations of flucarbazone were not reported in the study, the EEC for this risk quotient calculation was based on the application rate reported in the study, in terms of a.i./ha, converted to g a.e./ha and then using this value as the application rate, converted into a screening level concentration.

Table 4 Refined assessment for non-target terrestrial plants using SSD endpoints and spray drift exposure

Species sensitivity distribution (SSD) endpoint (g a.e./ha)	Application method	Spray droplet quality (ASABE)	Spray drift (% application)	Risk quotient*
Seedling emergence				
1.47	Ground	Medium	6	**1.2**
	Aerial	Medium	23	**4.4**
	Ground	Coarse	3	0.6
	Aerial	Coarse	17	**3.3**
Vegetative vigour				
1.10	Ground	Medium	6	**1.5**
	Aerial	Medium	23	**5.9**
	Ground	Coarse	3	0.8
	Aerial	Coarse	17	**4.4**

*bold text indicates exceedance of the level of concern

Table 5 Refined assessment for aquatic vascular plants (96 hr endpoint adjusted for uncertainty = 0.00011 mg a.e./L) using runoff and spray drift EECs

Runoff EEC for 80 cm depth (mg a.i./L)	Spray drift (% application)	Application method/ASABE Spray droplet quality	Spray drift EECs for 80 cm depth (mg a.i./L)	Risk quotient
0.002	N/A	N/A	N/A	**18.2**
N/A	3	Ground/coarse	0.00006	0.5
	17	Aerial/coarse	0.00034	**3.1**
	6	Ground/medium	0.00012	**1.1**
	23	Aerial/medium	0.00046	**4.2**

*bold text indicates exceedance of the level of concern

Table 6 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active ingredient endpoints*	Transformation products endpoints
CEPA toxic or CEPA toxic equivalent	Yes		Flucarbazone can be considered toxic to terrestrial invertebrates and aquatic organsims	Limited toxicity information is available for major transformation products. One ecotoxicity study available for effects of NMT on earthworms indicates NMT is not considered toxic to these organisms
Predominantly anthropogenic	Yes		-	-
Persistence	Soil	Half-life ≥ 182 days	Half-life = 11.4 – 92.5 days Flucarbazone does not meet the aquatic persistence criteria	No soil degradation information is available for major transformation products of flucarbazone
	Water	Half-life ≥ 182 days	Half-life = 873 - 1275 days Flucarbazone meets the aquatic persistence criteria	No aquatic degradation information is available for major transformation products of flucarbazone
	Sediment	Half-life ≥ 365 days	No data were available for the fate of flucarbazone in sediment	No sediment degradation information was available for major transformation products of flucarbazone

	Air	Half-life ≥ 2 days or evidence of long range transport	1.8 days (21 hrs) Not expected to persist in air thus not expected to undergo long range atmospheric transport	No air degradation information was available for major transformation products of flucarbazone
Bioaccumulation	Log K_{ow} ≥ 5		Log K_{ow} = -2.85 Flucarbazone is not expected to bioaccumulate	Log K_{ow} estimates for major transformation products of flucarbazone are listed as follows: Flucarbazone sulfonamide =1.42 Flucarbazone sulfonic acid = -0.12 *O*-desmethyl flucarbazone = 2.83 NMT = -0.22 NODT = -1.24 These transformation products are not expected to bioaccumulate.
	BCF ≥ 5000		Not available, based on Log K_{ow}, flucarbazone is not expected to bioaccumulate	Not available
	BAF ≥ 5000		Not available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No	No

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{ow}).

Appendix VIII Proposed label amendments for products containing flucarbazone

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements, and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

Label amendments for technical class products

On the primary display panel, replace "GUARANTEE" with "ACTIVE INGREDIENT".

The following label statements are proposed to be included under the heading **ENVIRONMENTAL PRECAUTIONS** for all registered flucarbazone technical grade active ingredients:

> "**TOXIC** to aquatic organisms."
>
> "**DO NOT** discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

Label Amendments for Commercial Class Products

On the primary display panel, replace "GUARANTEE" with "ACTIVE INGREDIENT".

