Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note REG2003-02

Picolinafen

The active ingredient picolinafen and associated end-use product AC 900001 Water-Dispersible Granular Herbicide, for the control of broadleaf weeds in spring wheat (including durum) and barley, grown in the Canadian prairie provinces and the Peace River Region of British Columbia, have been granted temporary registration under Section 17 of the Pest Control Products (PCP) Regulations.

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

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registrations for picolinafen Technical and the associated end-use product (EP), AC 900001 Water-Dispersible Granular Herbicide manufactured by BASF, for the control of broadleaf weeds in spring wheat (including durum) and barley, grown in the Prairie Provinces and the Peace River Region of British Columbia. These products are not currently registered in the United States.

A maximum residue limit (MRL) of 0.05 ppm will be proposed for residues of picolinafen on wheat and barley grain.

Methods for analysing picolinafen in environmental media are available to research and monitoring agencies upon request to the PMRA.

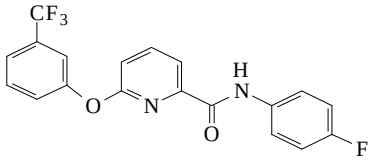
BASF Canada Inc. will be carrying out additional residue chemistry and environmental chemistry studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

The data package was provided in electronic format and the contents were formatted in accordance with an international standard developed under the auspices of the Organisation for Economic Co-operation and Development (OECD).

Table of Contents

1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Active substance	Picolinafen
Function	Herbicide
Chemical name 1. International Union of Pure and Applied Chemistry 2. Chemical Abstracts Service (CAS)	 4′-Fluoro-6-[(α,α,α-trifluoro-m-tolyl)oxy]picolinanilide or N-(p-Fluorophenyl)-6-[(a,a,a-trifluoro-m-tolyl)oxy]picolinamide N-(4-Fluorophenyl)-6-[3-(trifluoromethyl)phenoxy]-2-pyridinecarboxamide
CAS number	137641-05-5
Molecular formula	$C_{19}H_{12}F_4N_2O_2$
Molecular weight	376.3
Structural formula	
Nominal purity of active substance	99.4% (Limits: 96–100%)
Identity of relevant impurities of toxicological, environmental, or other significance	The technical grade picolinafen contains no impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances as identified in App. II of DIR99-03.

1.2 Physical and chemical properties of active substances and end-use product (EP)

Table 1.2.1 Technical product: Picolinafen

Property	Result	Comment
Colour and physical state	Grey-yellow to sand colour powder solid	
Odour	Musty smell, similar to phenol	
Melting point or range	107.2–107.6°C	
Boiling point or range	Decomposed at >230°C.	
Density	1.45	
Vapour pressure at 20°C	Temp. (°C) v.p. (Pa) 70 2.36×10^{-4} 80 8.49×10^{-4} 90 2.44×10^{-3} 20 1.6×10^{-7} (estimated)	Non-volatile under field conditions
Henry's Law Constant at 20°C	$K_H = 1.60 \times 10^{-3}$ Pa m^3/mole	Non-volatile from moist soil and water surfaces
Ultraviolet (UV) – visible spectrum	λ (nm) ϵ ($l \cdot mol^{-1} \cdot cm^{-1}$) 202 39 500 230 (shoulder) 14 600 290 13 000 No absorption at 350 – 400 nm was observed.	Potential for photolysis in the UV range
Solubility in water at 20°C	Solvent g/L pH 5 buffer 3.8×10^{-5} pH 7 buffer 4.7×10^{-5} pH 9 buffer 3.8×10^{-5} deionized water* 3.9×10^{-5}	Insoluble in water
Solubility (g/100 mL) in organic solvents at 20°C	Solvent Solubility acetone 5.7 dichloromethane 76.4 ethyl acetate 46.4 n-hexane 0.38 methanol 3.04	
n-Octanol–water partition coefficient (K_{ow})	Solvent log K_{ow} deionized water 5.37 pH 5 buffer 5.36 pH 7 buffer 5.43 pH 9 buffer 5.36	Potential for bioaccumulation but studies did not support this
Dissociation constant (pK_a)	None between the pH values of 2 and 12	Does not dissociate at environmentally relevant pH values

Property	Result	Comment
Stability (temperature, metal)	Stable during storage at 45°C for >3 months, at 37°C for >1 year The TGAI has no oxidizing properties.	

Table 1.2.2 End-use product: SF 09617

Property	Result
Colour	Brown
Odour	Faint, musty smell
Physical state	Free-flowing granules
Formulation type	Wettable granules
Guarantee	75% (limits: 73–77%)
Formulants	The product does not contain any U.S. EPA List-1 formulant or formulant known to be a TSMP Track-1 substance.
Container material and description	On label: Soluble bags, 4 × 267 g. In SPSF: Plastic, 0.05–5 kg.
Bulk density	Pour bulk density: 628 kg/m^3 Tap bulk density: 693 kg/m^3
pH of 1% dispersion in water	9.6
Oxidizing or reducing action	No evidence for oxidizing properties
Storage stability	Stable after 10 months in paper/SI/PE/block bottom bags and in HDPE bottles Freezer storage stability studies indicated that residues of picolinafen were stable at −18°C for up to 12 months in cereal matrices.
Explodability	No evidence for explosive properties

1.3 Details of uses

AC 900001 Herbicide is proposed as a foliar herbicide to be applied post-emergence for the control of broadleaf weeds in cereal crops—in spring wheat (*Triticum aestivum*), durum wheat (*Triticum durum*) and barley (*Hordeum vulgare*)—in the Prairie Provinces and Peace River Region of British Columbia. AC 900001 Herbicide is proposed as: an alone treatment; in a 2-way tank mix with 2,4-D ester LV500, LV600, LV700 (numerous registrations); or in a 3-way tank mix with 2,4-D ester plus Assert 300SC (active ingredient (a.i.) imazamethabenz) herbicide (PCP Reg. No. 21032). The product is to be applied by ground application and not more than once per season.

As an alone treatment, 50 g a.i./ha AC 900001 claims control of redroot pigweed (*Amaranthus retroflexus*) and stinkweed (*Thlapsi arvense*) and the suppression of volunteer canola (*Brassica napus* spp.), wild mustard (*Sinapis arvensis*), kochia (*Kochia scoparia*) and shepherd's purse (*Capsella bursa-pastoris*).

In a 2-way tank mix of 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester, the label claims control of wild buckwheat (*Polygonum convolvulus*) and kochia (*Kochia scoparia*) and the suppression of cleavers (*Galium spurium*) and chickweed (*Stellaria media*), plus the weeds listed for the AC 900001 alone treatment and the susceptible or easy-to-control weeds listed on the 2,4-D ester label.

In a 3-way tank mix, 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester plus 400 g a.i./ha Assert 300SC, the label claims control of the broadleaf weeds listed for the 2-way tank mix plus wild oats.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Product	Analyte	Method ID	Method Type	Linearity range	Recovery (%)	RSD (%)	LOQ (%)	Method
Technical	picolinafen	CFS-DPA M27/1/N	HPLC/UV at 290 nm	0.05–0.25 mg/mL	N/A	0.77	N/R	Accepted
Technical	Major impurities	CFS-DPA M28/3F	HPLC/UV at 220 nm	0.02–0.7%	87–114	1.2–5.8	0.001–0.03	Accepted

2.2 Methods for formulation analysis

Product	Analyte	Method ID	Method Type	Linearity range	Mean Recovery (%)	RSD (%)	Method
SF 09617	picolinafen	FAMS 086-01	HPLC/UV at 290 nm	4.8–7.2 mg/50 mL	100.1% (n = 6)	0.23	Accepted

2.3 Analytical methods for residue analysis

Two analytical methods, GC/NPD Method FAMS 079-01 and GC/MS Method M3313, were submitted for the determination of the residue of concern (ROC) in plant matrices. Method FAMS 079-01 was used for data gathering while Method M3313 was used for data gathering and proposed for enforcement. The method limits of quantification (LOQs) for picolinafen were the same for both methods: 0.05 mg/kg. Good linearity (correlation coefficient, r^2 >0.995), was observed in the range of 0.125–2000 ng/mL for picolinafen. The coefficients of variation (CVs) measured with respect to recoveries following spiking at the LOQ did not exceed 20%, indicative that methods have good repeatability.

Representative chromatograms of control samples showed no peaks above the chromatographic background. The spike sample chromatograms from both methods contained a well defined and symmetrical peak in the area of analytical interest with no carry-over to the following chromatograms. The interlaboratory validation (ILV) demonstrated good reliability and reproducibility of the GC/MS Method M3313 for the determination of residues of picolinafen in plant matrices.

For animal matrices, only one analytical method was submitted for data gathering and enforcement purposes: Method FAMS 109-01. The limits of detection (LODs) and the LOQs were reported to be 0.002 mg/kg and 0.02 mg/kg, respectively, for muscle, fat, and egg, and 0.001 mg/kg and 0.01 mg/kg, respectively, for milk. Good linearity (correlation coefficient, r^2 >0.9992), was observed in the range of 5–100 ng/mL for picolinafen. The CVs measured with respect to recoveries following spiking at the LOQ were within 20%, indicative of the method's good repeatability. Representative chromatograms of control samples showed no peak above the chromatographic background. The spike sample chromatograms from both methods contained a well defined and symmetrical peak in the area of analytical interest with no carry-over to the subsequent chromatograms. The ILV demonstrated good reliability and reproducibility for the determination of residues of picolinafen and CL 153815 in milk and tissues.

2.3.1 Methods for environmental residue analysis

Matrix	Method ID	Method	Spike level	Overall mean % Recovery (n)				LOQ	Method
				picolinafen	RSD (%)	CL 153815	RSD (%)		
Soil	M 3314	LC/MS	5 & 50 ppb	93.6 (8)	5.8	82.6 (8)	11.1	5 ppb	Accepted
Sediment		The applicant requested to use the soil method. The request was accepted based on the following: 1. No new transformation products formed in sediment. 2. Acetone-aqueous acetic acid solution is used as extraction solvent for soil.							Waiver accepted
Drinking water	P-14.106	GC/ECD	0.1 & 1.0 ppb	106 (10)	2	–	–	0.1 ppb	Accepted

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

A detailed review of the toxicological database available for the technical grade active ingredient (TGAI), picolinafen, and the end-use product (EP), AC 900001 750 g/kg WG (SF 09617) Herbicide, has been completed. Data submitted were complete and comprehensive, and included the full battery of studies currently required for registration of a new TGAI and EP based on Use Site Categories (USC) 13 and 14. The scientific and

regulatory quality of the toxicology database is considered sufficient to adequately define the toxicity of this chemical for its intended purpose.

Picolinafen was incompletely absorbed, up to 60 and 84% of the administered oral dose for males and females, respectively, following low-dose administration (10 mg/kg bw). At the high dose (1000 mg/kg bw), absorption decreased to approximately 17–25% of the administered dose for both sexes. The decreased absorption at the high dose was considered to be due to saturation of absorption processes. The majority was absorbed within 24 h following single or multiple low-dose administration and within 48 h following single high-dose administration. No significant tissue accumulation was evident; less than 0.5% of the administered dose remained in the tissue/carcass at sacrifice (168 hours post-dosing). The majority of radioactivity was eliminated within 24 (greater than 75% of administered dose) and 48 (greater than 80% of the administered dose) hours following low- and high-dose administration, respectively. Fecal/biliary excretion was the major route of excretion of metabolites of the pyridine-labelled picolinafen, whereas urinary excretion was the major route of excretion of metabolites of the aniline-labelled picolinafen. Picolinafen was extensively metabolized with hydrolytic cleavage of amide bond followed by a variety of biotransformation including N-acetylation, hydroxylation, methylation, dehalogenation, and formation of mercapturic and sulfate conjugates. In the feces the major residue was identified as the parent compound, picolinafen. The major urinary metabolites were identified as CL 153815 and its glucuronic acid conjugate, the sulfate conjugate of 2-amino-5-fluorophenol and the sulfate conjugate of 4′-hydroxyacetanilide (CL 1009639). The major biliary metabolites were identified as CL 153815 and the glucuronide ester of CL 153815, p-fluoroaniline, 4′-fluoroacetanilide and 4′-hydroxyacetanilide. There were slight gender differences in absorption, metabolism, and excretion.

Technical picolinafen has low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is minimally irritating to the eyes, non-irritating to the skin, and is not considered to be a skin sensitizer. The EP, AC 900001 750 g/kg WG (SF 09617) Herbicide, has low acute toxicity by the oral, dermal, and inhalation routes, is minimally irritating to the eyes, mildly irritating to the skin, and is not considered to be a skin sensitizer. The formulants were on the United States (U.S.) Environmental Protection Agency (EPA) List 3, 4A, or 4B, and/or the Canadian Registered Products List, and were of no toxicological concern.

Picolinafen was tested in a battery of in vitro (bacterial and mammalian cell gene mutation assays and mammalian cells chromosomal aberration assay) and in vivo (mouse micronucleus assay) mutagenicity studies. There was no evidence of genotoxicity potential in any of these assays; therefore, the weight of evidence suggests that picolinafen was not genotoxic under the conditions of the tests performed.

The subchronic and chronic toxicity of picolinafen was investigated in the mouse, rat, and dog. A 28-day repeat-dose dermal toxicity study was also carried out in rats. Following subchronic and chronic dietary exposure, treatment-related hematological findings, increased spleen and/or liver weights and histopathological findings indicative of

regenerative hemolytic anemia were noted for all species tested. Similar findings were also noted in the rat 2-generation reproduction study, in the rat and rabbit developmental studies, and in the 28-day repeat dose dermal toxicity study. The rat appears to be the most sensitive species with NOAELs of 10.5, 6.4, and 2.4 mg/kg bw/d following 28-day, 90-day, and 2-year dietary administration, respectively.

Hematological findings were generally characterized by lower red blood cell (RBC) count, hemoglobin (HGB), and hematocrit (HCT), with associated increases in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and reticulocyte counts. Other hematological findings associated with hemolytic anemia included significantly elevated methemoglobin levels and Heinz body formation, and significantly reduced oxyhemoglobin levels. Elevated methemoglobin levels and Heinz body formation are indicative of oxidative hemolysis of red blood cells. Changes in methemoglobin and oxyhemoglobin levels and Heinz body formation were generally noted at the higher dose levels in mice (at 1000 ppm and above following 28-day and 90-day dietary administration) and rats (at 1000 ppm following 28-day dietary administration). Erythrocyte osmotic fragility was significantly lower for rats following 28-day dietary administration at a dose level of 1000 ppm. This was most likely associated with Heinz body attachment to the RBC membrane and with the increased population of circulating immature cells, as indicated by the increase in reticulocyte counts noted at this dose level. Increased red blood cell distribution width and diameter were noted in rats following 28-day dietary administration at 1000 ppm. This correlated with elevated reticulocyte counts.

Histopathological findings were generally characterized by increased incidence/severity of hemosiderin deposition in the spleen and/or Kupffer cells of the liver and extramedullary hematopoiesis in the spleen and/or liver. Under normal physiological conditions a certain amount of hemosiderin deposition is routinely observed in the spleen due to normal breakdown of effete red blood cells; however, for all species tested, increased incidence/severity were noted for both sexes at the higher dose levels. The increased incidence/severity of extramedullary hematopoiesis was most likely a compensatory response to the increased hemolysis of red blood cells noted for all species tested. Other histopathological findings associated with regenerative hemolytic anemia included increased erythropoietic activity in the bone marrow and liver at higher doses. This was noted in rats following 28-day dietary administration at 1000 ppm and was indicated by a change in the myeloid:erythroid ratio from 2:1 in the controls to 1:1 in rats at 1000 ppm. For males, this shift to a more immature, stronger population of red cells at 1000 ppm was considered to account for the slight but significant decrease in erythrocyte osmotic fragility. For females, this correlated with an increased incidence of erythropoiesis in the bone marrow (femur/joint and sternum).

The histopathological findings were often observed in the absence of hematological effects, particularly at lower doses. This was most likely due to compensatory mechanisms adequately compensating for increased hemolysis of red blood cells. At the higher doses, these compensatory mechanisms may not have been sufficient to compensate for the increased hemolysis of red blood cells and, therefore, anemia was manifest. The presence of

hemolytic anemia following exposure to picolinafen was most likely due to the aniline group. Hemoglobin may be oxidized to methemoglobin in the presence of oxidant compounds such as aniline when given in sufficient levels in vivo. In addition, oxidant compounds such as aniline can also lead to Heinz body formation. The increase in methemoglobin and Heinz body formation can lead to an increased susceptibility of the red blood cell to hemolysis.

In rats, serum bilirubin levels were significantly elevated in both sexes following 28-day dietary administration at 1000 ppm. Elevated serum bilirubin levels were also noted in dogs following 90-day dietary administration at 2500 ppm. In the absence of any alterations in other liver function markers, this was considered to reflect increased RBC hemolysis and hemoglobin breakdown observed in these animals. Elevated serum bilirubin levels were not observed in mice. Gross pathological findings associated with the anaemic state were generally limited to discolouration of the spleen, liver, kidney, lungs, heart, or small intestines in all species tested.

Although findings indicative of hemolytic anemia were noted in dogs following 90-day and 1-year dietary administration, the main target organ appeared to be the thyroid as indicated by increased thyroid weight, diffuse hypertrophy of the thyroid follicular epithelial cells, and scattered foci of thyroid follicular cell hyperplasia, at 500 ppm (17.3 and 20.2 mg/kg bw/d and above for males and females, respectively) and above following 90-day dietary administration and at 1500 ppm (42.7 and 47.1 mg/kg bw/d for males and females, respectively) and above following 1-year dietary administration (the differences noted following 90-day and 1-year dietary administration were due to dose selection). Hormone levels (thyroxine, tri-iodothyronine and thyroid stimulating hormone [TSH]) were not determined. Lower body weight and/or body-weight gain were also noted in dogs at 2500 ppm (equal to 87.5 and 92.1 mg/kg bw/d for males and females, respectively) following 90-day dietary administration and at 150 ppm (1.7 and 1.8 mg/kg bw/d and above for males and females, respectively) and above following 1-year dietary administration. The NOAEL following 90-day dietary administration was 50 ppm (equal to 1.7 and 1.8 mg/kg bw/d for males and females, respectively). The NOAEL following 1-year dietary administration was 50 ppm (equal to 1.4 and 1.6 mg/kg bw/d for males and females, respectively).

Following subchronic and chronic administration, mice also exhibited treatment-related findings in the liver, including centrilobular hepatocellular hypertrophy and hepatocellular vacuolation. These were noted following 28-day, 90-day and 78-week dietary administration. The NOAELs for mice were 23.4, 10.2, and 6.9 mg/kg bw/d following 28-day, 90-day, and 78-week dietary administration, respectively.

In the 78-week dietary study, there was no evidence to indicate that picolinafen was oncogenic in the mouse. In the rat 2-year dietary study, there was a non-statistically significant, increased incidence of benign neoplasms (benign pheochromocytomas) in the adrenal gland medullary region for males at 500 ppm (highest dose tested). The incidence was within recent historical control data for benign medullary neoplasms. In addition, there

was no decrease in the time-to-appearance of the induced tumour and no dose-response relationship in proliferative changes usually associated with neoplasms, benign or malignant, in the adrenal medulla. Published literature indicates that proliferative lesions of the adrenal medulla in male rats occurs at relatively high incidences and can be spontaneous (age-related) in nature. Based on these findings, the slight increased incidence of benign neoplasms in the adrenal gland medullary region noted for males at 500 ppm, was most likely spontaneous in nature and not treatment-related. The weight of evidence suggests that picolinafen is not likely to be oncogenic in humans.

There was no evidence in the toxicology database to suggest a significant increase in toxicity with increased duration of exposure in mouse, rat, or dog. In addition, there was no evidence in the toxicology database to indicate a significant difference in gender sensitivity.

In a 4-week repeat-dose dermal toxicity study in the rat, treatment-related hematological findings, increased spleen weights, and histopathological findings indicative of hemolytic anemia were noted for both sexes at 100 mg/kg bw/d and above. Hematological findings were first apparent at 1000 mg/kg bw/d by day 5 and appeared to be reversible following an 8-week recovery period. The NOAEL for systemic toxicity was 75 mg/kg bw/d.

In the rat 2-generation reproduction study, reproduction function, reproductive parameters and litter parameters were not influenced by treatment in the first and second generation (P1/P2) parental animals at any dose level up to and including 500 ppm (equal to 39 and 42 mg/kg bw/d in males and females, respectively), the highest dose tested. Hematological findings, increased spleen weights, and histopathological findings indicative of regenerative hemolytic anemia were noted for P1/P2 males and females at 250 ppm (equal to 19 and 21 mg/kg bw/d for males and females, respectively) and above. Hematological findings including lower red blood cell count, hemoglobin, and hematocrit were also noted for male and female second generation (F2) pups at 250 ppm and above on lactation day 21 (only time point evaluated). Although the hematological findings noted in the F2 offspring may be secondary to maternal toxicity, a direct treatment-related effect cannot be dismissed; therefore, these findings were considered to be toxicologically relevant. The NOAEL for parental and offspring toxicity was 50 ppm (equal to 3.7 and 4.0 mg/kg bw/d in males and females, respectively). On the basis of the parental and offspring NOAELs in the rat 2-generation reproductive toxicity study (one litter/generation), there was no indication that neonates were quantitatively more sensitive than adults to the toxic effects of picolinafen.

In the rat and rabbit developmental toxicity studies, hematological findings, increased spleen weights, and histopathological findings indicative of regenerative hemolytic anemia were noted in the rats at 100 mg/kg bw/d and above, and in the rabbits at 20 mg/kg bw/d and above. The NOAEL for maternal toxicity was 50 mg/kg bw/d for rats and 5 mg/kg bw/d for rabbits. In the rat developmental toxicity study, the NOAEL for developmental toxicity was 1000 mg/kg bw/d, the highest dose tested, based on the absence of any adverse treatment-related effects on the developmental parameters examined. In the rabbit

developmental study, there was a possible slight decrease in embryonal-fetal viability manifest as slight increases in abortion (1 on day 21, 1 on day 23), post-implantation loss, total number of resorptions (early and late), and mean resorption rate, at 50 mg/kg bw/d. Although these effects on embryonal-fetal viability were not statistically significant from controls and were within historical control range for animals of this strain, a treatment-related effect could not be dismissed since the increased incidence was noted at the highest dose tested. The NOAEL for developmental toxicity was 20 mg/kg bw/d, based on a possible slight decrease in embryonal-fetal viability at 50 mg/kg bw/d, the highest dose tested. On the basis of the maternal and developmental NOAELs in the rat and rabbit developmental toxicity studies, there was no quantitative evidence in either species to indicate an increased susceptibility of the fetus to *in utero* exposure to picolinafen. There was no evidence of any treatment-related irreversible structural changes in either species; therefore, picolinafen was not considered to be teratogenic in rats or rabbits. There was no evidence of any treatment-related developmental findings in either species.

The treatment-related findings noted in the thyroid (increased thyroid weight, diffuse hypertrophy of the thyroid follicular epithelial cells, and scattered foci of thyroid follicular cell hyperplasia) in dogs following 90-day and 1-year dietary administration may be suggestive of a neurotoxicity potential. Similar lesions were not observed in the rat (including neonates) or mouse following subchronic or chronic dietary exposure and there was no other evidence in any species tested to indicate a neurotoxicity potential. Thyroid hormone (thyroxine, tri-iodothyronine, and TSH) levels were not determined. Thyroid hormones are crucial to normal growth and development in the central nervous system and in the absence of the hormone, brain development can be retarded; therefore, in the absence of thyroid hormone data and in the absence of any human data, these lesions cannot be disregarded and must be considered relevant to humans.

3.2 Determination of acceptable daily intake (ADI)

The most appropriate NOAEL of 1.4 mg/kg bw/d in the 1-year dietary study in dogs is recommended as the basis for the acceptable daily intake (ADI). Treatment-related findings at the LOAEL (next highest dose level) included lower body weight and body-weight gain for males (approximately 20 and 48%, respectively). As a safety factor of 100 to account for intra- and inter-species variations was considered to be adequate, no additional safety factor is required. The recommended ADI is 0.014 mg/kg bw/d.

$$\text{ADI} = \frac{\text{NOAEL}}{\text{SF}} = \frac{1.4 \text{ mg/kg bw/d}}{100} = 0.014 \text{ mg/kg/day of picolinafen}$$

Margin of Exposure (MOE) for other critical endpoint(s): calculated as NOAEL ÷ ADI:

Developmental Toxicity:	NOAEL = 20 mg/kg bw/d (rabbit). The MOE for developmental toxicity is 1428 compared to the ADI.

2-generation reproduction study:

Reproductive Toxicity:	NOAEL = 39 mg/kg bw/d. The MOE is 2785 compared to the ADI.
Offspring Toxicity:	NOAEL = 3.7 mg/kg bw/d The MOE is 264 compared to the ADI

Hematological and histopathological findings indicative of regenerative hemolytic anemia were noted in all species tested. The most sensitive species appears to be the rat. The most appropriate NOAEL for regenerative hemolytic anemia is 50 ppm (equal to 2.4 and 3.0 mg/kg bw/d for males and females, respectively), as determined in the 2-year rat dietary study. The MOE for regenerative hemolytic anemia is 171 compared to the ADI.

In the dog, treatment-related effects were noted in the thyroid in the 28-day, 90-day, and 1-year dietary studies. Treatment-related findings included increased thyroid weight, enlarged thyroid, diffuse hypertrophy of the thyroid follicular epithelial cells, and scattered foci of thyroid follicular cell hyperplasia. The most appropriate NOAEL for thyroid effects is 150 ppm (equal to 4.4 and 5.7 mg/kg bw/d for males and females, respectively). The MOE for thyroid effects is 314 compared to the ADI.

3.3 Acute reference dose (ARD)

An acute reference dose (ARD) was not established since picolinafen was considered unlikely to present an acute hazard. There was no significant treatment-related finding in the acute, short-term, 2-generation reproduction or developmental toxicity studies to indicate a concern in acute dietary risk assessment.

3.4 Toxicological endpoint selection—occupational and bystander risk assessment

Technical picolinafen has low acute toxicity by the oral, dermal, and inhalation routes of exposure, is minimally irritating to the eyes and non-irritating to the skin, and is not considered to be a skin sensitizer. The EP, AC 900001 750 g/kg WG (SF 09617) Herbicide, has low acute toxicity by the oral, dermal, and inhalation routes, is minimally irritating to the eyes and mildly irritating to the skin, and is not considered to be a skin sensitizer.

Picolinafen was incompletely absorbed, up to 60 and 84% of the administered dose for males and females, respectively, following low-dose administration (10 mg/kg bw). At the high dose (1000 mg/kg bw), absorption decreased to approximately 17–25% of the administered dose for both sexes. No significant tissue accumulation was evident (less than 0.5% of the administered dose remained in the carcass at 168 hours post-dosing). The majority of radioactivity was eliminated within 24 to 48 hours following low- and high-dose administration, respectively. Picolinafen was extensively metabolized. There were gender differences in absorption, metabolism, and excretion.

Following subchronic and chronic dietary exposure, treatment-related hematological and histopathological findings indicative of regenerative hemolytic anemia were noted for all species tested. Similar findings were also noted in the rat 2-generation reproduction study and in the rat and rabbit developmental studies. Hematological findings were generally characterized by lower red blood cell count, hemoglobin, and hematocrit, with associated increases in mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and reticulocyte counts. Histopathological findings were generally characterized by increased incidence/severity of hemosiderin deposition in the spleen and/or Kupffer cells of the liver and extramedullary hematopoiesis in the spleen and/or liver. The rat appears to be the most sensitive species with NOAELs of 10.5, 6.4, and 2.4 mg/kg bw/d following 28-day, 90-day, and 2-year dietary administration, respectively.

Although findings indicative of hemolytic anemia were noted in dogs following 90-day and 1-year dietary administration, the main target organ appeared to be the thyroid, as indicated by increased thyroid weight, diffuse hypertrophy of the thyroid follicular epithelial cells, and scattered foci of thyroid follicular cell hyperplasia. Thyroid hormones (thyroxine, tri-iodothyronine, and TSH) are crucial to normal growth and development in the central nervous system and in the absence of thyroid hormones, brain development can be retarded; however, hormone levels were not determined. Similar lesions were not observed in the rat (including neonates) or mouse following subchronic or chronic dietary exposure and there was no other evidence in any species tested to indicate a neurotoxicity potential. In the absence of any thyroid hormone data and in the absence of any human data, these lesions cannot be disregarded and must be considered relevant to humans. The most appropriate NOAEL for the treatment-related findings noted in the thyroid in dogs is 4.4 mg/kg bw/d as indicated in the 1-year dietary study.

Following subchronic and chronic administration, treatment-related findings were also noted in the liver and included centrilobular hepatocellular hypertrophy and hepatocellular vacuolation. These findings were only noted in mice with NOAELs of 23.4, 10.2, and 6.9 mg/kg bw/d following 28-day, 90-day, and 78-week dietary administration, respectively.

In a rat 4-week repeat-dose dermal toxicity study, the NOAEL for systemic toxicity was 75 mg/kg bw/d based on hematological and histopathological findings indicative of hemolytic anemia at the LOAEL, 100 mg/kg bw/d (next highest dose level). There was no treatment-related finding in the thyroid.

There was no evidence in the toxicology database to suggest a significant increase in toxicity with increased duration of exposure in mouse, rat, or dog. In addition, there was no evidence in the toxicology database to indicate a significant difference in gender sensitivity.

In the rat 2-generation (one litter/generation) reproduction study, hematological and histopathological findings indicative of regenerative anemia were noted in P1/P2 parental

animals and in F2 pups at 19 mg/kg bw/d and above. The NOAEL for parental and offspring toxicity was 3.7 mg/kg bw/d. On the basis of the parental and offspring NOAELs, there was no indication that neonates were quantitatively more sensitive than adults to picolinafen. Reproduction function, reproductive parameters, and litter parameters were not influenced by treatment.

In the rat and rabbit developmental toxicity studies, hematological and histopathological findings indicative of regenerative hemolytic anemia were noted in rats at 100 mg/kg bw/d and above, and in rabbits at 20 mg/kg bw/d and above. The NOAEL for maternal toxicity was 50 mg/kg bw/d for rats and 5 mg/kg bw/d for rabbits. In the rat, the NOAEL for developmental toxicity was 1000 mg/kg bw/d, the highest dose tested, based on the absence of any adverse treatment-related effects on the developmental parameters examined. In the rabbit, there was a possible slight decrease in embryonal-fetal viability, manifest as slight increases in abortion (1 on day 21, 1 on day 23), post-implantation loss, total number of resorptions (early and late), and mean resorption rate at 50 mg/kg bw/d; however, the differences from controls were not statistically significant and the values were within historical control range for animals of this strain. The NOAEL for developmental toxicity was 20 mg/kg bw/d, the highest dose tested. On the basis of the maternal and developmental NOAELs in the rat and rabbit developmental toxicity studies, there was no evidence in either species to indicate a quantitative increase in susceptibility of the fetus to *in utero* exposure to picolinafen. There was no evidence of any treatment-related irreversible structural changes in either species; therefore, picolinafen was not considered to be teratogenic in rats or rabbits.

Occupational exposure will be predominately via the dermal route, and of short- to intermediate-term duration. Although a 4-week repeat dose dermal toxicity study is available, it is not considered adequate for occupational and bystander risk assessment since it does not adequately account for the treatment-related findings noted in the thyroid in dogs following 90-day and 1-year dietary administration. To account for these findings, it is recommended that the dog 90-day dietary study be used for the proposed exposure scenarios. The recommended NOAEL is 1.7 mg/kg bw/d. A safety factor of 100 to account for intra- and inter-species variations is considered to be adequate, and no additional safety factor was used because there was an adequate MOE to the NOAEL of 4.4 mg/kg bw/d for thyroid effects in the 1-year dietary dog study.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

AC 900001 (EP) is a water-dispersible granular formulation packaged in water soluble packets and has a guarantee of 750 g picolinafen/kg. The product is proposed for use on spring wheat, including durum, and barley to control broadleaf weeds. Application would be post-emergent, using ground equipment only. The proposed application rate is

50 g a.i./ha with a maximum of one application per season. AC 900001 may be tank mixed with 2,4-D ester and Assert 300SC Wild Oat Herbicide.

The label specifies that handlers wear chemical-resistant gloves and dust- or splash-proof goggles or face shield during mixing/loading, clean-up, and repair activities. No re-entry interval is specified. A preharvest interval of 60 days is proposed for AC 900001. The label also proposed that treated fields may be grazed or cut for forage of hay 30 days after application.

Mixer/loader/applicator exposure duration is expected to be short-term for farmers, and short- to intermediate-term for custom applicators for the proposed uses of AC 900001 herbicide.

Mixer/loader/applicator exposure

Chemical-specific data for assessing human exposure during pesticide handling activities were not submitted. Exposure estimates were calculated using PHED (Pesticide Handlers Exposure Database) version 1.1 for farmers and custom applicators mixing/loading water-dispersible granular formulation in water-soluble packets, and for farmers and custom applicators applying liquid using groundboom. PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. The PHED estimates meet criteria for data quality, specificity, and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides.

To estimate exposure for each use scenario, appropriate subsets of A and B grade data were created from the mixer/loader and applicator database files of PHED. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The exposure values are based on open mixing/loading and workers wearing one layer of clothing and gloves during mixing/loading, and one layer of clothing, without gloves, during application. There is no adequate PHED subset for mixing/loading a water-dispersible granular formulation in water-soluble packaging. As such, a 90% protection factor was applied to the exposure value for mixing/loading a water-dispersible granular formulation.

The exposure estimates and MOEs for mixing/loading/applying AC 900001 are presented in Table 3.5.1. The MOEs were calculated from the combined dermal and inhalation exposure from mixing, loading, and applying picolinafen.

Table 3.5.1 Exposure estimates and resulting MOEs for mixer/loader/applicators

Crop	Exposure Scenario Mixer/Loader/Applicator	Exposure (μg a.i./kg bw/d)[a]	MOE[b]
Spring wheat	groundboom/farmer	5.1	333
	groundboom/custom applicator	10.8	157

[a] Used maximum application rate and area treated per day for each crop;
Dermal absorption is considered equivalent to oral absorption;
Body weight is 70 kg

[b] MOE = NOAEL/Daily Dose (Short- and Intermediate-term NOAEL = 1.7 mg/kg/d)

Based on a NOAEL of 1.7 mg/kg/day from a 90-day dietary dog study, the margin of exposure (MOE) for a farmer and a custom operator mixing/loading/applying AC 900001 herbicide by groundboom to wheat would be 333 and 157, respectively. Since the target MOE is 100, the MOEs for mixer/loader/applicator exposure are acceptable for the proposed uses of AC 900001.

3.5.2 Bystanders

Not applicable.

3.5.3 Workers

Re-entry activities are minimal for spring wheat and barley. Therefore, re-entry exposure for workers would be negligible.

3.5.4 Consumers

Not applicable.

4.0 Residues

4.1 Integrated food residue chemistry summary

Nature of the residue in plants
[^{14}C]-picolinafen uniformly labeled in the aniline ring ([aniline-^{14}C]-picolinafen) and at the 2 and 6 positions of the pyridine ring ([pyridine^{14}C]-picolinafen), formulated as a 200 g/L emulsifiable concentrate (EC) formulation, was applied to wheat (variety: Turbo) at the end of the tillering stage (BBCH-Code 25-29), at a nominal rate of 100 g a.i./ha. Based on the very low radioactive residues detected in seed and husk, there was minimal translocation of the parent and its associated metabolites from the point of application to the seed. The parent, picolinafen, was the predominant residue in the 0- and 27-DAT foliage and 86-DAT straw. The substituted picolinic acid metabolite (CL 183513), formed as a result of the cleavage of the amide bond of the parent molecule, was also detected in

wheat matrices. The residue of concern (ROC) may be defined as the parent, picolinafen. The metabolism of picolinafen in plants is well understood.

Confined accumulation in rotational crops

[^{14}C]-picolinafen uniformly labeled in the aniline ring ([aniline-^{14}C]-picolinafen) and at the 2 and 6 positions of the pyridine ring ([pyridine^{14}C]-picolinafen) and formulated as an emulsifiable concentrate, was applied to either wheat at the 4- to 6-leaf stage or to loam soil at a nominal rate of 100 g a.i./ha. Carrots, peas, sugar beets, and sunflowers were planted 30 days while lettuce, soybean and carrots were planted 11 months following the foliar post-emergence treatment to wheat. In a separate trial, lettuce, soybean, and carrots were planted 30 days after direct application to soil. When harvested at maturity, there was no measurable residue in the raw agricultural commodities (RACs) of the rotational crops; therefore, no attempt was made to identify or characterize the nature of the radioactive residues. Furthermore, the soil metabolism study demonstrated that picolinafen undergoes rapid transformation to CL 153815, classified as slightly to moderately persistent under aerobic conditions, and CL 7693, a minor transformation product that is strongly bound to soil and not expected to be readily available for uptake or transport. The magnitude of the residues (MORs) in the rotational crops from the confined crop rotation study did not trigger a need for field accumulation studies.

Nature of the residue in animals

[^{14}C]-picolinafen uniformly labeled in the aniline ring ([aniline-^{14}C]-picolinafen) and at the 2 and 6 positions of the pyridine ring ([pyridine^{14}C]-picolinafen) was administered orally (gelatin capsule), by balling gun, to eight lactating goats (La Mancha strain) at low doses (6.3 and 10.8 ppm) and high doses (47.2 and 65.1 ppm) daily for 7 consecutive days. Picolinafen was rapidly excreted, primarily as the unchanged parent compound, with minimal transfer to the tissues and milk. In the pyridine-label study, only the parent, picolinafen, was identified in fat samples, while in kidney, liver, and milk, the substituted picolinic acid metabolite, CL 153815, accounted for all of the identified residues. Similarly, in the aniline labeled study, only the parent was identified in fat samples. In liver, the metabolite CL 44167, resulting from the acetylation of the p-fluoroaniline metabolite, accounted for the majority of the radioactive residue. However, in kidney and milk samples, the aniline-specific metabolite, CL 6497, resulting from the elimination of the fluorine substitutent of CL 44167, was the predominant metabolite.

The preliminary results of the poultry metabolism study (final study not yet submitted by the registrant) showed the parent as the predominant residue in fat. An overall comparison of the metabolites identified in goat, hen, and rat demonstrated that the metabolism of picolinafen in all three species appears to proceed via the same major metabolic pathways.

The metabolic profiles in plant and animal suggest two major pathways: hydrolytic cleavage of the amide bond to yield the substituted picolinic acid, CL 153815, and p-fluoroaniline, CL 7693, followed by further degradation and conjugation. Based on these studies, the ROC in plant matrices, for risk assessment and enforcement purposes, may be defined as the parent compound, picolinafen. For risk assessment purposes, the

ROC in animal matrices may be defined as the parent compound only, picolinafen. For enforcement, the ROC may be defined as the parent and the substituted picolinic acid, CL 153815.

Methods for residue analysis of plants and plant products
Two analytical methods, GC/NPD Method FAMS 079-01 and GC/MS Method M3313, were submitted for the determination of the ROC in plant matrices. Method FAMS 079-01 was used for data gathering, while Method M3313 was proposed for enforcement and used for data gathering for the supervised residue trials. The method LOQ for picolinafen was the same for both methods: 0.05 mg/kg. The recoveries were within the guideline requirement of 70–120% and the CVs, measured with respect to recoveries following spiking at the LOQ, did not exceed 20%, indicating that the methods have good repeatability. The interlaboratory validation (ILV) supports the reliability and reproducibility of the GC/MS Method M3313 for the determination of residues of picolinafen in plant matrices.

Methods for residue analysis of food of animal origin
A HPLC/MS/MS method FAMS 109-01 was submitted for data gathering and enforcement purposes. The LODs and the LOQs of the matrices described are 0.002 mg/kg and 0.02 mg/kg, respectively, for muscle, fat and egg, and 0.001 mg/kg and 0.01 mg/kg, respectively, for milk. The recoveries of the parent and the metabolite were within guideline requirements of 70–120% and the CVs, measured with respect to recoveries following spiking at the LOQ, were within 20%. The ILV demonstrated good reliability and reproducibility for the determination of residues of picolinafen and CL 153815 in milk and tissues.

Storage stability data—plant/animals
Submitted freezer storage stability studies indicated that residues of AC 900001 were stable at –18°C for up to 12 months in wheat whole green plant, straw, and grain.

In the absence of measurable residues of picolinafen and CL 153815 in meat, meat by-products, milk, and eggs, following exposure to feed treated according to the proposed use pattern, a freezer storage stability study for animal matrices was not required.

Crop field trials
Supervised residue trials demonstrated that when wheat and barley, grown throughout the Canadian prairie provinces and North and South Dakota, U.S.A. (zones 5, 7, 7A, and 14), are treated with the proposed EP, AC 900001 750 g/kg WG (SF 09617), at a seasonal application rate of 50 g a.i./ha and harvested at maturity, residues in grain did not exceed the method LOQ (0.05 mg/kg). Therefore, a MRL of 0.05 ppm should be established to cover residues of picolinafen in or on wheat and barley grain. Residue decline studies in wheat and barley forage demonstrated that residues of picolinafen dissipated rapidly as a function of post-treatment time.