Add to **DIRECTIONS FOR USE** for **Water-Soluble Packages**

Using Water-Soluble Packages Dissolved Directly in Spray tanks:
Water-Soluble Packages (WSPs) are designed to dissolve in water. Agitation may be used, if necessary, to help dissolve the WSP. Failure to follow handling and mixing instructions can increase your exposure to the pesticide products in WSPs.

"Handling Instructions

Follow these steps when handling pesticide products in WSPs.

1. Mix in spray tank only.
2. Handle WSP(s) in a manner that protects package from breakage and/or unintended release of contents. If package is broken, put on a minimum of coveralls, chemical-resistant gloves, chemical-resistant footwear, and a NIOSH-approved N95 (minimum) filtering facepiece respirator (dust mask) that is properly fit tested and then continue with mixing instructions.
3. Keep the WSP(s) in outer packaging until just before use.
4. Keep the WSP dry prior to adding to the spray tank.

5. Handle with dry gloves and according to the label instructions for PPE.
6. Keep WSP intact. Do not cut or puncture WSP.
7. Reseal the WSP outer packaging to protect any unused WSP(s).

Mixing Instructions

Follow the steps below when mixing this product, including if tank mixed with other pesticide products. If being tank mixed, the mixing directions 1 through 9 below take precedence over the mixing directions of the other tank mix products. All other directions for use of all tank mixed products should be followed provided they do not conflict. Do not tank mix this product with products that prohibit tank mixing or have conflicting mixing directions.

1. If a basket or strainer is present in the tank hatch, remove prior to adding the WSP to the tank.
2. Fill tank with water to approximately one-third to one-half of the desired final volume of spray.
3. Stop adding water and stop any agitation.
4. Place intact/unopened WSP(s) into the tank.
5. Do not spray water from a hose or fill pipe to break or dissolve the WSP(s).
6. Start mechanical and recirculation agitation from the bottom of tank without using any overhead recirculation, if possible. If overhead recirculation cannot be turned off, close the hatch before starting agitation.
7. Dissolving the WSP(s) may take up to 5 minutes or longer, depending on water temperature, water hardness and intensity of agitation.
8. Stop agitation before tank lid is opened.
9. Open the lid to the tank, exercising caution to avoid contact with dusts or spray mix, to verify that the WSPs have fully dissolved and the contents have been thoroughly mixed into the solution.
10. Do not add other allowed products or complete filling the tank until the bags have fully dissolved and pesticide is thoroughly mixed.
11. Once the WSP have fully dissolved and any other products have been added to the tank, resume filling the tank with water to the desired level, close the tank lid, and resume agitation.
12. Use the spray solution when mixing is complete.
13. Maintain agitation of the diluted pesticide mix during transport and application.
14. It is unlawful to use any registered pesticide, including WSPs, in a manner inconsistent with its label."

Based on the current occupational exposure and risk assessment, the following label statements are proposed to be included under the **PRECAUTIONS** section, and sub-section **PROTECTIVE CLOTHING** or **PERSONAL PROTECTIVE EQUIPMENT:**

For labels with use directions for ground application only:

> "Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Gloves are not required during application within a closed cab."

For labels with use directions for both ground and aerial application:

"Wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes during mixing, loading, application, clean-up and repair. Gloves are not required during application within a closed cab and/or cockpit."

The following label statements are proposed to be included under the section of **PRECAUTIONS** of all end use products:

> "**DO NOT** enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."
>
> "Apply only to agricultural crops when the potential for drift to areas of human habitation and human activity, such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."

Add to **ENVIRONMENTAL PRECAUTIONS**:

> "Toxic to aquatic plants and non-target terrestrial plants. Observe spray buffer zones specified under **DIRECTIONS FOR USE**.
>
> This product demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of this product in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination.
>
> To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.
>
> Avoid application when heavy rain is forecast.
>
> Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body."