Processed food/feed
There was no measurable residue of picolinafen in wheat and barley grain when treated according to the proposed use pattern. Furthermore, the wheat metabolism study demonstrated that when treated at 2× the proposed use pattern, residues in seed were low (0.004 ppm). Therefore, the processing study, to determine residues in processed fractions (bran, germ, shorts, and middlings), was not required.

Meat/milk/poultry/eggs
When treated according to the proposed use pattern, residues in feed commodities (forage, hay, straw) did not exceed 0.2 ppm. Furthermore, the metabolism study demonstrated a minimal transfer of residues of picolinafen and CL 153815 in tissues and milk following exposure to highly exaggerated dietary doses (300–400× the maximum anticipated dietary burden). Based on this information, a dairy cattle feeding study was not required. Since anticipated residues of picolinafen and CL 153815 in livestock matrices are not expected to exceed the method LODs of the proposed enforcement method FAMS 109-01, MRLs for meat, meat by-products, and milk will not be established. Upon submission of the poultry metabolism study, the requirement for a poultry feeding study will be assessed.

Dietary risk assessment
The proposed use of picolinafen on wheat and barley in Canada does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults, and seniors.

5.0 Fate and behaviour in the environment

The fate and behaviour of picolinafen in the environment was investigated using [pyridine-2,6-^{14}C] (Figure 5.1) and [aniline-U-^{14}C] labelled-picolinafen (Figure 5.2).

Figure 5.1 pyridine-2,6-^{14}C-picolinafen

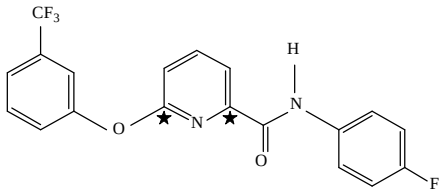
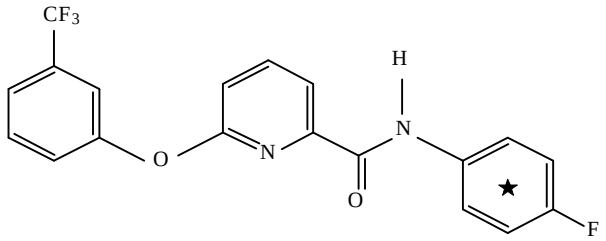


Figure 5.2 aniline-U-^{14}C-picolinafen



5.1 Physical and chemical properties relevant to the environment

All chemical and physical properties required for the active ingredient were provided and are summarized in Table 1.2.1. Picolinafen is insoluble in water and non-volatile from moist soil and water surfaces under field conditions. Picolinafen does not dissociate at environmentally relevant pH values. The log K_{ow} of greater than 5 indicates that picolinafen has potential to bioaccumulate, but bioconcentration and metabolism studies did not support this (Sections 5.6 and 3.1). The UV–visible absorption spectrum maximum at 290 nm indicates that there is potential for phototransformation.

A summary of physical and chemical data for the major transformation product, CL 153815 was requested by the PMRA (Appendix I, Table 4). The physical and chemical properties of CL 153815 are dependent on pH. It is a relatively strong acid and is an anion at environmentally relevant pH values (pH 5 to pH 9). It is very soluble in water at all pH values and the solubility increases as the alkalinity increases. Because solubility in water was mathematically estimated using log K_{ow} values, empirical data for solubility in water are required. Photolysis is not expected to be an important route of transformation of CL 153815 based on the UV–visible absorption spectrum maxima of less than 290 nm. CL 153815 is also expected to be non-volatile from moist soil and water surfaces; however, its potential to leach is much greater than the parent because of its high solubilility in water and anionic state at environmentally relevant pH values.

5.2 Abiotic transformation

Abiotic reactions are not important in the transformation of picolinafen or its major transformation product (CL 153815) in the environment (Appendix I, Table 5).

5.3 Biotransformation

The biotransformation of picolinafen occurs by cleavage of the amide bond to form the transformation products, CL 153815 (major product, 6-(3-trifluoromethylphenoxy)-2-pyridine carboxylic acid) and CL 7693 (minor product, 4-fluoroaniline). These are incorporated into the soil or sediment matrices where they are strongly bound. Carbon dioxide is the terminal transformation product. No organic volatile products are formed. The biotransformation pathway is proposed in Figure 5.3.1.

In aerobic laboratory studies, picolinafen is non-persistent in soil under aerobic conditions (DT_{50} <2–14 days), according to the classification of Goring et al. (1975). CL 153815 is the only major transformation product and is classified as slightly to moderately persistent under aerobic conditions (DT_{50} 30–77 days). The second cleavage product, CL 7693, is a minor transformation product that is strongly bound to soil and not expected to be readily available for uptake or transport. Mineralization of picolinafen was extensive.

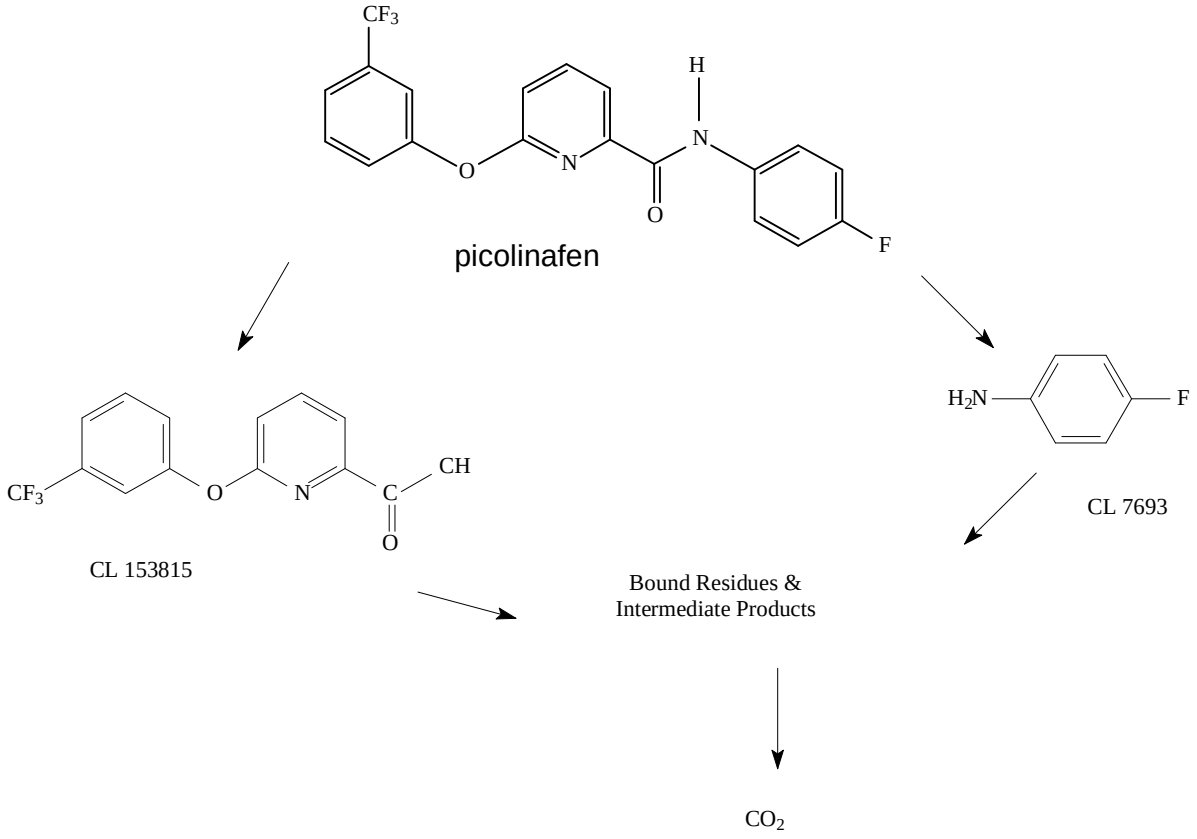
Under anaerobic conditions in soil, very little mineralization of picolinafen occurred. Although the conditions during the first 14 days of the study were aerobic, the results of the water/sediment studies indicate that picolinafen will be non-persistent in anaerobic soil. The concentration of the transformation product CL 153815 increased in the anaerobic soil for 63 days (maximum 87% applied radioiactivity [AR]). CL 153815 persisted until the end of the study (120 days after treatment [DAT]). CL 153815 is classified as persistent in soil under anaerobic conditions.

Picolinafen was non-persistent in natural water systems under aerobic (water) and anaerobic (sediment) conditions (DT_{50} 1.1–1.4 days in water; DT_{50} 8.6–12.7 days in sediment), according to the classification of McEwen and Stephenson (1979). CL 153815 is classified as slightly persistent in the aerobic water phase (DT_{50} 10.9–24.4 days) and persistent in the anaerobic sediment phase (no dissipation) of natural water systems. Overall, CL 153815 is classified as moderately persistent in total water systems (DT_{50} 45.3–70.1 days).

In the anaerobic aquatic sediment/water systems, picolinafen was slightly persistent in the water phase (DT_{50} 15.4 days) and non-persistent in the sediment phase (DT_{50} 6.4 days), according to the classification of McEwen and Stephenson (1979). Overall, picolinafen is classified as slightly persistent in total anaerobic water systems (DT_{50} 18.7 days). CL 153815 is classified as persistent in anaerobic water systems (DT_{50} 197 days in water; DT_{50} 645 days in sediment).

A summary of biotransformation rates of picolinafen and the major transformation product, CL 153815, is presented in Appendix I, Table 6. Overall, picolinafen is non-persistent under aerobic and anaerobic conditions in soil and natural water systems. CL 153815 is moderately persistent under aerobic conditions in soil and natural water systems. CL 153815 is persistent in soil, sediment, and water under anaerobic conditions.

Figure 5.3.1 Proposed biotransformation pathway of picolinafen in soil.



5.4 Mobility

The K_{oc} values (≥15 100) indicate that picolinafen will bind strongly to the soil and be immobile in the soil, according to the classification of McCall et al. (1981). The mobility of CL 153815 is classified as low to medium based on the K_{oc} values range, 160–783. However, physical and chemical properties and the persistence of CL 153815 indicate that it has potential to leach and contaminate ground water (Appendix I, Table 7).

Picolinafen and CL 153815 are not expected to volatilize under field conditions, given their low Henry's Law Constants (K_H 1.6×10^{-3} and 1.6×10^{-3} Pa m^3/mol at 20°C, respectively). These compounds did not occur in organic volatile traps of soil and aquatic system incubations.

5.5 Dissipation and accumulation under field conditions

Terrestrial field dissipation studies at three locations in the Canadian prairies indicate that picolinafen is slightly to moderately persistent in typical soils in the Canadian prairie region (DT_{50} 15–62 days), according to the classification of Goring et al. (1975). Picolinafen was more persistent in the field than in the laboratory. The potential for carry-over of

picolinafen is negligible; however, 53–64% of CL 153815 residues carried over to the next growing season under field conditions. Field data are summarized in Appendix I, Table 8.

CL 153815 and picolinafen did not leach below the 15-cm soil depth under typical field conditions. While the lack of downward movement of picolinafen is supported by the adsorption/desorption results (K_{oc} >15 000; immobile classification), the physical and chemical properties of CL 153815 (see Appendix I, Table 7) and the adsorption/desorption data (K_{oc} 160–783), indicate that there is potential for CL 153815 to leach should there be above-normal rainfall.

5.6 Bioconcentration

Bioconcentration factors (BCFs) of picolinafen in the bluegill sunfish were 420–540 at 2 μg/L, and 600–730 at 20 μg/L. The time for 50% depuration was very short (0.89–1.7 days at 2 μg/L, and 1.2–1.4 days at 20 μg/L), with 95% depuration within 7.3 days. Because picolinafen is not persistent in aquatic systems and the depuration rate of picolinafen in fish is fast, bioconcentration is not of concern under the specific conditions of use.

Picolinafen was metabolized in the bluegill sunfish by hydroxylation of the *p*-fluoroaniline ring to yield two isomeric hydroxylated derivatives (CL 410856 and CL 411016), followed by sulfate conjugation of these two hydroxylated derivatives (CL 1000624 and CL 1000625), and by hydrolysis of the amide bond of picolinafen to yield CL 153815 as the major metabolite. There was a very minor amount of CL 7693. In addition, hydrolysis of the amide bond of the hydroxylated and sulfate conjugated metabolites was also expected to occur, thereby giving rise to hydroxylated derivatives of CL 7693 and sulfate conjugates of the hydroxylated derivatives of CL 7693. Therefore, the data obtained from this study adequately define the uptake/depuration potential and the metabolic pathway of picolinafen. The proposed metabolic pathway for picolinafen is shown in Figure 5.6.1.

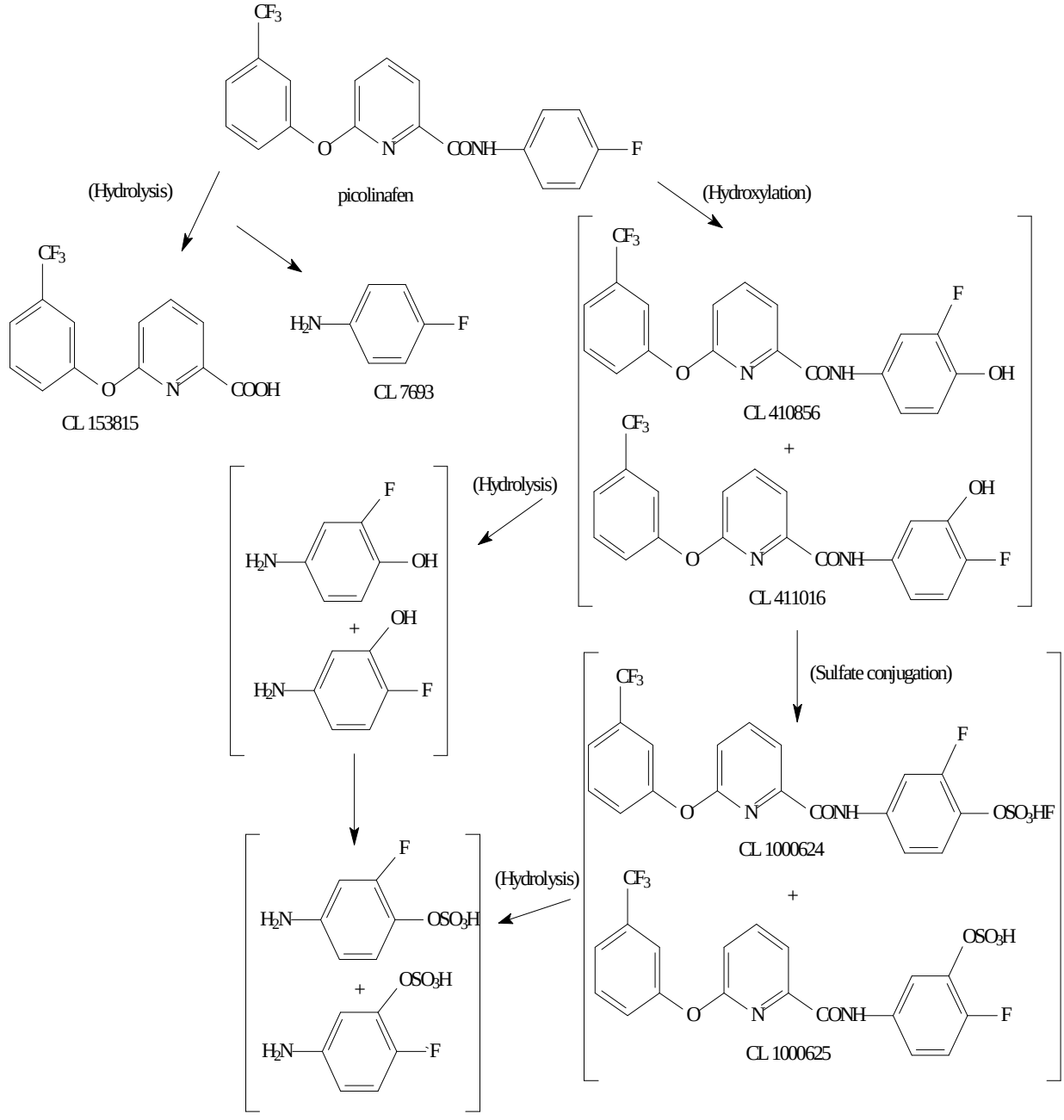


Figure 5.6.1 Proposed metabolic pathway of picolinafen in fish

5.7 Summary of fate and behaviour in the terrestrial environment

AC 900001 Herbicide will be introduced to the terrestrial environment by application using ground equipment, once per year at a rate of 50 g a.i./ha as early as April 20 in the Peace River region of British Columbia, until approximately June 25 in the prairie region of Alberta, Saskatchewan, and Manitoba.

The residues relevant to the environment are picolinafen and its principal transformation product, CL 153815. No other compound has been identified that accounts for greater than 10% of the applied parent.

The physical and chemical properties of picolinafen and CL 153815 are summarized in Table 1.2.1 and Appendix I, Table 4, respectively. Picolinafen is insoluble in water, whereas CL 153815 is very soluble in water. Both compounds are non-volatile from moist soil and water surfaces. Picolinafen and CL 153815 are expected to be stable to hydrolysis and photolysis.

The biotransformation of picolinafen occurs by cleavage of the amide bond to form the major product, CL 153815 (6-(3-trifluoromethylphenoxy)-2-pyridine carboxylic acid) and the minor product, CL 7693 (minor product, 4-fluoroaniline). In soil, these transformation products become bound. Carbon dioxide is the terminal transformation product. The proposed biotransformation pathway appears in Figure 5.3.1.

In aerobic laboratory studies, picolinafen is non-persistent in soil under aerobic conditions (DT_{50} <2–14 days), according to the classification of Goring et al. (1975). CL 153815 is classified as moderately persistent under aerobic conditions (DT_{50} 30–77 days). The cleavage product, CL 7693, is strongly bound to soil. Mineralization of picolinafen is significant.

Under anaerobic conditions in soil, picolinafen is expected to be non-persistent. However, CL 153815 is expected to be persistent based on its accumulation under anaerobic conditions for the first 63 days, with no decline for the remaining 57 days of the study.

Terrestrial field dissipation studies at three locations in the Canadian prairies indicate that picolinafen is slightly to moderately persistent in typical soils in the Canadian prairie region (DT_{50} 15–62 days), according to the classification of Goring et al. (1975). Picolinafen was more persistent in the field than in the laboratory. The potential for carry-over of picolinafen is negligible; however, 53–64% of CL 153815 residues carried over to the next growing season under field conditions.

CL 153815 and picolinafen did not leach below the 15-cm soil depth under typical field conditions. While the lack of downward movement of picolinafen is supported by the adsorption/desorption results (K_{oc} >15 000; immobile classification), the physical and chemical properties of CL 153815 (see Appendix I, Table 7) and the

adsorption/desorption data (K_{oc} 160–783), indicate that there is potential for CL 153815 to leach should there be above-normal rainfall.

5.8 Summary of fate and behaviour in the aquatic environment

Contamination of aquatic environments could occur by spray drift during application or by run-off from treated soil.

The transformation of picolinafen in aerobic sediment/water systems occurs by the same mechanism as in soil, with cleavage of the amide bond to form the major product, CL 153815 [6-(3-trifluoromethylphenoxy)-2-pyridine carboxylic acid], and the minor product, CL 7693 (4-fluoroaniline). These products partition to the sediment under laboratory conditions.

Both picolinafen and its major transformation product, CL 153815, are stable to hydrolysis, and are considered to be stable to phototransformation in water under environmentally relevant conditions. Neither is expected to volatilize from water surfaces. Picolinafen is insoluble in water, whereas CL 153815 is very soluble.

A summary of biotransformation rates of picolinafen and the major transformation product, CL 153815, in aquatic systems under laboratory conditions, is presented in Appendix I, Table 6. Overall, picolinafen is non-persistent in aerobic water systems (DT_{50} 6.2 days) and slightly persistent in anaerobic water systems (DT_{50} 18.7 days), according to the classification of McEwen and Stephenson (1979). CL 153815 is moderately persistent in aerobic water systems (DT_{50} 45.3–70.1 days), but will be persistent in anaerobic water systems (DT_{50} 197 days in water; DT_{50} 645 days in sediment).

5.9 Expected environmental concentrations (EECs)

5.9.1 Soil

For assessing risk to earthworms, the EEC for picolinafen was calculated to be 0.022 mg a.i./kg based on the following assumptions:

- Maximum proposed application rate of 50 g a.i./ha is applied to bare soil.
- Product is applied once per season (year).
- The product is evenly distributed in the 0–15 cm depth of the soil.
- The bulk density of the soil is 1.5 g/cm^3.

The accumulated concentration of CL 153815 would plateau at 0.026 mg/kg soil after approximately 13 years, assuming initial maximum concentration of 0.0092 mg/kg soil (from Fairview field study at 1× label rate) and 64% carry-over (from Minto field study).

5.9.2 Aquatic systems

Habitat

For initial screening of risk to aquatic organisms in surface waters, direct over-spray is considered a conservative scenario in estimating the amount of active ingredient entering surface water. Assuming a water depth of 30 cm for agricultural ponds and an application rate of 50 g a.i./ha, the EEC in pond water as a result of direct over-spray is calculated to be 0.0167 mg a.i./L. The limit of solubility of picolinafen in water is 0.047 mg a.i./L.

Drinking water

Level I drinking water concentrations of picolinafen and its transformation product, CL 153815, in ground water sources as a result of leaching were estimated over a 20-year period using the model LEACHM. The results indicated that picolinafen is not expected to reach ground water (0 μg/L). The maximum annual average concentration of CL 153815 in ground water was estimated to be 0.15 μg/L.

Level I drinking water concentrations in surface water sources (reservoirs and dugouts) as a result of run-off were estimated using the model PRZM/EXAMS. Two screening scenarios were used for modeling. Both scenarios used data for soils that are highly susceptible to run-off:

- A dugout scenario (volume 2667 m^3 and 3.87 ha drainage area) using weather data typical of a region where dugouts are the primary source of drinking water.
- A reservoir scenario (volume 144 320 m^3 and 172.8 ha drainage area) using weather data typical of a region where reservoirs are the primary source of drinking water.

Due to the conservative nature of the scenarios used for modeling, the EEC values in drinking water as a result of leaching or run-off represent upper bound estimates of potential pesticide exposure. The picolinafen concentrations were determined to be 1.61 and 0.08 μg a.i./L for acute and chronic exposures, respectively, while the corresponding CL 153815 concentrations were 1.15 and 0.61 μg/L. Water model input parameters for the screening assessment are summarized in Appendix I, Table 9.

5.9.3 Vegetation and other food sources

Data that could be used to estimate the dissipation of picolinafen on contaminated food sources for wildlife were not provided. Therefore, a scenario that assumes no transformation will occur on the surface of wildlife food sources was adopted. The estimated EEC values in vegetation are provided in Appendix I, Table 10, based on the nomogram in Hoerger and Kenaga (1972) and Kenaga (1973), which was modified by Fletcher et al. (1994). Based on these values, the estimated EECs in the diet of non-target species immediately after application of AC 900001 Herbicide for representative non-target species are: bobwhite quail (8.8 mg a.i./kg diet), mallard duck (1.7 mg a.i./kg

diet), rat (25 mg a.i./kg diet), mouse (25 mg a.i./kg diet), and rabbit (38 mg a.i./kg diet) (Appendix I, Table 11).

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The toxicities of picolinafen and its transformation product, CL 153815, are summarized in Appendix I, Table 12. With the exception of plants, picolinafen and CL 153815 are not inherently toxic to any non-target terrestrial organisms.

6.2 Effects on aquatic organisms

Technical picolinafen is not acutely toxic to fish or freshwater invertebrates. Toxic effects to aquatic organisms will be limited by the solubility of the compound in water (0.047 mg a.i./L). Chronic effects in *Daphnia magna* (21-day NOEC of 0.007 mg a.i./L for survival, reproduction, and growth), fish (early-life stage NOEC of 0.0064 mg a.i./L for growth), algae (72-h NOEC of 0.000068 mg a.i./L for biomass), and vascular plants (14-day NOEC of 0.006 mg a.i./L for frond number), however, were all observed at concentrations below the limit of solubility in water. The most sensitive organism was the green alga, *Selenastrum capricornutum*.

CL 153815 is classified as practically non-toxic to freshwater invertebrates (*D. magna* LC_{50} >98 mg/L). Algae are not very sensitive to CL 153815. The most sensitive endpoint was biomass, for which the EC_{50} and NOEC were 27 and 12 mg/L, respectively.

The toxicities of technical picolinafen and its transformation product (CL 153815) are summarized in Appendix I, Table 13.

6.3 Effects on biological methods of sewage treatment

Data are not required.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic risk assessment of pest control products. Environmental risk is characterized using the margin of safety (MOS) method, which is the ratio of the toxicity endpoint to the EEC. Risks are then classified based on the scheme presented in Appendix I, Table 14.

6.4.1 Environmental behaviour

Picolinafen is insoluble in water and non-volatile from moist soil and water surfaces. It is stable to hydrolysis and phototransformation. Biotransformation is the most important

transformation process for picolinafen and its major transformation product, CL 153815, in aquatic and terrestrial systems.

Picolinafen is classified as slightly to moderately persistent in soil under field conditions (DT_{50} 15–62 days), and non-persistent in aquatic systems (DT_{50} 6.2–18.7 days). CL 153815 is classified as slightly to moderately persistent in aerobic soil (DT_{50} 30–77 days), moderately persistent in aquatic systems (DT_{50} 45.3–70.1 days), and persistent under anaerobic conditions (DT_{50} 197 days in water; DT_{50} 645 days in sediment; no dissipation in soil). The potential for carry-over of picolinafen in soil to the next growing season is negligible; however, 53–64% of CL 153815 carried over to the next growing season under field conditions.

CL 153815 and picolinafen did not leach below the 15-cm soil depth under typical field conditions. While the lack of downward movement of picolinafen is supported by the adsorption/desorption results (K_{oc} >15 000; immobile classification), the physical and chemical properties of CL 153815 (see Appendix I, Table 7) and the adsorption/desorption data (K_{oc} 160–783), indicate that there is potential for CL 153815 to leach should there be above-normal rainfall.

Bioconcentration factors (BCFs) of picolinafen in fish ranged from 420 to 730. The time for 50% depuration was very short (0.89–1.7 days), with 95% depuration within 7.3 days. Because picolinafen is not persistent in aquatic systems and its depuration rate in fish is fast, bioconcentration of picolinafen is not of concern under the specific conditions of use. Based on the rat metabolism study, picolinafen and CL 153815 do not accumulate in mammals.

6.4.2 Terrestrial organisms

Earthworms: For risk assessment, the lowest toxicity data from the studies available are used. The estimated initial EEC for one application is 0.022 and 0.026 mg/kg for picolinafen and CL 153815, respectively. Taking the EEC data for one application, the MOS for short-term toxicity (LC_{50}/EEC) for technical picolinafen is >45 454 (>1000/0.022). For CL 153815, the MOS for short-term toxicity is 18 326 (476.5/0.026). In addition, the short term MOS for one application using the NOEC from the acute test amounts to 5045 (111/0.022) for picolinafen and 4807 (125/0.026) for CL 153815. The MOS values for earthworms indicate that the risk of lethal and sub-lethal effects of picolinafen and CL 153815 to earthworms is negligible (Appendix I, Table 15). Therefore, no restriction on use of AC 900001 Herbicide is required for the protection of earthworms.

Honeybees: Products that are applied as sprays can be evaluated initially by considering the likely exposure of bees and the toxicity of the product. According to the classification by Atkins et al. (1981), picolinafen is classified as relatively non-toxic to honeybees (LD_{50} values were >150 and >200 μg a.i./bee for oral and contact exposures, respectively). No

restriction is required for the protection of honeybees for products that fall into this category.

Other arthropod species: The intended use of AC 900001 Herbicide covers one application per season at a maximum rate of 50 g a.i./ha to control weed species. Non-target arthropods are likely to be exposed to formulated picolinafen by direct spray, and contact on fresh or dry residues. As a screening scenario, the predicted initial environmental concentration to which non-target organisms are exposed is assumed to be equivalent to the maximum nominal field rate of 50 g a.i./ha. The field rates tested were 2× and 0.012× the maximum nominal field rate. The studies indicate that twice the maximum field application rate results in less than 30% lethal or sublethal effects in all four species (classified as "harmless" according to Hassan et al. 1994). Therefore, the risk of lethal and sub-lethal effects of AC 900001 Herbicide to other arthropod species is low. No restriction on use of AC 900001 Herbicide is required for the protection of other terrestrial arthropod species.

Birds: The possibility that birds will be exposed to picolinafen, directly or indirectly, cannot be ruled out. Birds may be exposed to picolinafen mainly by the consumption of contaminated feed. The risk assessment procedure is directed at risks to individuals as there is currently no commonly used criterion for judging the significance of effects for population-level processes. The margin of safety (MOS) values for bobwhite quail mortality (LC_{50}/EEC) and effects on body weight (NOEC/EEC) are 604 (5314/8.8) and 30 (270/8.8), respectively. The MOS values for mallard duck mortality (LC_{50}/EEC) and effects on body weight and feed consumption (NOEC/EEC) are 3130 (5314/1.7) and 429 (729/1.7), respectively. Therefore, the risk of lethal and sublethal effects in birds is negligible (Appendix I, Table 15). No restriction on the use of AC 900001 Herbicide is required for the protection of birds.

Small wild mammals: The possibility that mammals will be exposed to picolinafen, directly or indirectly, cannot be ruled out. Mammals may be exposed to picolinafen mainly by the consumption of contaminated feed. As with birds, the risk assessment procedure is directed at risks to individuals. The lethal endpoint used was the 2-year dietary LC_{50} of >500 mg/kg bw for rats, while the sublethal endpoint used was the 78-week NOEC of 40 mg/kg diet for tissue effects (such as increased liver weight) in mice. The MOS values for mortality (LC_{50}/EEC) and sublethal effects (NOEC/EEC) are 20 (500/25) and 1.6 (40/25), respectively. Therefore, the risk of lethal and sublethal effects in small wild mammals is negligible (Appendix I, Table 15). No restriction on the use of AC 900001 Herbicide is required for the protection of small wild mammals.

Terrestrial plants: The lowest EC_{25} of 60 g formulation/ha (vegetative vigour of lettuce) was used to determine the risk of AC 900001 Herbicide to non-target plants following a direct over-spray at the maximum recommended application rate (67 g formulation/ha). The MOS (EC_{25}/EEC) after a single application was calculated to be 0.8. Therefore, plants are at moderate risk of growth reduction following a direct over-spray (Appendix 1, Table 15). No buffer zone is required for the protection of non-target plants. No

restriction on the use of AC 900001 Herbicide is required for the protection of non-target terrestrial plants.

6.4.3 Aquatic organisms

Although the proposed use does not include direct application to water, the possibility that aquatic organisms will be exposed to picolinafen, directly or indirectly, cannot be ruled out. The first step is to identify the degree of risk expected by comparing the EEC in surface water as a result of direct over-spray with acute toxicity (NOEC/EEC). This will give a margin of safety (MOS). The most sensitive organism tested was the green alga, *Selenastrum capricornutum* (NOEC of 0.000068 mg a.i./L). The results of the screening scenario (direct over-spray) indicate that green algae are at very high risk of short-term toxicity (Appendix I, Table 16). Additional acute toxicity studies with a broader range of species indicate that two other species are also at risk (*Lemna gibba* and *Anabaena flos-aquae*).

6.5 Risk mitigation

No restriction on the use of AC 900001 Herbicide is required for the protection of non-target terrestrial organisms.

Low to very high risk has been predicted for three species of aquatic plants. Therefore the following restrictions are required on the label under the general heading, "ENVIRONMENTAL HAZARDS":

> "Do not apply to terrains where there is potential for surface run-off to enter aquatic systems.
> Do not apply when rainfall is forecast for the next 48 hours."

As well as applying the restrictions outlined above, it is recommended that unsprayed buffer zones should be observed around all aquatic systems. The size of the buffer zone was determined to be 32 metres, using a model based on the expected drift from a boom sprayer (based on Nordby and Skuterud, 1975). The input parameters were the lowest NOEC (0.000068 mg a.i./L for green algae) and the highest EEC (0.0167 mg a.i./L). The following label statement is required under the general heading, "ENVIRONMENTAL HAZARDS":

> "Over-spray or drift to sensitive aquatic habitats should be avoided.
> A buffer zone of 32 metres is required between the downwind point of direct application and the closest edge of sensitive aquatic habitats including sloughs, coulees, ponds, prairie potholes, lakes, rivers, streams, reservoirs, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers.
>
> Do not apply during periods of dead calm or when winds are gusty."

Two-way and three-way tank mixes with 2,4-D ester and Assert 300SC are recommended on the AC 900001 Herbicide label for the control of a greater range of weed species. The following label statement is required under the general heading "TANKMIXING INSTRUCTIONS" to mitigate risk to non-target species from application of the recommended tank mixes:

> "Consult the label of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture."

7.0 Efficacy

7.1 Mode of action

AC 900001, a Group 12 herbicide, inhibits the activity of phytoene desaturase, an enzyme responsible for the conversion of phytoene to phytofluene in the carotenoid biosynthetic pathway of plants. Inhibition of this enzyme leads to a reduction in carotenoid pigments and ultimately, destruction of leaf chlorophyll in the foliage of sensitive species. Symptomology in the field occurs as bleaching or whitening (often with mauve discolouration) of leaf tissue, followed by necrosis and death.

7.2 Effectiveness against pests

Over 4 years, across the Canadian prairie provinces, a total of 122 trials were conducted as modified Randomized Complete Block Design with 4 replicates. Each trial included a reduced application rate to confirm that the requested rate is the lowest to provide effective and consistent weed control.

7.2.1 AC 900001 (alone treatment)

Redroot pigweed (*Amaranthus retroflexus*): Control ratings for redroot pigweed were reported in 34 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 67.2% (n = 8) at less than (<) 41 days after treatment (DAT) and 77.2% (n = 13) at greater than (>) 41 DAT. Mean control ratings at the 1× rate were 86.7% (n = 21) at <41 DAT and 91.3% (n = 34) at >41 DAT. The data supports a claim of redroot pigweed (1- to 4-leaf stage) control in spring wheat, durum wheat, and barley at 50 g a.i./ha AC 900001.

Stinkweed (*Thlapsi arvense*): Control ratings for stinkweed were reported in 13 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 36.6% (n = 4) at <41 DAT and 68.3% (n = 7) at >41 DAT. Mean control ratings at the 1× rate were 68.9% (n = 7) at <41 DAT and 83.2% (n = 13) at >41 DAT. The data supports a claim of stinkweed (1- to 6-leaf stage) suppression in spring wheat, durum wheat and barley at 50 g a.i./ha AC 900001.

Wild Mustard (*Sinapis arvensis*): Control ratings for wild mustard were reported in 56 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 52.7% (n = 15) at <41 DAT and 59.4% (n = 23) at >41 DAT. Mean control ratings at the 1× rate were 66.1% (n = 30) at <41 DAT and 76.9% (n = 43) at >41 DAT. The data supports a claim of wild mustard (1- to 8-leaf stage) suppression in spring wheat, durum wheat, and barley at 50 g a.i./ha AC 900001.

7.2.2 AC 900001 + 2,4-D Ester Tank Mix

The weed claim for the 2-way tank mix of 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester includes the weed list from the AC 900001 alone treatment, the weeds listed as susceptible or easy to control on the 2,4-D ester label, and kochia, chickweed, and wild buckwheat.

Confirmatory data made available supports the weed claims from the components of the 2-way tank mix.

Kochia (*Kochia scoparia*): Control ratings for kochia were reported in 23 trials conducted over 2 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 77.4% (n = 8) at <41 DAT and 77.5% (n = 8) at >41 DAT. Mean control ratings at the 1× rate were 92.6% (n = 14) at <41 DAT and 90.0% (n = 23) at >41 DAT. The data supports a claim of kochia (2- to 9-leaf stage) control in spring wheat, durum wheat, and barley when applied at 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester.

Chickweed (*Stellaria media*): Control ratings for chickweed were reported in 15 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 68.8% (n = 5) at <41 DAT and 61.3% (n = 5) at >41 DAT. Mean control ratings at the 1× rate were 82.2% (n = 15) at <41 DAT and 60.1% (n = 14) at >41 DAT. The data supports a claim of chickweed (1- to 8-leaf stage) suppression in spring wheat, durum wheat, and barley when applied at 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester.

Wild Buckwheat (*Polygonum convolvulus*): Control ratings for wild buckwheat were reported in 33 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 72.3% (n = 7) at <41 DAT and 65.8% (n = 10) at >41 DAT. Mean control ratings at the 1× rate were 82.5% (n = 22) at <41 DAT and 79.3% (n = 33) at >41 DAT. The data supports a claim of wild buckwheat (1- to 4-leaf stage) suppression in spring wheat, durum wheat, and barley when applied at 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester.

7.2.3 AC 900001 + 2,4-D Ester + Assert 300SC Tank Mix

The weed claim for the 3-way tank mix of 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester plus 400 g a.i./ha Assert 300SC includes the weed list from the 2-way tank mix plus wild oats. The tank mix of 2,4-D ester plus Assert 300SC is presently registered

for use on spring wheat, durum wheat, and barley in the Canadian prairie provinces and Peace River Region of British Columbia.

Confirmatory data made available supports the weed claims accepted for the 2-way tank mix. The addition of Assert 300SC did not reduce the level of broadleaf weed control.

Wild Oat (*Avena fatua*): Control ratings for wild oat were reported in 53 trials conducted over 3 years across the Canadian prairie provinces. Mean control ratings at the ½× rate were 76.9% (n = 5) at <41 DAT and 83.9% (n = 9) at >41 DAT. Mean control ratings at the 1× rate were 87.4% (n = 18) at <41 DAT and 92.6% (n = 32) at >41 DAT. The data support a claim of wild oat (1- to 3-leaf stage) control in spring wheat, durum wheat, and barley when applied at 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester plus 400 g a.i./ha Assert 300SC.

To be consistent with the use directions on the Assert 300SC label when applied at 400 g a.i./ha, the 3-way tank mix is restricted to the Brown and Dark Brown Soil Zone control for wild oat control.

7.3 Phytotoxicity to target plants (including different cultivars) or to target plant products (OECD 7.4)

Replicated small-plot field trials were conducted between 1997 and 1999 across the prairie provinces of Canada on spring wheat, durum wheat, and barley. Tolerance was assessed up to three times during the growing season as a visual estimate of crop injury (early season ratings (7–18 DAT), mid season ratings (18–45 DAT) and late season ratings (46–106 DAT)). Yields were reported as a percentage of the untreated weedy check (UTC) for each crop tested.

7.3.1 Spring wheat (*Triticum aestivum*)

A total of 28 trials over 3 years (1997–1999) reported the tolerance of spring wheat. Of these trials, 15 reported crop yield. Trials were conducted on 12 spring wheat varieties: AC Barrie, AC Splendor, AC Taber, CDC Teal, Conway, Domain, Imi-SWP, Invader, Laura, Majestic, Michael, and Roblin. Treatments were applied at the 3-leaf to 3-tiller stage, with the majority applied at the 3- to 5-leaf stage of growth.

7.3.1.1 AC 900001 (alone treatment)

A total of 27 trials over 3 years across the Canadian prairie provinces reported the tolerance of spring wheat. Yield was reported in 14 trials over 2 years.

Early season crop injury rating at the 1× rate was 4% (n = 25) and at the 2× rate, 4% (n = 14). Mid-season crop injury rating at the 1× rate was 0% (n = 26) and at the 2× rate, 0% (n = 13). Late season crop injury rating at the 1× rate was 0% (n = 20) and at the 2× rate, 0% (n = 11).

When yield was compared to the UTC, the reported 1× rate was 199% (*n* = 14) and the 2× rate was 116% (*n* = 8).

Although slight injury was reported shortly after application, the crop recovered without a yield reduction. The data supports the addition of the alone treatment for use in spring wheat when applied between the 3- to 5-leaf stage of growth.

7.3.1.2 AC 900001 + 2,4-D Ester Tank Mix

A total of 20 trials over 3 years across the Canadian prairie provinces reported the tolerance of spring wheat. Yield was reported in 11 trials over 2 years.

Early season crop injury rating at the 1× rate was 9% (*n* = 19) and at the 2× rate, 13% (*n* = 7). Mid-season crop injury rating at the 1× rate was 3% (*n* = 19) and at the 2× rate, 8% (*n* = 6). Late season crop injury rating at the 1× rate was 2% (*n* = 15) and at the 2× rate, 5% (*n* = 6).

When yield was compared to the UTC, the reported 1× rate was 129% (*n* = 11) and the 2× rate was 109% (*n* = 4).

Although injury was reported shortly after application, the crop recovered without a yield reduction. The data supports the addition of the 2-way tank mix for use in spring wheat when applied at the 3- to 5-leaf stage of growth.