Add to **DIRECTIONS FOR USE** (For PCP Numbers: 26447, 26448, 29500, 30342, 30580, 30663, 32602, 29558):

> "**Field sprayer application**: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Apply only by fixed-wing or rotary aircraft equipment which has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.

Label rates, conditions and precautions are product specific. Read and understand the entire label before opening this product. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.

Ensure uniform application. To avoid streaked, uneven or overlapped application, use appropriate marking devices."

Add to **DIRECTIONS FOR USE** for all commercial products

"As this product is not registered for the control of pests in aquatic systems, **DO NOT** use to control aquatic pests.

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

Add to **DIRECTIONS FOR USE** (PCP Number 30430 - Sierra® 2.0 Herbicide):

"**Field sprayer application**: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) medium classification. Reduce drift caused by turbulent wingtip vortices. Nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan.

Apply only by fixed-wing or rotary aircraft equipment which has been functionally and operationally calibrated for the atmospheric conditions of the area and the application rates and conditions of this label.

Label rates, conditions and precautions are product specific. Read and understand the entire label before opening this product. Apply only at the rate recommended for aerial application on this label. Where no rate for aerial application appears for the specific use, this product cannot be applied by any type of aerial equipment.

Ensure uniform application. To avoid streaked, uneven or overlapped application, use appropriate marking devices.

Use Precautions

Apply only when meteorological conditions at the treatment site allow for complete and even crop coverage. Apply only under conditions of good practice specific to aerial application as outlined in the National Aerial Pesticide Application Manual, developed by the Federal/Provincial/Territorial Committee on Pest Management and Pesticides.

Product Specific Precautions

Read and understand the entire label before opening this product. If you have questions, call the manufacturer listed on the product label or obtain technical advice from the distributor or your provincial agricultural representative. Application of this specific product must meet and/or conform to the following:
Volume: Apply the recommended rate in a minimum spray volume of 28 litres per hectare."

Spray buffer zones

The spray buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands), sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop		Spray Buffer Zones (metres) Required for the Protection of:		
			Freshwater Habitat of Depths:		Terrestrial Habitat:
			Less than 1 m	Greater than 1 m	
Field sprayer	Spring and winter wheat		2	1	1
Aerial (ASABE coarse spray quality	Spring and winter wheat	Fixed wing	5	1	20
		Rotary wing	5	2	25

Aerial (ASABE medium spray quality)	Spring and winter wheat	Fixed wing	15	3	40
		Rotary wing	15	4	35

The spray buffer zones presented in this table are for flucarbazone. As spray buffer zones are active specific, for coformulated products care must be taken to ensure the correct spray buffer zones remain on the label. For all non-coformulated products, the spray buffer zones for flucarbazone apply for both aquatic and terrestrial habitats.

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) spray buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASABE) category indicated on the labels for those tank mix partners.

The spray buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Spray Buffer Zone Calculator on the Pest Management Regulatory Agency web site.

Add under **STORAGE** for all commercial products:

"Store this product away from food or feed."

Add under **DISPOSAL:**

For recyclable Containers:

"Disposal of Container:

DO NOT reuse this container for any purpose. This is a recyclable container, and is to be disposed of at a container collection site. Contact your local distributor/dealer or municipality for the location of the nearest collection site. Before taking the container to the collection site:

1. Triple- or pressure-rinse the empty container. Add the rinsings to the spray mixture in the tank.

2. Make the empty, rinsed container unsuitable for further use.

If there is no container collection site in your area, dispose of the container in accordance with provincial requirements."

For returnable containers:

"Disposal of Container:

DO NOT reuse this container for any purpose. For disposal, this empty container may be returned to the point of purchase (distributor/dealer)."

For containers that can be refilled for the user by the distributor/dealer:

“Disposal of Container:

For disposal, this container may be returned to the point of purchase (distributor/dealer). It must be refilled by the distributor/dealer with the same product. **DO NOT** reuse this container for any other purpose.”

For all commercial products, add:

“Disposal of unused, unwanted product

For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in case of a spill, and for clean-up of spills.”