7.3.1.3 AC 900001 + 2,4-D Ester + Assert 300SC Tank Mix

A total of 15 trials over 3 years across the Canadian prairie provinces reported the tolerance of spring wheat. Yield was reported in 8 trials over 3 years.

Early season crop injury rating at the 1× rate was 10% (*n* = 14) and at the 2× rate, 12% (*n* = 8). Mid-season crop injury rating at the 1× rate was 4% (*n* = 14) and at the 2× rate, 6% (*n* = 8). Late season crop injury rating at the 1× rate was 2% (*n* = 12) and at the 2× rate, 4% (*n* = 6).

When yield was compared to the UTC, the reported 1× rate was 137% (*n* = 8) and the 2× rate was 142% (*n* = 5).

Crop injury at the 1× and 2× rates were more than double that reported for the AC 900001 alone treatment although yield was not affected. The data supports the addition of the 3-way tank mix for use in spring wheat when applied at the 3- to 5-leaf stage of growth.

7.3.2 Durum wheat (*Triticum durum*)

A total of 18 trials over 3 years (1997–1999) reported the tolerance of durum wheat. Of these trials, 16 reported crop yield. Trials were conducted on 3 durum wheat varieties: AC Morse, Kyle, and Sceptre. Treatments were applied at the 3-leaf to 1-tiller stage, with the majority applied at the 3- to 4-leaf stage.

7.3.2.1 AC 900001 (alone treatment)

A total of 18 trials over 3 years across the Canadian prairie provinces reported the tolerance of durum wheat. Yield was reported in 16 trials over 3 years.

Early season crop injury rating at the 1× rate was 4% (n = 17) and at the 2× rate, 8% (n = 9). Mid-season crop injury rating at the 1× rate was 2% (n = 16) and at the 2× rate, 2% (n = 9). Late season crop injury ratings at the 1× rate was 1% (n = 10) and at the 2× rate, 1% (n = 5).

When yield was compared to the UTC, the reported 1× rate was 105% (n = 16) and the 2× rate was 101% (n = 8).

There was a two-fold increase in the initial crop injury ratings following a 2× application rate of AC 900001 but crops recovered without yield reduction. The data support the addition of the alone treatment for use in durum wheat when applied at the 3- to 4-leaf stage of growth.

7.3.2.2 AC 900001 + 2,4-D Ester Tank Mix

A total of 17 trials over 2 years across the Canadian prairie provinces reported the tolerance of durum wheat. Yield was reported in 15 trials over 2 years.

Early season crop injury rating at the 1× rate was 13% (n = 16) and at the 2× rate, 18% (n = 6). Mid-season crop injury rating at the 1× rate was 4% (n = 16) and at the 2× rate, 5% (n = 5). Late season crop injury rating at the 1× rate was 2% (n = 9) and at the 2× rate, 2% (n = 2).

When yield was compared to the UTC, the reported 1× rate was 106% (n = 15) and the 2× rate was 99% (n = 5).

There was a two-fold increase in crop injury ratings for the 2-way tank mix compared to the alone treatment in durum wheat. Durum wheat also showed sensitivity to an overspray scenario with yield reductions when compared to the 1× tank mix rate.

The data support the addition of the 2-way tank mix for use in durum wheat when applied at the 3- to 4-leaf stage of growth.

7.3.2.3 AC 900001 + 2,4-D Ester + Assert 300SC Tank Mix

A total of 13 trials over 2 years across the Canadian prairie provinces reported the tolerance of durum wheat. Yield was reported in 11 trials over 2 years.

Early season crop injury rating at the 1× rate was 15% (*n* = 12) and at the 2× rate, 17% (*n* = 7). Mid-season crop injury rating at the 1× rate was 8% (*n* = 13) and at the 2× rate, 8% (*n* = 8). Late season crop injury rating at the 1× rate was 2% (*n* = 6) and at the 2× rate, 3% (*n* = 5).

When yield was compared to the UTC, the reported 1× rate was 111% (*n* = 11) and the 2× rate was 103% (*n* = 7).

Crop injuries at the 1× and 2× rates were more than double those reported for the AC 900001 alone treatment, although yield was not affected. Durum wheat also showed sensitivity to an overspray scenario, with yield reductions when compared to the 1× tank mix rate.

The data support the addition of the 3-way tank mix for use in durum wheat when applied at the 3- to 4-leaf stage of growth.

7.3.3 Spring barley (*Hordeum vulgare*)

A total of 19 trials over 2 years (1998–1999) reported the tolerance of barley. Of these trials, 16 reported crop yield. Trials were conducted on seven spring barley varieties: AC Lacombe 6-row, Brier, Foster, Harrington, Manley, Richard, and Stein 2-row. Treatments were applied at the 3- to 4-leaf stage of growth.

7.3.3.1 AC 900001 (alone treatment)

A total of 19 trials over 2 years across the Canadian prairie provinces reported the tolerance of barley. Yield was reported in 16 trials over 2 years.

Early season crop injury rating at the 1× rate was 6% (*n* = 15) and at the 2× rate, 9% (*n* = 10). Mid-season crop injury rating at the 1× rate was 2% (*n* = 17) and at the 2× rate, 3% (*n* = 11). Late season crop injury rating at the 1× rate was 1% (*n* = 17) and at the 2× rate, 3% (*n* = 10).

When yield was compared to the UTC, the reported 1× rate was 117% (*n* = 16) and the 2× rate was 116% (*n* = 10).

Although slight injury was reported shortly after application, the crop recovered without a yield reduction. The data support the addition of the alone treatment for use in spring barley at the 3- to 4-leaf stage of growth.

7.3.3.2 AC 900001 + 2,4-D Ester Tank Mix

A total of 15 trials over 2 years across the Canadian prairie provinces reported the tolerance of barley. Yield was reported in 12 trials over 2 years.

Early season crop injury rating at the 1× rate was 14% (*n* = 12) and at the 2× rate, 14% (*n* = 4). Mid-season crop injury rating at the 1× rate was 7% (*n* = 12) and at the 2× rate, 8% (*n* = 4). Late season crop injury rating at the 1× rate was 5% (*n* = 13) and at the 2× rate, 4% (*n* = 5).

When yield was compared to the UTC, the reported 1× rate was 125% (*n* = 12) and the 2× rate was 103% (*n* = 4).

Crop injury was reported shortly after application of the 1× and 2× treatments but crops recovered without a yield reduction. The data support the addition of the 2-way tank mix for use in spring barley at the 3- to 4-leaf stage of growth.

7.3.3.3 AC 900001 + 2,4-D Ester + Assert 300SC Tank Mix

A total of 12 trials over 2 years across the Canadian prairie provinces reported the tolerance of barley. Yield was reported in 9 trials over 2 years.

Early season crop injury rating at the 1× rate was 15% (*n* = 9) and at the 2× rate, 21% (*n* = 8). Mid-season crop injury rating at the 1× rate was 10% (*n* = 10) and at the 2× rate, 12% (*n* = 8). Late season crop injury rating at the 1× rate was 6% (*n* = 9) and at the 2× rate, 8% (*n* = 7).

When yield was compared to the UTC, the reported 1× rate was 129% (*n* = 9) and the 2× rate was 126% (*n* = 7).

Crop injuries at the 1× and 2× rates were more than double those reported for the AC 900001 alone treatment, although yield was not affected. The data support the addition of the 3-way tank mix for use in spring barley at the 3- to 4-leaf stage of growth.

7.4 Impact on succeeding crops (OECD 7.5.1)

The mode of action of picolinafen does not lend itself to residual herbicide carry-over into the year following application. As a Group 12 herbicide, the product is absorbed through the foliage of plants and works by disrupting and destroying the photosynthetic process of sensitive species. It does not have soil activity and therefore is not anticipated to have residual effects in the year following application.

The environmental degradation profiles of picolinafen and its major transformation product, CL 153815, do not suggest residual herbicide carry-over into the year following application of AC 900001 in Canadian Prairie soils.

There is no requirement for a re-cropping statement on the label for an alone treatment of AC 900001. However, when used in combination with Assert 300SC, the user is advised to follow all recommendations, precautions, and restrictions that appear on the label.

7.5 Sustainability

7.5.1 Survey of alternatives

No other Group 12 herbicide is currently registered in western Canada for use in cereal crops to control broadleaved weeds.

However, there are numerous post-emergent broadleaf weed herbicides, with different modes of action, that may be used alone or in various tankmix combinations for use in cereal crops to control broadleaf weeds in western Canada. Other Groups of broadleaf herbicides that may be used alone or in various tank mix combinations include the Group 2 herbicides such as metsulfuron-methyl, chlorsulfuron, triasulfuron, tribenuron-methyl, thifensulfuron-methyl, and sulfosulfuron; Group 4 herbicides such as 2,4-D, MCPA, picloram, dicamba, clopyralid, and mecoprop; Group 5 herbicides such as metribuzin; Group 6 herbicides such as bromoxynil and bentazon; and Group 7 herbicides such as linuron.

7.5.2 Compatibility with current management practices including integrated pest management (IPM)

Application of AC 900001 would not exclude the sequential use of other herbicides with different modes of action for control of annual and perennial species not controlled by the product alone or when tank mixed.

There is no re-cropping restriction in the year following an alone treatment of AC 900001, or when tank mixed with 2,4-D ester. When AC 900001 is tank mixed with 2,4-D ester plus Assert 300SC, re-cropping restrictions appear on the Assert 300SC label.

7.5.3 Information on the occurrence or possible occurrence of the development of resistance

The introduction of a novel mode of action product for broadleaf weed control would assist in maintaining and perhaps extending the current weed control products on the market.

To address the issue of development of herbicide resistance, the AC 900001 label includes the resistance-management statement as outlined on the Regulatory Directive entitled *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action* (DIR99-06) as follows:

Herbicide resistance management:
For resistance management, AC 900001 is a Group 12 herbicide. Any weed population may contain or develop plants naturally resistant to AC 900001 and other Group 12 herbicides. The resistant biotypes may dominate the weed population if these herbicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay herbicide resistance:

- Where possible, rotate the use of AC 900001 or other Group 12 herbicides with different herbicide groups that control the same weeds in a field.

- Use tank mixtures with herbicides from a different group when such use is permitted.

- Herbicide use should be based on an IPM program that includes scouting, historical information related to herbicide use, and crop rotation, and considers tillage (or other mechanical), cultural, biological, and other chemical control practices.

- Monitor treated weed populations for resistance development.

- Prevent movement of resistant weed seeds to other fields by cleaning harvesting and tillage equipment and planting clean seed.

- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or integrated weed-management recommendations for specific crops and weed biotypes.

- For further information or to report suspected resistance, contact AgSolutions at 1-800-454-2673 or at www.agsolutions.ca.

7.6 Conclusions

The data made available indicate that spring wheat, durum wheat, and barley, grown in the prairie provinces and the Peace River region of Canada, are expected to be acceptably tolerant to a post-emergent application of AC 900001 when applied according to label directions. Control of redroot pigweed and suppression of stinkweed and wild mustard can be expected following application of 50 g a.i./ha.

The weed claim for the 2-way tank mix of 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-ester includes the weed list from the AC 900001 alone treatment, the weeds listed as susceptible or easy to control on the 2,4-D ester label, and the control of kochia and the suppression of chickweed and wild buckwheat.

The weed claim for the 3-way tank mix of 50 g a.i./ha AC 900001 plus 280 g a.e./ha 2,4-D ester plus 400 g a.i./ha Assert 300SC includes the weed list from the 2-way tank mix plus the control of wild oats.

There is no requirement for a re-cropping statement on the label for an alone treatment of AC 900001. However, when used in combination with Assert 300SC, the user is advised to follow all recommendations, precautions, and restrictions that appear on the label.

8.0 Toxic Substances Management Policy (TSMP) considerations

During the review of AC 900001 Herbicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product is not a TSMP Track-1 substance.

- Picolinafen does not meet the criteria for persistence. Picolinafen values for half-life in water (1.1–1.4 days), soil (15–62 days), and sediment (6.4–12.7 days) are below the TSMP Track-1 cut-off criteria for water (≥182 days), soil (≥182 days), and sediment (≥365 days). The criterion for half-life in air is not relevant since picolinafen is non-volatile and is not expected to be present in the vapour phase under environmental conditions.

- The transformation product, CL 153815, meets the criterion for persistence in sediment. The CL 153815 half-life in sediment (645 days) exceeds the TSMP Track-1 cut-off criterion (≥365 days).

- Picolinafen and its transformation product, CL 153815, are not bioaccumulative. Although the log K_{ow} of picolinafen is >5, laboratory data have shown that the bioconcentration factor (BCF) in fish is <1000, which is below the TSMP Track-1 cut-off criterion of BCF ≥5000. In addition, picolinafen is metabolized by fish and rapidly depurated with a half-life of <2 days. Based on the rat metabolism study, picolinafen and CL 153815 do not accumulate in mammals. In addition, the estimated log K_{ow} values of CL 153815 are 2.95 at pH 5, 1.15 at pH 7 and 0.66 at pH 9, which are below the TSMP Track-1 cut-off criterion of log K_{ow} ≥5.

- The toxicity of picolinafen and its transformation product, CL 153815, are summarized in Sections 3.6, 4.7, and 6.4. AC 900001 Herbicide is predicted to

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1 The federal Toxic Substances Management Policy is available through Environment Canada's Web Site at: www.ec.gc.ca/toxics.

2 The PMRA's Strategy for Implementing the Toxic Substances Management Policy, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-Mail pminfoserv@hc-sc.gc.ca; or through our Web Site at www.hc-sc.gc.ca/pmra-arla.

pose a risk to aquatic plants following a direct over-spray. However, its conditions of use can be adequately mitigated to minimize exposure of aquatic habitats.

- Picolinafen (technical grade) does not contain by-products or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- The formulated product does not contain any formulant known to contain TSMP Track-1 substances.

Therefore, the use of AC 900001 Herbicide is not expected to result in the entry of TSMP Track-1 substances into the environment.

9.0 Regulatory decision

Picolinafen and the end-use product AC 900001 Herbicide have been granted temporary registration for use on spring wheat (including durum) and barley, pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation of the following studies:

- poultry metabolism study
- physicochemical data on transformation product.

List of abbreviations

a.e.	acid equivalent
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
bwg	body-weight gain
°C	degree Celsius or centigrade
CAS	Chemical Abstracts Service
CD	caesarian derived
CV	coefficient of variation
d	day(s)
DAT	days after treatment
DT_{50}	disappearance time for 50% of highest amount
DT_{90}	disappearance time for 90% of highest amount
EC	emulsifiable concentrate
EC_{50}	effective concentration, 50% population
EEC	expected environmental concentration
ELS	early-life stage
F	female(s)
F0	Parental animals
F1	1st generation offspring
F2	2nd generation offspring
GIT	gastro-intestinal tract
GSD	geometric standard deviation
h	hour(s)
HCT	hematocrit
HD	high dose
HDT	highest dose tested
HGB	hemoglobin
HPLC	
ILV	interlaboratory validation
IPM	integrated pest management
K_{ow}	*n*-octanol–water partition coefficient
K_d	adsorption coefficient
K_{oc}	organic carbon adsorption coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LD	low dose
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection

LOEC	lowest-observed-effect concentration
LOQ	limit of quantification
M	male(s)
MAS	maximum average score (at 24, 48, and 72 hours)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MIS	maximum irritation score
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMAD	mass median aerodynamic diameter
MOE	margin of exposure
MOLD	multiple oral low dose
MOR	magnitude of residue
MOS	margin of safety
MRL	maximum residue level
ND	not detected
ng	nanograms
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
P1	1st generation parental animals
P2	2nd generation parental animals
PC	positive control
pK_a	dissociation constant for the acid form
PHED	Pesticide Handlers Exposure Database
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell
ROC	resicue of concern
SOHD	single oral high dose
SOLD	single oral low dose
T3	tri-iodothyronine
T4	thyroxine
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSH	thyroid stimulating hormone
TS	test substance
μg	micrograms
μL	micro litre
UTC	untreated check
UV	ultraviolet
WBC	white blood cell
y	year

References

Atkins, E.L., Kellum, D., Atkins, K.W. 1981. Reducing pesticide hazards to honeybees: Mortality prediction techniques and integrated management strategies. Leaflet 2883. University of California, Berkeley, California, U.S.A.

Cohen, S.Z., Creeger, S.M., Carsel, R.F., Enfield, C.G. 1984. Potential for pesticide contamination of ground water resulting from agricultural uses. *In* Krugger, R.F., Seiber, J.N., eds., *Treatment and disposal of pesticide wastes*. American Chemical Society Symposium Series No. 259, Washington, DC, U.S.A., pp 297–325.

Goring, C.A.I., Laskowski, D.A., Hamaker, J.H., Meikle, R.W. 1975. Principles of pesticide degradation in soil. *In* Haque, R., Freed, V.H., eds., *Environmental dynamics of pesticide*s. Plenum Press, New York, NY, U.S.A., pp 135–172.

Hassan, S.A., Bigler, F., Bogenshütz, H., Boller, E., Brun, J., Calis, J.N.M., Coremans-Pelseneer, J., Duso, C., Grove, A., Heimback, U., Helyer, N., Hokkanen, H., Lewis, G.B., Mansour, F., Moreth, L., Polgar, L., Samsre-Petersen, L., Sauphanor, B., Stäubli, A., Sterk, G., Vainio, A., van de Veire, M., Viggiani, G., Bogt, H. 1994. Results of the sixth joint pesticide testing programme of the IOBC/WPRS - working group “pesticides and beneficial organisms”. Entomophaga 39(1):107-119.

McCall, J.P., Laskowski, D.A., Swann, R.L., Dishburger, H.J. 1981. Measurement of sorption coefficients of organic chemicals and their use in environmental fate analysis. *Proceedings*, Test protocols for environmental fate and movement of toxicants, Association of Official Environmental Chemists, 94th annual meeting, Washington, DC, U.S.A., October 21–22, 1980, pp 89–109.

McEwen, F.L., Stephenson, G.R. 1979. *The use and significance of pesticides in the environment*. John Wiley and Sons Inc, Toronto, Ontario, Canada.

Appendix I Summary tables

Table 1 Toxicology

METABOLISM—Picolinafen Technical			
Absorption: Picolinafen was incompletely absorbed; at the LD (10 mg/kg bw) absorption (expressed as % AD) was approx. 51/67% for males/females, respectively, for ^{14}C-pyridine label and approx. 60/84% for males/females, respectively, for ^{14}C-aniline label; at the HD (1,000 mg/kg bw), absorption decreased to approx. 25/23% for males/females, respectively, for ^{14}C-pyridine label and to approximately 17% for both sexes for ^{14}C-aniline label; majority absorbed within 24 h following SOLD and MOLD, respectively and within 48 h following SOHD; decreased absorption at HD considered to be due to saturation of absorption processes. **Distribution:** highest residues found in fat, liver, kidneys, and lungs for pyridine label and in blood, spleen, liver, kidneys, lungs, and heart for aniline label; mean recovery of radioactivity in tissue/carcass at sacrifice (168 h post-dosing) was low, less than 0.5% of AD for all groups irrespective of label, indicating little potential for accumulation. **Metabolism:** extensively metabolized with hydrolytic cleavage of amide bond followed by a variety of biotransformation including N-acetylation, hydroxylation, methylation, dehalogenation and formation of mercapturic and sulfate conjugates; **Feces**: major residue was picolinafen (95–99%); **Urine**: pyridine label—major metabolites were CL 153815 (84.1/58.2% M/F) and its glucuronic acid conjugate (7.3/29.2% M/F); aniline label—major metabolites were sulfate conjugate of 2-amino-5-fluorophenol (52.9%) and sulfate conjugate of 4′-hydroxyacetanilide (CL 1009639, 26.1%); **Bile**: pyridine-label major metabolites were CL 153815 (86.4/89.5% M/F) and the glucuronide ester of CL 153815 (9.4/5.8% M/F); aniline label major metabolites were p-fluoroaniline, 4′-fluoroacetanilide and 4′-hydroxyacetanilide (64.6%). **Excretion:** major route of excretion following SOLD was via feces for pyridine-label and via urine for aniline-label; a greater proportion of AD was eliminated in urine following MOLD in comparison to SOLD; major route of excretion following SOHD for the pyridine label was via the feces and for the aniline-label urine and fecal excretion were comparable for males whereas fecal excretion was 2-fold greater than urinary excretion for females; rate of excretion following SOHD was slightly slower for females but not males for pyridine-label and slower for both sexes for aniline label when compared to SOLD; >75 and 90% of AD were eliminated within 24 h following SOLD and MOLD, respectively, irrespective of label; >88% of AD eliminated within 48 h following SOHD for pyridine label; >90% of AD eliminated within 48 and 72 h for females at males, respectively, following SOHD administration for aniline label; biliary excretion accounted for approx. 34/25% (M/F) and 8/12% (M/F) of AD within 48 h following SOLD for pyridine and aniline label, respectively, and for approx. 17/12% (M/F) and 2% (both sexes) of AD within 48 h following SOHD for pyridine and aniline label, respectively. There were gender differences in absorption, metabolism, and excretion.			
STUDY	**SPECIES/STRAIN AND DOSES**	**NOAEL and LOAEL mg/kg bw/day**	**TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS**
ACUTE STUDIES—Picolinafen Technical			
Oral	5 Sprague-Dawley rats/sex **Dose Level**: 5000 mg/kg bw	LD_{50} greater than 5000 mg/kg bw for both sexes	No treatment-related mortality, clinical signs, necropsy finding, or change in bw in either sex. One female died on d 6; death attributed to dosing accident. **LOW TOXICITY**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Dermal	5 Sprague-Dawley rats/sex **Dose Level**: 4000 mg/kg bw	LD_{50} greater than 4000 mg/kg bw for both sexes	No mortality; no treatment-related clinical sign or necropsy finding in either sex; 5/5 males and 4/5 females exhibited a bw gain, the remaining female exhibited a bw loss (4 g). **LOW TOXICITY**
Inhalation-Limit Test (4-hour nose-only)	5 Sprague-Dawley rats/sex **Dose Level**: Analytical—5.9 mg/L air Nominal—13.0 mg/L air (MMAD—5.8 μm, GSD—1.6)	LC_{50} greater than 5.9 mg/L air for both sexes	No mortality; no treatment-related necropsy findings or changes in bw in either sex. Laboured breathing noted during exposure. Secretory responses (clear nasal discharge, salivation and chromodacryorrhea) and respiratory responses (laboured breathing and moist rales) were noted immediately following exposure, resolved by d 3. **LOW TOXICITY**
Eye Irritation	6 male New Zealand White rabbits **Dose Level**: 0.1mL (equal to 0.032 g)	MIS: 2.67/110 at 1 h MAS (for 24, 48, and 72 h): 0.22/110.	Minimal conjunctival redness (grade 1) noted in 6 animals at 1 h, persisted in 1 animal at 24 h; minimal conjunctival discharge (grade 1) in 2 animals at 1 h and in 1 animal at 24 h, completely resolved by 48 h **MINIMALLY IRRITATING**
Skin Irritation	6 male New Zealand White rabbits **Dose Level**: 0.5 g moistened with 0.5 mL water	MAS (for 24, 48, and 72 hrs): 0.0/8	No sign of dermal irritation was observed at any time during the study period. **NON-IRRITATING**
Skin Sensitization (Guinea Pig Maximization Test)	Crl:(HA)BR strain guinea pigs Treated: 20 males Naive control: 20 males **Dose Levels**: **Intradermal induction**: 5% w/v suspension TS in 0.5% CMC in distilled water **Topical induction**: 25% w/w mixture TS in petrolatum **Challenge treatment**: 25% w/w mixture TS in petrolatum	No dermal reaction observed at 24 or 48 h after challenge treatment	**NOT A DERMAL SENSITIZER**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES—AC 900001 750 g/kg WG (SF 09617)			
Oral — mouse	CD-1 mice 5 animals/sex **Dose Level**: 5000 mg/kg bw	LD_{50} greater than 5000 mg/kg bw for both sexes	No mortality; no treatment-related clinical observation or necropsy finding in either sex. All animals gained wt during study except 2 females (1 lost 0.3 g and 1 exhibited no overall change in bw). **LOW TOXICITY**
Oral — rat	Sprague-Dawley rats 5 animals/sex **Dose Level**: 5000 mg/kg bw	LD_{50} greater than 5000 mg/kg bw for both sexes	No mortality; no treatment-related clinical observation, necropsy finding, or change in bw in either sex **LOW TOXICITY**
Dermal	Sprague-Dawley rats 5 animals/sex **Dose Level**: 4000 mg/kg bw	LD_{50} greater than 4000 mg/kg bw for both sexes	No mortality; no treatment-related clinical sign, necropsy finding, or change in bw in either sex **LOW TOXICITY**
Inhalation (4-hour nose-only)	Sprague-Dawley rats 5 animals/sex **Dose Level**: Analytical—3.83 mg/L air Nominal—7.6 mg/L air (MMAD—2.8 μm, GSD—1.9)	LC_{50} greater than 3.83 mg/L air for both sexes	No mortality; no treatment-related necropsy findings or change in bw in either sex. Laboured breathing and secretory responses (lacrimation, chromodacryorrhea, dried red/black red material facial area) were noted immediately following exposure, and completely resolved by day 11. **LOW TOXICITY**
Eye Irritation	New Zealand White rabbits 3 males **Dose Level**: 0.1 mL aliquot (equal to 0.054 g)	MIS: 4.67/110 at 1 h MAS (for 24, 48, and 72 h): 0.0/110.	At 1 h slight conjunctival redness (grade 1) observed in 3/3 animals, slight conjunctival chemosis (grade 1) in 1/3 animals, and slight to moderate conjunctival discharge (grade 1–2) in 2/3 animals, completely resolved by 24 h **MINIMALLY IRRITATING**
Skin Irritation	New Zealand White rabbits 3 males **Dose Level**: 0.5 g	MIS: 1.67/8 at 1 h MAS (for 24, 48, and 72 h): 0/8.	At 1 h, 3/3 animals exhibited very slight erythema (grade 1), 2/3 animals exhibited very slight edema (grade 1), completely resolved by 24 h **MILDLY IRRITATING**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Skin Sensitization (Buehler method)	Dunkin Hartley Haz:(DH)FBR albino guinea pigs 10 animals/sex in test group and 5 animals/sex in control group **Dose Level**: 0.3 cc aliquot of TS moistened with 0.3 mL sterile water for both induction and challenge treatments	At 24 h following challenge treatment, 1 treated male exhibited very faint erythema (grade 0.5), completely resolved by 48 h No sign of dermal irritation in any of the other treated animals or in any of the control animals at 24 or 48 h following challenge treatment	**NOT A DERMAL SENSITIZER**
SHORT TERM — Picolinafen Technical			
28-day dietary—mouse	5 CD-1 [Crl:CD-1(ICR)BR] mice/sex/dose **Dose Levels**: 0, 100, 1000, 2000, 3500, or 7000 ppm (equal to 0, 23.4, 227, 438, 839, and 11 721 mg/kg bw/d for males and 0, 28.0, 235, 598, 1140, and 2019 mg/kg bw/d for females)	**NOAEL**: 100 ppm (equal to 23.4/28.0 mg/kg bw/d in M/F) **LOAEL**: 1000 ppm (equal to 227/235 mg/kg bw/d in M/F)	≥**1000 ppm**: discolouration (pale) of spleen (F); centrilobular hepatocellular hypertrophy (M); extramedullary hematopoiesis/ hemosiderin deposition of spleen (M/F) ≥**2000 ppm**: increased spleen and liver wt (M/F); discolouration of spleen, liver, kidney, lungs, heart, and/or small intestines (M/F); centrilobular hepatocellular hypertrophy (F); hemosiderin deposition in Kupffer cells of liver (M/F) ≥**3500 ppm**: increased reticulocyte count, MCHC and increased reticulocyte count, MCH and MCHC (M/F); Heinz body formation (F) **7000 ppm**: decreased bw/bwg (M); increased MCV (M/F); Heinz body formation (M); slight decrease RBC count (F). Findings considered to indicate regenerative hemolytic anemia for M/F at 3500 ppm and above; possibly suggestive of regenerative hemolytic anemia in M/F at 1000 and 2000 ppm

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
28-day dietary—rat	10 Crl:CD(SD)BR rats/sex/dose **Dose Levels**: 0, 25, 50, 100, or 1000 ppm (equal to 0, 2.7, 5.4, 10.5, and 107 mg/kg bw/d for males and 0, 3.0, 5.9, 11.7, and 119 mg/kg bw/d for females)	**NOAEL**: 100 ppm (equal to 10.5/11.7 mg/kg bw/d in M/F) **LOAEL**: 1000 ppm (equal to 107/119 mg/kg bw/d in M/F)	**1000 ppm**: decreased RBC counts, HGB, HCT, MCHC, oxyhemoglobin, and osmotic fragility, and increased MCV, RBC distribution width and diameter, reticulocyte counts, MCH, methemoglobin, Heinz body formation, and erythropoietic activity in bone marrow in one or both sexes; increased WBC and lymphocyte counts (F); increased serum bilirubin (M/F); increased spleen and liver wt (M/F); enlargement and discolouration of spleen; extramedullary hematopoiesis in spleen (M/F); active erythropoietic foci in liver (M/F); hemosiderin deposition in spleen, Kupffer cells, and kidney (M/F); lymphocyte depletion marginal zones white pulp, congestion and focal capsular inflammation and/or fibrotic proliferation in spleen (M/F); centrilobular hepatocellular hypertrophy (M) Findings for M/F at 1000 ppm considered indicative of regenerative hemolytic anemia

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
90-day dietary—mouse	10 CD-1 strain [Crl:CD-1(ICR)BR] mice/sex/dose **Dose Levels**: 0, 50, 500, 1000, or 2000 ppm (equal to 0, 10.2, 103, 202, and 388 mg/kg bw/d for males and 0, 12.7, 148, 280, and 577 mg/kg bw/d for females)	**NOAEL**: 50 ppm (equal to 10.2/12.7 mg/kg bw/d in M/F) **LOAEL**: 500 ppm (equal to 103/148 mg/kg bw/d in M/F)	≥**500 ppm**: increased liver (M) and spleen (F) wt; centrilobular hepatocellular hypertrophy (M); hemosiderin deposition (M/F) and extramedullary hematopoiesis (F) in spleen ≥**1000 ppm**: decreased RBC counts, HCT, and HGB, and increased reticulocyte counts and Heinz body formation in one or both sexes; increased liver (F) and spleen (M) wt; enlarged spleen (M/F); centrilobular hepatocellular hypertrophy and hepatocellular vacuolation (F); extramedullary hematopoiesis in spleen (M). **2,000 ppm**: decreased food cons. (M); increased MCV (F); discoloured spleen (F); hemosiderin deposition Kupffer cells in liver (M/F). Findings for M/F at ≥1000 ppm considered indicative of regenerative hemolytic anemia and possibly indicative for M/F at 500 ppm. No apparent increase of hematopoietic activity in bone marrow, liver, or other tissue **Control wk 13 bw** M: 40.5 g; F: 31.3 g **Control wk 13 daily food cons.**: M: 7.9 g/animal; F: 7.4 g/animal

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
90-day dietary—rat	10 Crl:CD(SD)BR rats/sex/dose **Dose Levels**: 0, 80, 400, or 800 ppm (equal to 0, 6.4, 32, and 65 mg/kg bw/d in males and 0, 6.8, 35, and 69 mg/kg bw/d in females)	**NOAEL**: 80 ppm (equal to 6.4/6.8 mg/kg bw/d in M/F) **LOAEL**: 400 ppm (equal to 32/35 mg/kg bw/d in M/F)	≥**400 ppm**: decreased RBC, HCT, and HGB (M/F); increased reticulocytes (M) and MCV (M/F); increased spleen and liver wt (M/F); increased incidence or severity of hemosiderin deposition in spleen and Kupffer cells of liver (M/F). **800 ppm**: decreased bw, bwg, and food cons. (F). Findings in M/F at ≥400 ppm considered indicative of hemolytic anemia; no apparent increase of hematopoietic activity in spleen, bone marrow, liver, or other tissue **Control wk 13 bw:** M: 546.8 g; F: 336.2 g **Control wk 13 daily food cons.**: M 30.2 g/animal F: 23.2 g/animal
90-day dietary—dog	4 Beagle dogs/sex/dose **Dose Levels**: 0, 50, 500, or 2500 ppm (equal to 0, 1.7, 17.3, and 87.5 mg/kg bw/d for males and 0, 1.8, 20.8, and 92.1 mg/kg bw/d for females)	**NOAEL**: 50 ppm (equal to 1.7/1.8 mg/kg bw/d for M/F) **LOAEL**: 500 ppm (equal to 17.3/20.2 mg/kg bw/d for M/F)	≥**500 ppm**: lower RBC, HGB, and HCT(F); increased thyroid wt (M/F); diffuse hypertrophy and local hyperplasia of thyroid follicular cells (M/F) **2500 ppm**: lower bwg (M); lower RBC, HGB, and HCT (M); increased serum bilirubin (F); enlarged thyroid (M/F). Hematological findings for F at 500 ppm and M/F at 2500 ppm are considered indicative of hemolytic anemia. Thyroid hormone levels not determined

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
12-month dietary —dog	4 Beagle dogs/sex/dose **Dose Levels**: 0, 50, 150, or 1500 ppm (equal to 0, 1.4, 4.4, and 42.7 mg/kg bw/d for males and 0, 1.6, 5.2, and 47.1 mg/kg bw/d for females)	**NOAEL**: 50 ppm (equal to 1.4/1.6 mg/kg bw/d for M/F) **LOAEL**: 150 ppm (equal to 4.4/5.7 mg/kg bw/d for M/F)	≥ **150 ppm**: lower bw and bwg (M) **1500 ppm**: decreased RBC, HCT, and HGB at 3/6 mos and increased reticulocyte counts at 3/6/9 mos (F); increased thyroid/parathyroid wt (M/F); enlarged thyroid (M/F); diffuse hypertrophy of thyroid follicular epithelial cells (M/F); scattered foci of thyroid follicular cell hyperplasia (M). Hematological findings for F at 1500 ppm considered indicative of hemolytic anemia; at 12 mos no hematology finding and no correlating histopathological finding Thyroid hormone levels not determined
4-week dermal—rat	10 CD (Sprague-Dawley derived) [Crl: CD IGS BR] rats/sex/dose **Dose Levels**: 0, 25, 50, 75, 100, 200 or 1000 mg/kg bw/d (6 h/d, 7 d/wk for 26 d)	**Systemic Toxicity:** **NOAEL**: 75 mg/kg bw/d for both sexes **LOAEL**: 100 mg/kg bw/d for both sexes **Local dermal Irritation:** **NOAEL**: greater than 1000 mg/kg bw/d for both sexes **LOAEL**: not determined	≥ **100 mg/kg bw/d**: lower RBC count, HGB and HCT (M/F); increased spleen wt (M/F); increased severity of hemosiderin deposition and extramedullary deposition in spleen (M/F) ≥ **200 m/kg bw/d**: lower bwg (M) **1000 mg/kg bw/d**: lower bw and bwg (M/F) Findings in M/F at ≥100 mg/kg bw/d are considered indicative of regenerative hemolytic anemia. **Local dermal Irritation**: No treatment-related sign of local dermal irritation

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
CHRONIC TOXICITY/ONCOGENICITY—Picolinafen Technical			
78-week dietary —mouse	65 CD-1 (Crl:CD-1(ICR)BR strain) mice/sex/dose **Dose Levels**: 0, 40, 400, or 800 ppm (equal to 0, 6.9, 68.6, and 137.1 mg/kg bw/d for males and 0, 8.2, 81.0, and 165.8 mg/kg bw/d for females)	**Chronic Toxicity**: **NOAEL**: 40 ppm (equal to 6.9/8.2 mg/kg bw/d for M/F) **LOAEL**: 400 ppm (equal to 68.6/81.0 mg/kg bw/d for M/F)	≥ **400 ppm**: increased reticulocyte counts at 3 mos (M/F); increased liver wt (M/F); centrilobular hepatocellular hypertrophy (M); hemosiderin deposition (F) and extramedullary hematopoiesis (M) in spleen **800 ppm**: centrilobular hepatocellular hypertrophy (F); hemosiderin deposition in Kupffer cells (F); hemosiderin deposition (M) and extramedullary hematopoiesis (F) in spleen Hematological/histopathological findings may indicate slight regenerative hemolytic anemia; no significant relevant correlating change in RBC parameters or indices was noted for either sex at 400 or 800 ppm at 3, 6, 12, or 18 mos. No evidence to indicate any carcinogenic potential of picolinafen at any dose level up to and including 800 ppm, the HDT

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
2-year dietary—rat	55 Sprague-Dawley rats/sex/dose **Dose Levels**: 0, 50, 250, or 500 ppm (equal to 0, 2.4, 12.1, and 24.5 mg/kg bw/d for males and 0, 3.0, 15.0, and 31.0 mg/kg bw/d for females)	**Chronic Toxicity**: **NOAEL**: 50 ppm (equal to 2.4 and 3.0 mg/kg bw/d for M/F) **LOAEL**: 250 ppm (equal to 12.1/15.0 mg/kg bw/d for M/F)	≥**250 ppm**: lower RBC, HGB, and HCT 3/6 mos (M/F); increased spleen wt at 12 mos (M); increased severity hemosiderin deposition spleen at 12/24 mos (M/F) **500 ppm**: lower RBC and HGB at 12 mos (M); increased spleen wt 24 mos (M/F); enlarged spleen at 24 mos (F) Findings in M/F at ≥250 ppm considered indicative of hemolytic anemia; no apparent increase in hematopoietic activity in spleen, bone marrow, liver, or other tissue Slight, non-significant, increased incidence of benign neoplasms (benign pheochromocytomas) in adrenal gland medullary region in males at 500 ppm is considered spontaneous in nature; no evidence indicates any carcinogenic potential of picolinafen at any dose level up to and including 500 ppm, the HDT.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
REPRODUCTION/DEVELOPMENTAL TOXICITY—Picolinafen Technical			
Multi-generation —rat (1 litter/ generation)	30 CD (Sprague-Dawley derived) rats/sex/group **Dose Levels**: 0, 50, 250, or 500 ppm (equal to 0/0, 3.7/4.3, 19/21, and 39/43 mg/kg bw/d for P1/P2 males, respectively, during pre-mating; 0/0, 4.2/4.7, 22/24, and 44/49 for P1/P2 females, respectively, during pre-mating; 0/0, 4/4, 21/21, and 43/42 for P1/P2 females, respectively, during gestation; 0/0, 8/7, 36/36, and 74/65 for P1/P2 females, respectively, during lactation)	**Parental**: **NOAEL**: 50 ppm (equal to 3.7/4.0 mg/kg bw/d for M/F) **LOAEL**: 250 ppm (equal to 19/21 mg/kg bw/d for M/F) **Offspring**:: **NOAEL**: 50 ppm (equal to 3.7/4.0 mg/kg bw/d for M/F) **LOAEL**: 250 ppm (equal to 19/21 mg/kg bw/d for M/F) **Reproductive**: **NOAEL**: 500 ppm (equal to 39/42 mg/kg bw/d for M/F) **LOAEL**: not determined	**Parental:** ≥**250 ppm**: lower RBC counts, HGB, and HCT (P1/P2 both sexes); lower MCHC (P1/P2 M and P2 F); increased reticulocyte counts (P2 both sexes); increased incidence/severity hemosiderin deposition, extramedullary hematopoiesis, and congestion of red pulp in spleen (P1/P2 both sexes) **500 ppm**: lower MCHC (P1 females); increased reticulocyte counts (P1 both sexes) and MCV (P1/P2 M); increased spleen wt (P1/P2 both sexes) Hematological/histopathological findings at ≥250 ppm considered indicative of regenerative hemolytic anemia **Offspring**: lower RBC, HGB and HCT for F2 pups on lactation d 21 (only time point evaluated) for both sexes at 250 and 500 ppm **Reproductive**: No treatment-related finding