References

A. Information considered in the chemistry assessment

Studies/Information submitted by registrant

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3033488	2019, Product Identity and Composition of Flucarbazone-sodium Technical, DACO: 2.1, 2.11, 2.12, 2.2, 2.3, 2.3.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
3033489	2014, Five Batch Analysis of Active Ingredient and Impurities of Flucarbazone-sodium TC, DACO: 2.13
3033490	2018, Residual Content of in Flucarbazone-sodium Technical, DACO: 2.13.4
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1179288	1994, MKH 6562 study for acute dermal toxicity in rats, DACO: 4.2.2
1179289	1996, MKH 6562 study for acute inhalation toxicity in rats according to OECD No. 403, DACO: 4.2.3
1179290	1994, MKH 6562 study for skin and eye irritation/corrosion in rabbits, DACO: 4.2.4, 4.2.5
1179291	1994, MKH 6562 study for skin sensitization effect in guinea pigs (maximization test of Magnusson and Kligman), DACO: 4.2.6
1179292	1997, Trifluoromethoxysulfonamide (plant metabolite of MKH 6562) study for acute oral toxicity, DACO: 4.2.9
1179294	1997, MKH 6562 lactate conjugate (plant metabolite of MKH 6562) study for acute oral toxicity in rats, DACO: 4.2.9
1179295	1997, MKH 6562 sulfonamide alanine (plant metabolite of MKH 6562) study for acute oral toxicity in rats, DACO: 4.2.9
1179296	1998, MKH 6562 study on subchronic toxicity in B6C3F1 mice dietary administration over 3 months, DACO: 4.3.1
1179297	1998, MKH 6562 study for subchronic oral toxicity in rats (feeding study over 14 weeks and 5 weeks recovery period), DACO: 4.3.1
1179298	1996, MKH 6562 study for subacute oral toxicity in rats (feeding study), DACO: 4.3.3
1179299	1996, MKH 6562 study for subacute dermal toxicity in rats (four-week treatment), DACO: 4.3.5
1179300	1997, MKH 6562 subacute toxicity study in beagle dogs (4 week feeding study), DACO: 4.3.8
1179307	1998, MKH 6562 subchronic toxicity study in beagle dogs (13 week feeding study), DACO: 4.3.8
1179308	1995, MKH 6562 micronucleus test on the mouse, DACO: 4.5.7
1179309	1996, MKH 6562 test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro, DACO: 4.5.8
1179311	1998, MKH 6562 plaque-forming-cell assay in rats (feeding study over 4 weeks), DACO: 4.8