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Teratogenicity—rat	25 mated adult female CD (Sprague-Dawley) rats/dose (17 rats/dose for extension study) **Dose Levels**: Main Study: 0, 100, 500, or 1000 mg/kg bw/d Extension Study: 0, 5, 2,5 or 50 mg/kg bw/d	**Maternal Toxicity**: **NOAEL**: 50 mg/kg bw/d. **LOAEL**: 100 mg/kg bw/d **Developmental Toxicity:** **NOAEL**: 1000 mg/kg bw/d **LOAEL**: Not determined	**Maternal Toxicity:** ≥**100 mg/kg bw/d**: lower RBC counts, HGB and HCT; increased MCV, MCH, and reticulocyte counts; increased spleen wt; increased incidence/severity hemosiderin deposition and extramedullary hematopoiesis in spleen **500 mg/kg bw/d**: lower bw and bwg; increased MCHC **1000 mg/kg bw/d**: increased nucleated RBC counts Hematological/histopathological findings at 100 mg/kg bw/d and above are considered indicative of regenerative hemolytic anemia. **Developmental Toxicity**: No adverse treatment-related finding **Teratogenicity**: There was no evidence of any treatment-related irreversible structural change at any dose level up to and including 1000 mg/kg bw/d (HDT); therefore, under the conditions of this study, picolinafen was not teratogenic.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Teratogenicity—rabbit	25 mated adult female New Zealand White rabbits/dose **Dose Levels**: 0, 5, 20, or 50 mg/kg bw/d	**Maternal Toxicity**: NOAEL: 5 mg/kg bw/d LOAEL: 20 mg/kg bw/d **Developmental Toxicity:** NOAEL: 20 mg/kg bw/d LOAEL: 50 mg/kg bw/d	**Maternal Toxicity**: ≥**20 mg/kg bw/d**: lower bwg and food cons.; lower RBC, HGB, and HCT; elevated MCV and reticulocyte counts; hemosiderin deposition/congestion in spleen **50 mg/kg bw/d**: increased spleen wt: extramedullary hematopoiesis in spleen Hematological/histopathological findings at 20 and 50 mg/kg bw/d are considered indicative of regenerative hemolytic anemia. **Developmental Toxicity**: possible slight decrease embryonal-fetal viability manifest as slight increases in abortion (1 on day 21/1 on day 23), post-implantation loss, total number of resorptions (early/late) and mean resorption rate at 50 mg/kg bw/d, findings not statistically significantly different from controls and within historical control values. **Teratogenicity**: No evidence of any treatment-related irreversible structural changes at any dose level up to and including 50 mg/kg bw/d (HDT); therefore, under the conditions of this study, picolinafen was not teratogenic.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
GENOTOXICITY—Picolinafen Technical			
STUDY	**Species/Strain or Cell Type**	**Dose Levels**	**Significant Effects/Comments**
Bacterial reverse gene mutation assay (in vitro)	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* (WP2uvrA)	0, 100, 250, 500, 1000, or 2500 μg/plate ± S9 metabolic activation.	NEGATIVE
Mammalian cell gene mutation assay (in vitro)	Chinese hamster ovary (CHO) cells at the hypoxanthine-guanine-phosphoribosyl transferase (HGPRT) locus	0, 10, 25, 50, 100, 200, or 300 μg/mL ± S9 metabolic activation.	NEGATIVE
Mammalian cytogenetics (in vitro)	Chinese Hamster Ovary (CHO) cells	0, 10, 25, 100, 200, 400, 600, 800, or 1000 μg/mL (-) S9 metabolic activation; 0, 10, 25, 50, 100, 200, 300, 400, or 600 μg/mL (+) S9 metabolic activation	NEGATIVE
Micronucleus Assay (in vivo)	Male mouse bone marrow cells (erythrocytes)	0, 500, 1000, or 2000 mg/kg bw (sacrifice at 24 and 48 hours)	NEGATIVE

Table 2 Residues: Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES		
Crops (N=1)		**Picolinafen**
		Wheat
ROC for monitoring		picolinafen
ROC for risk assessment		picolinafen
Is metabolism profile in diverse crops similar?		Not applicable
ANIMAL STUDIES		
Animals (N=1)		Lactating goat
ROC for monitoring		picolinafen and CL 153815
ROC for risk assessment		picolinafen
Is metabolism profile in rat and ruminant similar?		Yes
Fat soluble residue		Yes
DIETARY RISK from food and water		
Chronic Non-Cancer Dietary Risk **ADI = 0.014 mg/kg bw** **EEC (picolinafen) = 0.08 µg/L** **EEC (CL 153815) = 0.61 µg/L**	**POPULATION**	**Level I ESTIMATED RISK (% of ADI)**
		Food (MRLs) + Combined EECs
	All infants <1 yr old	0.7
	Children 1 to 6 years	1.6
	Children 7 to 12 years	1.1
	Females 13+ years	0.6
	Males 13+ years	0.8
	Seniors 55+ years	0.5
	Total Population	0.8

Table 3 Residues: Integrated Food Residue Chemistry Table

PARAMETER		PERTINENT INFORMATION				
CHEMICAL		Picolinafen				
Crop	Formulation/ type	Method/Timing	Rate	Number/ season	Maximu m Rate	PHI (days)
Wheat (including durum) Barley	AC 900001/ WDG	Foliar/Postemergence (following the full expansion of the 3rd true leaf stage)	50 g a.i./ha	1	50 g a.i./ha	60
LABEL RESTRICTIONS		**Treated fields may be grazed or cut for forage or hay 30 days after application.** **DO NOT apply by air.** **DO NOT apply more than once per season.**				
NATURE OF THE RESIDUE—GOAT ***Radiolabelling positions***		[aniline-^{14}C]-picolinafen and [pyridine^{14}C]-picolinafen				
Distribution of Radioactivity		[^{14}C]-picolinafen was administered orally (gelatin capsule) by balling gun to eight lactating goats (La Mancha strain) at a low dose (6.3 to 10.8 ppm) and a high dose (47.2 to 65.1 ppm) daily for 7 consecutive days. Picolinafen was rapidly metabolized and excreted via the urine and feces. More than 90% of the administered radioactive dose was eliminated within 48 hours regardless of dose rate or radiolabelling position. Radioactivity found in tissues, milk, and blood accounted for <1% of the total applied dose, demonstrating the lack of potential for bioaccumulation. The highest residues were found in kidney (0.093–1.722 ppm) followed by liver (0.17–1.669 ppm), fat (0.032–0.259 ppm), milk (0.014–0.137 ppm), and muscle (<0.010–0.041 ppm) from the pyridine and aniline labeled group. The predominant pyridine-ring containing metabolite detected in kidney and liver (low- and high-dose groups) and milk (high-dose group) was the substituted picolinic acid, CL 153815, while in fat (high-dose group), the parent picolinafen accounted for all of the identified radioactivity. The aniline-ring containing metabolites CL 1009718, CL 1009639, CL 6497, and CL 44167 were the major metabolites identified in the kidney and liver (low and high dose) and milk (high dose) while in fat (aniline high dose), the parent was the major metabolite. All other aniline-ring containing metabolites were detected at concentrations not exceeding 10% of the total radioactive residues (TRRs).				
Proposed Metabolic Pathway		Based on the major metabolites that were identified in goat urine, feces, milk, and specific tissues, the major biotransformation processes for picolinafen in the goat metabolism include hydrolysis, oxidation, acetylation, and subsequent glucuronide and sulfate conjugations.				
Residue of Concern (ROC)		Picolinafen and the substituted picolinic acid CL 153815				

NATURE OF THE RESIDUE—HEN	
Radiolabelling positions	[fluoroaniline-^{14}C]-picolinafen and [pyridine^{14}C]-picolinafen
Distribution of Radioactivity	Based on the preliminary report of the poultry metabolism study (currently under progress with confirmed submission date of June, 2002), ^{14}C-picolinafen was administered orally to laying hens at nominal dose levels of 0.05 mg/kg feed/day and 12 mg/kg feed/day for thirteen consecutive days. At the low-dose rate, the majority of the radioactivity was excreta-related (102.9% AD) with the radioactivity in tissues accounting for <0.2% of the administered dose (0.000–0.002 ppm). Similarly, at the higher dose level, picolinafen was rapidly metabolized and excreted (97.81–101.31% AD) with the radioactivity in egg and tissues accounting for only <0.23% of the applied dose (0.008–0.676 ppm). The matrices for both ^{14}C-pyridine label and ^{14}C-fluoroaniline label high-dose studies will be analysed to confirm metabolite identification. However, preliminary analysis of fat samples collected from the treated hens have indicated that the parent picolinafen accounts for the majority of the TRRs (0.20 ppm). This is consistent with the goat metabolism study where the parent was identified as the predominant residue in fat. Preliminary analysis and quantitation of the residue in hen excreta indicated that the parent picolinafen was predominantly metabolized and excreted to more polar compounds. Identification of the metabolites has not been confirmed; however, based upon retention time, the registrant claims that both the parent and the hydrolysed product (CL 153815) appear to be present, as in the rat and goat study.
Proposed Metabolic Pathway	The registrant has also stated that many of the likely metabolites that are formed following the hydrolysis of picolinafen are well described in the literature (e.g., 4-acetamidophenol: the metabolite of 4-fluoroaniline, commonly known as acetaminophen).
Residue of Concern (ROC)	According to the registrant, the metabolism of picolinafen in hen is expected to proceed via the same pathways as those in the goat and rat since all animals possess the same enzymes required for the metabolism of this compound: hydrolysis, n-acetylation and phase I metabolism followed by various phase II transformations such as glucuronidation, sulfonation or mercapturic acid. To be determined upon submission of the entire study.

NATURE OF THE RESIDUE —WHEAT	
Radiolabelling positions	[aniline-^{14}C]-picolinafen and [pyridine^{14}C]-picolinafen
Distribution of Radioactivity	Picolinafen (formulated as a 200 g/L emulsifiable concentrate) was applied to wheat (variety: Turbo) at the end of the tillering stage (BBCH-Code 25-29) at a nominal rate of 100 g a.i./ha. Foliage samples were harvested 0 and 27 days after treatment while the ears and straw were harvested 86 days following application. The TRRs in the foliage and straw ranged from 0.2–3.7 ppm, while in seed and husk, TRRs were ≤0.004 ppm and ≤0.013 ppm, respectively, demonstrating that picolinafen and its degradates do not translocate significantly from the point of application to the seed. For the 0-DAT foliage, residues in the surface rinse accounted for the majority (average of 84%) of the radioactivity, with the parent, picolinafen, identified as the predominant component (79–82% of the TRRs). The remaining 16% of the TRRs were incorporated into the whole plant, most of which were extractable in acetone and identified as the parent compound (15–16 % of the TRRs). An average of 24% of the TRRs from the lower treated plant parts of the 27-DAT foliage were characterized as surface residues, the majority of which was identified as the parent compound (21% of the TRRs). Sequential extractions of the incorporated ^{14}C-residues with organic solvents released an additional 65% of the TRRs. The parent was identified as the predominant residue, accounting for an overall average of 45% of the TRRs. The acid metabolite CL 153815 and CL 7693 were also detected at low levels. Unextractable residues (11–12.5% of the TRRs) were subjected to acid cleavage with 0.1 M HCl followed by extraction with ACN:1M HCl, releasing an additional 7–9% of the TRRs. The ^{14}C-residues in the 86-DAT straw were evenly distributed among the surface rinse and incorporated radioactivity. The most prominent component in all fractions was the unchanged parent (average of 50% of the TRRs). To elucidate the binding of ^{14}C-residues to plant constituents, a selective extraction of main cell wall components was performed with the unextractable residues (average of 30% of the TRRs), demonstrating that 6–7% of the TRRs was found in water soluble polysaccharides and proteins, 1–3% in pectine, 7% in lignin and 4–6% in each of the noncellulosic polysaccharides and cellulose.
Proposed Metabolic Pathway	The metabolism of picolinafen appears to proceed via the cleavage of the amide bond, resulting in the formation of the acid metabolite CL 153815 (6-[(α, α, α-trifluoro-m-tolyl)oxy]-picolinic acid) and CL 7693 (p-fluoroaniline). The presence of the aniline metabolite can only be speculated, as very low levels of radioactivity co-chromatographed with the corresponding reference compound. This is most likely due to the extensive degradation of this metabolite and its subsequent incorporation into natural plant constituents.
Residue of Concern (ROC)	Picolinafen

CONFINED FIELD ACCUMULATION IN ROTATIONAL CROPS—Carrots, peas, sugar beets, sunflowers, lettuce, and soybeans		
Radiolabelling positions	[aniline-^{14}C]-picolinafen and [pyridine^{14}C]-picolinafen Radiolabelled picolinafen was applied once to either loam soil or wheat (primary crop) at a rate of 100 g a.i./ha, equivalent to 2× the proposed rate on wheat and barley. Carrots, peas, sugar beets, and sunflowers were planted 30 days after foliar treatment to wheat, while lettuce, soybean, and carrots were planted 11 months after foliar treatment to wheat. TRRs in secondary crops planted 30 days and 11 months after a post-emergence treatment with either label to wheat (primary crop) were all below the LOQ of 0.01 ppm. Results indicated that highest residue levels were found in carrot roots and tops (0.006 ppm) from the pyridine label and in sugar beet root (0.004 ppm) from the aniline label, when planted 30 DAT. At the 11-month planting interval, highest residue levels were 0.005 ppm in soybean straw (pyridine) and residues were all below 0.003 ppm from the aniline label. As TRRs were below the LOQ in the RACs of secondary crops, planted 30 days after post-emergence application to wheat, a supplemental trial was conducted where lettuce, carrot and soybean were planted 30 days after a bare-ground soil treatment with either aniline or pyridine label. Results from this trial showed that residue levels were also below the LOQ of 0.01 ppm when the test substances were applied directly to the soil. Highest residues were detected in soybean straw (0.003–0.006 ppm). Since there was no measurable residue in the RACs of all rotated crops, no attempt was made to identify or characterize the nature of ^{14}C-residues in these crops.	
Residue of Concern (ROC)	Picolinafen	
FIELD ACCUMULATION IN ROTATIONAL CROPS	The registrant submitted a rationale requesting a waiver of the requirement of a field crop rotation study. The rationale was accepted on the basis that TRRs in succeeding crops did not exceed 0.01 ppm when planted 30 days and 11 months after foliar application to wheat (primary crop) and 30 days following direct soil application.	
RESIDUE ANALYTICAL METHOD — PLANTS		
Method ID	FAMS 079-01	M 3313
Analytes	picolinafen	picolinafen
Instrument/Detector	GC/NPD	GC/MS

Instrument Parameters	Temperature program: 50ºC (1.3 min) to 280ºC (6.5 min) at 25°C/min Helium flow rate: 25 mL/min Injection volume: 1μL	Temperature program: 50ºC (0.5 min) to 250ºC (2 min) at 14.5°C/min Injector Temperature: 300ºC Transfer Line Temperature: 250ºC Carrier Gas and Flow Rate: Hydrogen at 5 psi Split Valve: Open at 0.5 min Injection Volume (Autoinjector): 1μL
Column	Fused silica capillary column, 15 m × 0.25 mm ID with 0.25μm film thickness Liquid phase: 5% phenyl-methylsilicone	5 m × 0.25 mm ID, 0.25 micron DB-5MS
Standardization method	External standard for retention time and detector response/calibration	External standard for retention time and detector response/calibration
Stability of primary and/or secondary standard solutions	2 months at 6ºC (± 4ºC)	3 months when stored in amber bottles with polyseal caps in refrigerator
Retention times	approximately 10.4 minutes	approximately 9.2 minutes
Limit of detection (LOD)	0.005 mg/kg	0.01 mg/kg
Limit of quantification (LOQ)	0.05 mg/kg	0.05 mg/kg
Repeatability/Precision	Recoveries of picolinafen in grain, straw, and whole plant ranged from 84–107% (SD <10%), indicating acceptable accuracy/precision in the range of 0.05–5.0 mg/kg.	Recoveries ranged from 71–150% (SD <22%) when wheat and barley forage, grain, hay, and straw are spiked with picolinafen at levels ranging from 0.05–5.70 mg/kg, indicating acceptable accuracy/precision.
Reproducibility	Method FAMS 079-01 was proposed as a data gathering method only; therefore, independent laboratory method validation [ILV] was not required.	An ILV was conducted to verify the reliability of method No. M 3313 for the determination of picolinafen residues in cereal matrices. When spiked with picolinafen at the method LOQ of 0.05 mg/kg recoveries were: barley hay, 88 ± 3.8 (n=4); barley forage, 117 ±10 (n=4); wheat grain, 114 ± 14 (n=4); and wheat straw, 81 ± 6.2 (n=5). The values obtained indicate that method No. M 3313 is reproducible.

Linearity	The method/detector response was linear (coefficient of determination, r^2>0.995) within the range of 0.05–2.0 μg/mL.	Procedural method validation was not provided and concurrent method validation did not test for linearity of the method/detector response; however, linearity checks conducted by the independent laboratory over a six-week period demonstrated that the method/detector response was linear (coefficient of determination, r^2>0.995) within the range of 0.125–0.5 ng/mL.
Specificity	The control chromatograms generally do not have peaks above the chromatographic background, and the spiked sample chromatograms contain a well defined and symmetrical peak within the area of analytical interest. There appeared to be no carry-over to the subsequent chromatograms.	The control chromatograms generally do not have peaks above the chromatographic background, and the spiked sample chromatograms contain only the analyte peak of interest. Peaks were well defined and symmetrical. There appeared to be no carry-over to the subsequent chromatograms.
MULTI-RESIDUE METHOD	Samples of wheat grain spiked with picolinafen at the LOQ (0.01 mg/kg) and 10× the LOQ, were analyzed according to the European DFG Multi-Residue Method S19 (GC/ECD) with modified extraction. When spiked at the LOQ, recoveries ranged from 85–95% (91 ± 4.6% (5.1); n = 5), demonstrating the capability of this method to be used for enforcement purposes.	
RESIDUE ANALYTICAL METHOD—ANIMALS		
Method ID	FAMS 109-01	
Analytes	picolinafen and CL 153815	
Instrument/Detector	HPLC with MS/MS detection	
Instrument Parameters	Temperature: ambient Injection volume: 50μL Mobile phase: acetonitrile:methanol:water (50:25:25, v:v:v) + 0.1% formic Flow rate: 1 mL/min	
Column	Luna 3μ C18 (2), 100 mm × 4.6 mm, Phenomex No. 00D-4251-E)	
Standardization method	External standard for retention time and detector response/calibration	
Stability of priary and/or secondary standard solutions	3 weeks at 6ºC (± 4ºC)	
Retention times	picolinafen approximately 7.4 minutes CL 153815 approximately 2.4 minutes	

Limit of detection (LOD)	Milk: 0.001 mg/kg Meat, egg and fat: 0.002 mg/kg
Limit of quantification (LOQ)	Milk: 0.01 mg/kg Meat, egg, and fat: 0.02 mg/kg
Repeatability/Precision	When spiked with picolinafen at the LOQ, recoveries ranged from 102 to 112% (107 ± 3.9) in milk, 68–78% (73 ±5.7) in meat, 65–95% (77 ± 15.7) in egg, and 69–75% (71 ± 3.2) in fat. When spiked with the metabolite CL 153815 at the LOQ, recoveries ranged from 96 to 116% (107 ± 7.5) in milk, 59–68% (64 ± 5.2) in meat, 61–83% (70 ± 12.2) in egg, and 62–68% (64 ± 3.7) in fat. Although recoveries were low for meat, eggs and fat, the CVs did not exceed 20%, indicating acceptable repeatability of the method.
Reproducibility	When spiked with picolinafen at the LOQ, the recoveries obtained by the independent laboratory were comparable ranging from 84 to 90% (87 ± 3.0) in milk, 81–90% (84 ± 5.0) in meat, 60–66% (63 ± 4.0) in eggs, and 68–75% (72 ± 4.2) in fat. When spiked with CL 153815 recoveries in milk, meat, egg and fat ranged from 95 to 111% (102 ± 7.1), 69–79% (73 ± 5.7), 69–77% (72 ± 6.0), and 68–75% (72 ± 2.7), respectively. These values indicate that the method has good reproducibility.
Linearity	The method/detector response in matrix was linear (coefficient of determination, $r^2 > 0.9992$) within the range of 5–100 ng/mL
Specificity	The control chromatograms generally have no peak above the chromatographic background, and the spiked sample chromatograms contain only the analyte peak of interest. Peaks were well defined and symmetrical. There appeared to be no carry-over to the subsequent chromatograms.
MULTI-RESIDUE METHOD	Samples of milk, meat, egg, and fat spiked with picolinafen at the LOQ (0.01 mg/kg for milk and 0.02 mg/kg for meat, egg, and fat) and 10× the LOQ, were analyzed according to the European DFG Multi-Residue Method S19 (GC/ECD) with modified extraction. At the LOQ, average recoveries of picolinafen in these matrices were 81 ± 9.3%, 83 ± 6.1%, 87 ± 6.2%, and 86 ± 4.3%, respectively, demonstrating the capability of this method to be used for enforcement purposes.