1179312	1998, MKH 6562 plaque-forming-cell assay in rats (feeding study over 4 weeks), DACO: 4.8
1179313	1996, MKH 6562 a liquid chromatographic method for the determination of MKH 6562 in dose mixtures, DACO: 4.8
1179314	1997, a liquid chromatographic method for the determination of MKH 6562 in animal ration, DACO: 4.8
1179315	1998, the homogeneity and stability of MKH 6562 in rodent ration, DACO: 4.8
1179316	1995, MKH 6562 orientative toxicologic study in mice to clarify the immunotoxic potential subacute two-week feeding study, DACO: 4.8
1179317	1994, MKH 6562 orientative toxicologic studies in rats acute oral toxicity in non-fasted animals subacute oral toxicity, two-week gavage administration
1179318	1998, A development toxicity study with MKH 6562 technical in the Sprague-Dawley rat, DACO: 4.5.2
1179320	1998, A development toxicity study with MKH 6562 in the Sprague-Dawley rat, DACO: 4.5.2
1179321	1996, A dose range-finding development toxicity study with MKH 6562 technical in the Sprague-Dawley rat, DACO: 4.5.2
1179322	1997, MKH 6562 developmental toxicity study in rabbits after oral administration, DACO: 4.5.3
1179323	1998, MKH 6562 developmental toxicity study in rabbits after oral administration, DACO: 4.5.3
1179324	1993, MHK 6562 salmonella/microsome test, DACO: 4.5.4
1179325	1996, MKH 6562 mutagenicity study for the detection of induced forward mutations in the V79-HPRT assay in vitro, DACO: 4.5.5
1179326	1996, MKH 6562 in vitro mammalian chromosome aberration test with Chinese hamster V79 cells, DACO: 4.5.6
1180148	1998, Trifluoromethoxysulfonamide (animal and plant metabolite of MKH 6562) study for acute oral toxicity in rats, DACO: 4.2.1
1180149	1998, MKH 6562 study for subchronic oral toxicity in B6C3F1 mice dietary administration over 3 months. Supplemental submission to AC no. 108199, DACO: 4.3.1
1180150	1998, MKH 6562 study for subchronic oral toxicity in rats (feeding study over 14 weeks and 5 weeks recovery period) supplemental submission to AC No. 108197, DACO: 4.3.1
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1180152	1998, MKH 6562 chronic toxicity study in beagle dogs (1 year feeding study). Supplemental submission to AC No. 108399, DACO: 4.3.2
1180153	1998, MKH 6562 chronic toxicity study in beagle dogs (1 year feeding study), Supplemental submission to AC No. 108399, DACO: 4.3.2
1180154	1998, MKH 6562 study on subacute toxicity in B6C3F1 mice (dietary administration over 4 weeks), DACO: 4.3.3
1180156	1997, MKH 6562 subacute toxicity study in beagle dogs (4 week feeding study) supplemental submission to AC No. 108186, DACO: 4.3.3
1180157	1998, MKH 6562 subchronic toxicity study in beagle dogs (13 week feeding study) supplemental submission to AC No. 108198, DACO: 4.3.1
1180158	1998, MKH 6562 combined chronic toxicity/carcinogenicity study in Wistar rats (dietary administration over 2 years), DACO: 4.4.4
1180166	1998, MKH 6562 combined chronic toxicity/carcinogenicity study in Wistar rats (dietary administration over 2 years), DACO: 4.4.4
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1180168	1998, MKH 6562 combined chronic toxicity/carcinogenicity study in Wistar rats (dietary administration over 2 years), supplemental submission to AC No. 108500. DACO: 4.4.4
1180169	1997, MKH 6562 oncogenicity study in B6C3F1 mice (dietary administration over 2 years), DACO: 4.4.3
1180174	1998, MKH 6562 oncogenicity study in B6C3F1 mice (dietary administration over 2 years), DACO: 4.4.3
1180175	1998, An acute oral neurotoxicity study with technical grade MKH 6562 in Fischer 344 rats, DACO: 4.5.11
1180176	1998, A subchronic dietary neurotoxicity screening study with technical grade MKH 6562 in Fischer 344 rats, DACO: 4.5.11
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1180191	1998, MKH 6562 pilot developmental toxicity study in rats after oral administration, DACO: 4.5.2
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1180194	1997, MKH 6562 developmental toxicity study in rabbits after oral administration, supplemental submission to AC No. 108182.
1180196	1998, The metabolism of [phenyl-UL-14C], DACO: 4.5.9
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1190317	1999, MKH 10868 metabolite of MKH 6562 Salmonella/microsome test plate incorporation and precipitation method, DACO: 4.5.4, 4.5.8
1190318	1999, An immunotoxicity study with MKH 6562 technical in the male Wistar rat, antibody plaque-forming cell assay, DACO: 4.8
1190319	1999, An immunotoxicity study with MKH 6562 technical in the female Wistar rat, antibody plaque-forming cell assay, DACO: 4.8
1190320	1999, An immunotoxicity study with MKH 6562 technical in the male Wistar rat, splenic T-cells, B-cells, and NK-cell assay, DACO: 4.8
1190321	1999, An immunotoxicity study with MKH 6562 technical in the female Wistar rat, splenic T-cells, B-cells, and NK-cell assay
1191196	1998, Oncogenicity study in B6C3F1 mice (dietary administration over 2 years) additional historical data on histopathology, supplemental to AC No. 108398, DACO: 4.4.3
1191197	1997, MKH 6562, subacute toxicity study in beagle dogs (4 week feeding study), supplemental submission to AC No. 108186, DACO: 4.3.8
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3225239	2018, USEPA flucarbazone-sodium. Draft human health risk assessment for registration review, DACO: 12.5
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C. Information considered in the dietary assessment

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1862472	Health Canada, 2009. Registration Decision (RD) document RD2009-02, Flucarbazone-sodium

3226458	United States Environmental Protection Agency, 2013, Flucarbazone-Sodium. Human Health Assessment Scoping Document in Support of Registration Review, DACO: 12.5
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D. Information considered in the occupational and non-occupational assessment

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1179330	1997, Aerobic Metabolism of [Phenyl-UL-14C]MKH 6562 in North Dakota Sandy Loam, DACO: 8.2.3.4.2
1179331	1998, Aerobic Metabolism of [Phenyl-UL-14C]MKH 6562 in Manitoba Sandy Loam, DACO: 8.2.3.4.2
1179332	1997, Degradation and Fate of [Phenyl-UL-14 C]MKH 6562 in Pond Water, DACO: 8.2.3.5.2
1179333	1998, Degradation and Fate of [Phenyl-UL-14 C]MKH 6562 in Pond Water, DACO: 8.2.3.5.2
1179334	1997, Aerobic Aquatic Biotransformation of [Triazolinon-3-14C] MKH6562, DACO: 8.2.3.5.2

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1179337	1995, Soil adsorption/desorption of MKH 6562, DACO: 8.2.4.2
1179342	1997, Acute Toxicity of MKH 6562 (tech.) to Earthworms (Eisenia fetida), DACO: 9.2.3.1
1179343	1996, Acute Toxicity of MKH 6562 to the Water flea (Daphnia magna) Under Static Conditions, DACO: 9.3.2
1179344	1996, Acute Toxicity of MKH 6562 (tech.) to Earthworms (Eisenia fetida), DACO: 9.3.3
1179345	1995, Acute Toxicity of MKH 6562 Technical to the Rainbow trout (Oncorhynchus mykiss) Under Static-Renewal Conditions, DACO: 9.5.2.1
1179346	1995, Acute Toxicity of MKH 6562 Technical to the Bluegill (Lepomis macrochirus) Under Static-Renewal Conditions, DACO: 9.5.2.2
1179347	1995, Technical MKH 6562: An acute oral LD50 with Northern bobwhite (Colinus virginianus), DACO: 9.6.2.1
1179348	1997, Technical MKH 66562: A Subacute Dietary LC50 With Northern Bobwhite, DACO: 9.6.2.4
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1179351	1996, Toxicity of MKH 6562 Technical to the Freshwater Green Alga Selenastrum capricornutum, DACO: 9.8.2
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1179355	1997, Toxicity of MKH 6562 70WG to Lemna gibba G3 Under Spray Application Conditions, DACO: 9.8.6
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1180134	1998, Tier 2 Seedling Emergence and Vegetative Vigor: Non-target Phytotoxicity Study Using MKH 6562 70% WG, DACO: 9.8.4

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1180202	1998, Aerobic Metabolism of [Triazolinone-3-14C]MKH 6562 in North Dakota Sandy Loam, DACO: 8.2.3.4.2
1180203	1998, Anaerobic Aquatic Metabolism of [Phenyl-UL-14C] MKH 6562 at 5°C, DACO: 8.2.3.5.6
1180204	1998, Adsorption/Desorption of [14C]N-Methyltriazolinone, an [14C]MKH 6562 Metabolite, in Four Soil Types, DACO: 8.2.4.2
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1180209	1998, Adsorption/Desorption of [14C]Flucarbazone Sulfonic Acid, an [14C]Flucarbazone Metabolite, in Four Soil Types, DACO: 8.2.4.2
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1180211	1998, Leaching of Aged [Phenyl-UL-14C]MKH 6562 Residues Through Tiffany Sandy Loam, DACO: 8.2.4.3.2
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