STORAGE STABILITY DATA ***Plant***	Samples of treated whole green plant and straw, collected from 1996 supervised residue trials (formulations: AC900001 750g a.i./kg WG and AC 900001 250 g a.i./L SC) and untreated grain spiked with picolinafen (98.7% a.i.) at a level of 0.5mg/kg were stored at -18°C for a duration of 12 months. The whole plant, straw, and grain commodities were analyzed using the GC/NPD data gathering method FAMS079-01. The average recoveries of picolinafen (triplicate samples) in the 12-month frozen samples were 112% (green plant), 75% (straw), and 96% (grain). Therefore, residues of picolinafen were stable under frozen storage (-18°C) in whole green plant, straw, and grain for up to 12 months.
Animal	The registrant requested a waiver of the animal storage stability study. The waiver was deemed acceptable based on the following: residues of picolinafen and the associated metabolites are not expected to exceed the method LOD in meat, milk, and eggs when livestock is exposed to feed treated with AC 900001 Herbicide under proposed conditions and the radioprofiles of fat samples, collected from the metabolism study, following storage, were qualitatively similar to the radioprofiles from the original analyses.
CROP FIELD TRIALS	Supervised crop field trials on wheat (20) and barley (16) were conducted in sites located throughout Manitoba, Saskatchewan, and Alberta, as well as North and South Dakota, U.S.A. (zones 5, 7, 7A, and 14). When treated with AC 900001 750 g a.i./kg (SFO9617) at a seasonal application rate of 50 g a.i./ha and harvested 27–115 days following application, residues of picolinafen were <0.05 ppm (method LOQ) in wheat grain and straw and barley grain and straw. In wheat hay, barley hay, and forage, harvested at maturity (28–108 days post application), residues of picolinafen ranged from <0.05 to 0.194 ppm, <0.05–0.066 ppm, and <0.05–0.0782 ppm, respectively.
RESIDUE DECLINE	Residue decline was evaluated by collecting barley forage samples at 0.1 (immediately following application), 7, 14, 21, and 28 days following application. The decline data demonstrated that residues of picolinafen dissipated rapidly by day 28 (<0.05 ppm) with a half-life of approximately 10 days. Therefore, with a grazing restriction of 30 days, cattle are not expected to be exposed to feed containing measurable residues of picolinafen, decreasing the likelihood of transfer of residues to meat and milk.
PROCESSED FOOD/FEED	The registrant has requested a waiver for the requirement of a processing study. The waiver was determined to be acceptable based on the following: residues of picolinafen in wheat and barley grain did not exceed the method LOQ (0.05 ppm) when treated according to the proposed label rate of 50 g a.i./ha/season and harvested 60 days following application, and the findings from the metabolism study where TRRs in seed did not exceed 0.004 ppm following treatment at 2× the proposed label rate.

<table>
<tr><td>DAIRY CATTLE AND POULTRY FEEDING</td><td colspan="2">The registrant submitted a rationale requesting a waiver for the requirement of livestock feeding studies. The rationale was deemed acceptable for the dairy cattle feeding study on the basis that residues in feed (forage, hay, straw, and grain) did not exceed 0.2 ppm, when treated according to the proposed use pattern, and that the lactating goat metabolism study demonstrated no accumulation of residues of picolinafen and CL 153815 in meat, meat by-products, and milk, when animals were exposed to highly exaggerated dietary doses.

Based on a theoretical calculation of the anticipated dietary burden, using maximum residues in wheat and barley forage, straw, hay, and grain (collected from the supervised residue trials) and the results from the lactating goat metabolism study, anticipated residues of picolinafen and CL 153815 in livestock matrices are not expected to exceed the LODs reported in the proposed enforcement method FAMS 109-01. Consequently, MRLs for meat, meat by-products, and milk will not be established.

The requirement of a poultry feeding study will be assessed upon submission and review of the laying hen metabolism study.</td></tr>
<tr><td>PROPOSED MRLs</td><td colspan="2">Barley and wheat grain 0.05 ppm</td></tr>
<tr><td>U.S. TOLERANCES</td><td colspan="2">Not registered in the U.S.</td></tr>
<tr><td>CODEX MRLs</td><td colspan="2">Picolinafen has not been reviewed by the JMPR (Joint Meeting on Pesticide Residues)</td></tr>
<tr><td rowspan="5">DIETARY RISK ASSESSMENT (DRA)
DEEM™ Version 7.76
1994–1998 Continuing Survey of Food Intake for Individuals

ADI = 0.014 mg/kg bw
EEC Picolinafen = 0.08 μg/L
EEC (CL 153815) = 0.61 μg/L</td><td>POPULATION</td><td>Level I ESTIMATED RISK (% of ADI)
Food (MRLs) + Combined EECs</td></tr>
<tr><td>All infants <1 yr</td><td>0.7</td></tr>
<tr><td>Children 1–6 yrs</td><td>1.6</td></tr>
<tr><td>Females 13+</td><td>0.6</td></tr>
<tr><td>Total Population</td><td>0.8</td></tr>
</table>

Table 4 Environmental Assessment: Physical and chemical properties of the transformation product, CL 153815, that are relevant to the environment

Property	Value	Comments
Solubility in water	pH 5 120 mg/L pH 7 18 400 mg/L pH 9 72 400 mg/L (estimated)	Estimates indicate CL 153815 is very soluble in water. Empirical data are required.
Vapour pressure	7.87×10^{-6} mm Hg (estimated)	Slightly volatile Empirical data are required.
Henry's Law Constant	1.6×10^{-8} atm.m^3/mol (estimated)	Non-volatile from moist soil and water surfaces
log K_{ow}	2.95 at pH 5 1.15 at pH 7 0.66 at pH 9 (estimated)	Not likely to bioaccumulate Empirical data are required.
pK_a	3.25	Relatively strong acid Anion at environmentally relevant pH conditions (pH 5 to pH 9) Potential for leaching.
UV–visible absorption	λ_{max} <290 nm	Photolysis is not expected to be an important route of transformation.

Table 5 Environmental Assessment: Summary of abiotic transformation rates of picolinafen and the major transformation product, CL 153815

Fate Process	picolinafen	CL 153815	Interpretation
Hydrolysis	Stable at pH 4, pH 7, and pH 9	Not expected between pH 5 and pH 9	Hydrolysis in soil is not a transformation pathway for picolinafen or CL 153815.
Photolysis—soil	DT_{50} = 30 d, 1st order	No data	Photolysis in soil is not an important transformation pathway for picolinafen.
Photolysis—water	DT_{50} = 12.1 d DT_{50} = 24.8 d, pH 5 DT_{50} = 31.4 d, pH 7 DT_{50} = 22.6 d, pH 9	Very slowly photolysed; stable under alkaline conditions	Photolysis in water is not an important transformation pathway for picolinafen or CL 153815.

Table 6 Environmental Assessment: Summary of biotransformation rates of picolinafen and its major transformation product, CL 153815

Fate Process	Picolinafen	CL 153815	Interpretation[a]
Aerobic soil	DT_{50} =<2–14 d DT_{90} = 34–149 d	DT_{50} = 30–77 d	picolinafen is non-persistent. CL 153815 is slightly to moderately persistent.
Anaerobic soil	Data inconclusive	No dissipation	CL 153815 is persistent.
Aerobic water layer	DT_{50} = 1.1–1.4 d DT_{80-90} = 4.5–5.8 d	DT_{50} = 10.9–24.4 d DT_{90} = 36.3–81 d	picolinafen is non-persistent. CL 153815 is slightly persistent.
Aerobic water/ anaerobic sediment	DT_{50} = 6.2 d DT_{90} = 20.5–20.6 d	DT_{50} = 45.3–70.1 d DT_{90} = 151–233 d	picolinafen is non-persistent. CL 153815 is moderately persistent.
Anaerobic water/ anaerobic sediment	DT_{50} = 18.7 d DT_{90} = 62.2 d	Persistent in both phases	picolinafen is non-persistent. CL 153815 is persistent.
Anaerobic water layer	DT_{50} = 15.4 d DT_{90} = 51.2 d	DT_{50} = 197 d DT_{90} = 654 d	picolinafen is slightly persistent. CL 153815 is persistent.
Anaerobic sediment layer	DT_{50} = 6.4–12.7 d DT_{90} = 21.3–42.2 d	DT_{50} = 645 d	picolinafen is non-persistent. CL 153815 is persistent.

[a] Classification of Goring et al. (1975) for persistence in soil and classification of McEwen and Stephenson (1979) for persistence in aquatic systems

Table 7 Environmental Assessment: Properties of CL 153815 that support its potential to leach and contaminate ground water

Property	CL 153815 value	Cohen et al. (1984) criterion	Meets criterion?
Solubility in water	≥120 mg/L	>30 mg/L	Yes
K_d	≥6.3	<5	No
K_{oc}	160–783	<300	Yes
Henry's Law Constant	1.6×10^{-8} atm.m^3/mol	$<10^{-2}$ atm.m^3/mol	Yes
Ionic state	Negatively charged at ambient pH	Negatively charged at ambient pH	Yes
Hydrolysis half-life	Stable	>20 weeks	Yes
Photolysis half-life	Stable	>1 week	Yes
Half-life in soil	>4 weeks	>2–3 weeks	Yes

Table 8 Environmental Assessment: Summary of the field dissipation of picolinafen and its major transformation product, CL 153815

System	picolinafen	CL 153815	Interpretation
Terrestrial	$t_{1/2}$ = 59–62 d $t_{9/10}$ = 195–208 d ND 147 DAT Fairview, AB $t_{1/2}$ = 44 d $t_{9/10}$ = 148 d ND 359 DAT Lethbridge, AB $t_{1/2}$ = 15 d $t_{9/10}$ = 50 d ND 361 DAT Minto, MB No residue below 15-cm soil depth	Max 9.2 µg/kg 90 DAT 6.9 µg/kg 148 DAT Fairview, AB Max 11.1 µg/kg 60 DAT 5.9 µg/kg 359 DAT ND 451 DAT Lethbridge, AB Max 9.8 µg/kg 90 DAT 6.3 µg/kg 361 DAT ND 453 DAT Minto, MB No residue below 15-cm soil depth	picolinafen is slightly to moderately persistent, and is not expected to carry-over to the next growing season. 53–64% of CL 153815 carried over to the next growing season. No leaching under typical field conditions

DAT=days after treatment; Max=maximum; ND=not detected

Table 9 Environmental Assessment: Water modelling input parameters

Parameter	picolinafen	CL 153815
Maximum allowable rate per year	0.05 kg a.i./ha	0.05 kg a.i./ha (assumed 100% conversion)
Maximum number of applications per year	1	1
Minimum interval between applications	Not applicable	Not applicable
Timing of applications	April 20 (earliest date)	April 20 (earliest date)
Method of application	Groundboom	Groundboom
Molecular weight	376.3	283.21
Solubility in water at pH 7	4.7×10^{-8} mg a.i./L	18 400 mg/L (estimated)
Vapour pressure	1.24×10^{-9} mm Hg	7.87×10^{-6} mm Hg (estimated)
Henry's Law Constant	1.6×10^{-8} atm.m^3/mol	1.6×10^{-8} atm.m^3/mol (estimated)
K_{ow} at pH 7	269153	14.125 (estimated)
Hydrolysis half-life	Stable	Stable
Photolysis half-life in soil	Stable	Stable
Photolysis half-life in water	31 d	Stable
Aerobic soil biotransformation	DT_{50} = 14 d (longest value)	DT_{50} = 77 d (longest value)
Aerobic aquatic biotransformation	whole system DT_{50} = 6.4 d (longest value)	whole system DT_{50} = 71.1 d (longest value)
Anaerobic aquatic biotransformation	whole system DT_{50} = 18.7 d	Stable
Adsorption K_d	248 L/kg (smallest value)	6.3 L/kg (smallest value)
Adsorption K_{oc}	15 100 L/kg (smallest value)	160 L/kg (smallest value)

Table 10 Environmental Assessment: Maximum EEC in vegetation and insects after a direct overspray

Matrix	EEC (mg a.i./kg fw)[a]	Fresh/dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	11	3.3[b]	35
Leaves and leafy crops	5.6	11[b]	62
Long grass	4.9	4.4[b]	22
Forage crops	6.0	5.4[b]	32
Small insects	2.6	3.8[c]	9.9
Pods with seeds	0.54	3.9[c]	2.1
Large insects	0.44	3.8[c]	1.7
Grain and seeds	0.44	3.8[c]	1.7
Fruit	0.67	7.6[c]	5.1

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al. (1994)

[b] Fresh/dry weight ratios from Harris (1975)

[c] Fresh/dry weight ratios from Spector (1956)

Table 11 Environmental Assessment: Maximum EEC in diets of birds and mammals

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	8.8
Mallard duck	30% large insects 70% grain	1.7
Rat	70% short grass 20% grain/seeds 10% large insects	25
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	25
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	38

Table 12 Environmental Assessment: Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value (effect in brackets)	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute (14-d)	picolinafen	LC_{50} >1000 mg a.i./kg NOEC (↓ body weight) 111 mg a.i./kg	—
		CL 153815	LC_{50} 476.5 mg a.i./kg NOEC (↑ mortality) 125 mg a.i./kg	—
Bee	Oral	picolinafen	LD_{50} >150 µg a.i./bee NOEC 150 µg a.i./bee*	Relatively non-toxic[c]
	Contact	picolinafen	LD_{50} >200 µg a.i./bee NOEC 200 µg a.i./bee*	Relatively non-toxic[c]
Predatory mite	Contact inert surface	SF09617 (74.7%) 133 g product/ha (2× field rate)	0% (↑ mortality) 10% (↓ reproduction)	Harmless[b]
		SF09617 (74.7%) 0.8 g product/ha (0.012× field rate)	0.4% (↑ mortality) 13.5% (↓ reproduction)	
Ground dwelling predator (spider)	Contact inert surface	SF09617 (74.7%) 133 g product/ha (2× field rate)	0% (↑ mortality) 1% (↑ food uptake)	Harmless[b]
		SF09617 (74.7%) 0.8 g product/ha (0.012× field rate)	5% (↑ mortality) 7% (↓ food uptake)	
Ground dwelling predator (beetle)	Contact inert surface	SF09617 (74.7%) 133 g product/ha (2× field rate)	0% (↑ mortality) 0% (↓ food uptake)	Harmless[b]
Parasitoid	Contact inert surface	SF09617 (74.7%) 133 g product/ha (2× field rate)	0% (↑ mortality) 6% (↓ reproduction)	Harmless[b]
		SF09617 (74.7%) 0.8 g product/ha (0.012× field rate)	0% (↑ mortality) 24% (↓ reproduction)	

Organism	Exposure	Test substance	Endpoint value (effect in brackets)	Degree of toxicity[a]
Birds				
Bobwhite quail	Acute	picolinafen	LC_{50} >2250 mg/kg bw NOEL (↓ body weight) 1350 mg/kg bw	Practically non-toxic
	Acute dietary (8-d)	picolinafen	LC_{50} >5314 mg/kg diet NOEC (↓ body weight) 270 mg/kg diet	Practically non-toxic
	Chronic dietary (28-d)	picolinafen	LC_{50} >2700 mg/kg diet NOEC 2700 mg/kg diet*	—
	Reproduction	picolinafen	NOEC 864 mg/kd diet*	—
Mallard duck	Acute	picolinafen	LC_{50} >2250 mg/kg bw NOEL 2250 mg/kg bw*	Practically non-toxic
	Acute dietary (8-d)	picolinafen	LC_{50} >5314 mg/kg diet NOEC (↓ body weight, ↓ food uptake) 729 mg/kg diet	Practically non-toxic
	Chronic dietary (28-d)	picolinafen	LC_{50} >2700 mg/kg diet NOEC (↓ egg number) 300 mg/kg diet	—
	Reproduction	picolinafen	NOEC 864 mg/kd diet*	—
Mammals				
Rat	Acute	picolinafen	LD_{50} >5000 mg a.i./kg bw NOEL 5000 mg a.i./kg bw*	Practically non-toxic
	Dietary (2 years)	picolinafen	LC_{50} >500 mg a.i./kg diet NOEC (tissue effects) 50 mg a.i./kg diet	—
	Reproduction (1-gen)	picolinafen	LC_{50} >500 mg a.i./kg diet NOEC 500 mg a.i./kg diet*	—
Mouse	Dietary (78-wk)	picolinafen	LC_{50} >800 mg a.i./kg diet NOEC (tissue effects) 40 mg a.i./kg diet	—
Vascular plants				
Vascular plant (lettuce)	Seedling emergence	SF09617 (74.7%)	EC_{25} 102 g formulation/ha	—
	Vegetative vigour	SF09617 (74.7%)	EC_{25} 60 g formulation/ha	—

[a] U.S. EPA classification, where applicable

[b] Classification by Hassan et al. (1994) for laboratory tests conducted with inert substrates: <30% harmless; 30–79% slightly harmful; 80–99% moderately harmful; >99% harmful

[c] Atkins et al. (1981) classification

* No effects at highest dose tested

Table 13 Environmental Assessment: Effects on aquatic organisms

Organism	Exposure	Test substance	Endpoint value (mg/L) (effect in brackets)	Degree of toxicity[a]
Freshwater species				
Daphnia magna	Acute (48-h)	picolinafen	LC_{50} >0.45 NOEC 0.45*	Not toxic at solubility limit
		CL 153815	LC_{50} >98 NOEC (↑ mortality) 6.0	Practically non-toxic
	Chronic (21-d)	picolinafen	LOEC (↓ survival, ↓ reproduction, ↓ growth) 0.0149 NOEC (↓ survival, ↓ reproduction, ↓ growth) 0.00706	—
Sediment dwelling midge	Chronic (28-d)	picolinafen	LC_{50} >0.69 NOEC (↓ growth) 0.18	Not toxic at solubility limit
Rainbow trout	Acute (96-h)	picolinafen	LC_{50} >0.68 NOEC 0.68*	Not toxic at solubility limit
	Acute (96-h)	CL 153815	LC_{50} >100 NOEC 100*	Practically non-toxic
	ELS	picolinafen	LOEC (↓ growth) 0.012 NOEC (↓ growth) 0.0064	—
	Sub-chronic (28-d)	picolinafen	NOEC 0.094*	—
Bluegill sunfish	Acute (96-h)	picolinafen	LC_{50} >0.57 NOEC 0.57*	Not toxic at solubility limit
Blue-green alga	Chronic (120-h)	picolinafen	EC_{50} (↓ body weight) 0.34 NOEC (↓ body weight) 0.017	—
Green alga	Chronic (72-h)	picolinafen	EC_{50} (↓ body weight) 0.00018 NOEC (↓ body weight) 0.000068	—
		CL 153815	EC_{50} (↓ body weight, ↓ growth) 27 NOEC (↓ body weight, ↓ growth) 12	—
Vascular plant	Chronic (14-d)	picolinafen	EC_{25} (↓ frond number) 0.026 EC_{50} (↓ frond number) 0.046 NOEC (↓ frond number) 0.006	—

[a] U.S. EPA classification, where applicable

* No effects at highest dose tested

Table 14 Environmental Assessment: Risk classification scheme

Margin of safety (MOS)	Degree of risk
≥10	Negligible
1 to <10	Low
0.1 to <1	Moderate
0.01 to <0.1	High
0.001 to <0.01	Very high
<0.001	Extremely high

Table 15 Environmental Assessment: Margin of safety values for terrestrial organisms

Organism	Test substance	EEC	Toxicity	MOS	Degree of risk
Short-term risk of mortality					
Earthworm	picolinafen	0.022 mg/kg soil	LC_{50} >1000 mg/kg soil	45 454	Negligible
	CL 153815	0.026 mg/kg soil	LC_{50} 476.5 mg/kg soil	18 326	Negligible
Bobwhite quail	picolinafen	8.8 mg/kg diet	LC_{50} >5314 mg/kg diet	603	Negligible
Mallard duck	picolinafen	1.7 mg/kg diet	LC_{50} >5314 mg/kg diet	3 125	Negligible
Rat	picolinafen	25 mg/kg diet	LC_{50} >500 mg/kg diet	20	Negligible
Short-term risk of sub-lethal effects					
Earthworm	picolinafen	0.022 mg/kg	NOEC 111 mg/kg	5 045	Negligible
	CL 153815	0.026 mg/kg	NOEC 125 mg/kg	4 807	Negligible
Bobwhite quail	picolinafen	8.8 mg/kg diet	NOEC 270 mg/kg diet	30	Negligible
Mallard duck	picolinafen	1.7 mg/kg diet	NOEC 729 mg/kg diet	428	Negligible
Rat	picolinafen	25 mg/kg diet	NOEC 40 mg/kg diet	1.6	Low
Lettuce	picolinafen	67 g product/ha	EC_{25} 60 g product/ha	0.8	Moderate

Table 16 Environmental Assessment: Margin of safety values for aquatic species

Organism	EEC (mg a.i./L)	Toxicity (mg a.i./L)	MOS	Degree of risk
Short-term risk to most sensitive species				
S. capricornutum	0.0167	NOEC 0.000068	0.004	Very high
Short-term risk to other species				
L. gibba	0.0167	NOEC 0.006	0.35	Moderate
A. flos-aquae	0.0167	NOEC 0.017	1	Low
D. magna	0.0167	NOEC 0.45	26	Negligible
O. mykiss	0.0167	NOEC 0.68	40	Negligible
L. macrochirus	0.0167	NOEC 0.57	34	Negligible