Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2002-03

Pymetrozine (TGAI)
Endeavor 50WG
Fulfill 50WG

The active ingredient pymetrozine and associated end-use products, Endeavour 50WG for the control of aphids, including green peach aphid and melon aphid, and whiteflies, including greenhouse whitefly and silverleaf whitefly, on non-food greenhouse uses on flowering and ornamental plants; and Fulfill 50WG for the control of aphids, including buckthorn, foxglove, green peach and potato aphids, on potatoes, are proposed for full registration under Section 13 of the Pest Control Products (PCP) Regulations.

This proposed regulatory decision document (PRDD) provides a summary of data received and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comment on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address below.

(publié aussi en français)

December 5, 2002

This document is published by the Alternative Strategies and Regulatory Affairs Division, Pest Management Regulatory Agency. For further information, please contact:

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ISBN: 0-662-33257-1
Catalogue number: H113-19/2002-1E-IN

Foreword

The submissions for registration of the active ingredient pymetrozine and associated end-use products, Endeavour 50WG for the control of aphids, including green peach aphid and melon aphid, and whiteflies, including greenhouse whitefly and silverleaf whitefly, on non-food greenhouse uses on flowering and ornamental plants, and Fulfill 50WG for the control of aphids, including buckthorn, foxglove, green peach and potato aphids, on potatoes, an insecticide developed by Syngenta Crop Protection Canada Inc., has been reviewed by Health Canada's Pest Management Regulatory Agency (PMRA) under the User Requested Minor Use Registration Program (URMUR). This active ingredient and associated uses were reviewed as reduced risk pesticides under the United States (U.S.) Environmental Protection Agency's (EPA) Reduced Risk Pesticides Program.

The submissions have been reviewed by the PMRA under the User Requested Minor Use Registration Program (URMUR). Reviews from the U.S. EPA as well as reviews from other Organisation for Economic Co-operation and Deveolopment (OECD) countries were provided with the submissions as required for URMURs. User support included the Keystone Vegetable Producers Association, Potato Growers of Alberta, Saskatchewan Seed Potato Growers Association, Alberta Agriculture, Food and Rural Development, Western Potato Council, Saskatchewan Agriculture and Food, PEI Department of Agriculture and Forestry, Prince Edward Island Potato Board, B.C. Potato and Vegetable Growers Association, Cavendish Farms, Manitoba Agriculture, B.C. Ministry of Agriculture, Food and Fisheries, and Agriculture and Agri-Food Canada, Research Branch.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations and has found it sufficient pursuant to Section 18.b, to allow a determination of the safety, merit and value of pymetrozine and associated end-use products, Endeavor 50WG and Fulfill 50WG. The PMRA has concluded that the use of pymetrozine and associated end-use products, Endeavor 50WG and Fulfill 50WG in accordance with their labels have merit and value consistent with Section 18.c of the PCP Regulations and do not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of pymetrozine and associated end-use products, Endeavour 50WG for the control of aphids, including green peach aphid and melon aphid, and whiteflies, including greenhouse whitefly and silverleaf whitefly, on non-food greenhouse uses on flowering and ornamental plants; and Fulfill 50WG for the control of aphids, including buckthorn, foxglove, green peach and potato aphids, on potatoes, are proposed for full registration under Section 13 of the PCP Regulations.

A maximum residue limit (MRL) of 0.02 ppm is proposed to cover residues of pymetrozine in or on potatoes.

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

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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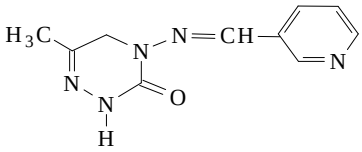
1.0 The active substance, its properties, uses, classification and labelling

1.1 Identity of the active substance and preparation containing it

Table 1.1 Identity of the active substance and preparation containing it

Active substance	**Pymetrozine**
Function	Insecticide
Chemical name • International Union of Pure and Applied Chemistry • Chemical Abstract Services (CAS)	 (E)-6-methyl-4-[(pyridin-3-ylmethylene)-amino]-4,5-dihydro-2H-[1,2,4]triazin-3-one 1,2,4-triazin-3(2H)-one, 4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene)amino]
CAS number	123312-89-0
Molecular formula	$C_{10}H_{11}N_5O$
Molecular weight	217.2
Structural formula	
Nominal purity of active	98.3% nominal (limits: 95–100%)
Identity of relevant impurities of toxicological, environmental or other significance	Based on the raw materials, the manufacturing process used and the chemical structures of the active and impurities, the technical substance is not expected to contain any toxic microcontaminants as identified in Section 2.13.4 of DIR98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, or any TSMP Track-1 substances as identified in Appendix II of DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. The residual hydrazine (a starting material) in the product is expected to be below the EPA limit of 15 ppm hydrazine, as it will react with cyclohexanone, another raw material used in the manufacturing process.

1.2 Physical and chemical properties of active substance

Table 1.2 Technical product

Property	Result	Comment
Colour and physical state	White-beige, solid	
Odour	Slightly sweet odour	
Melting point or range	217°C	
Boiling point or range	N/A	
Specific gravity	1.36 g/cm^3	
Vapour pressure at 25°C	$<4 \times 10^{-6}$ Pa	Pymetrozine is considered to be non-volatile under field conditions.
Henry's Law Constant (Pa/m^3/mol)	$<3.0 \times 10^{-6}$ (1/H = 8.3E+8)	Pymetrozine is considered to be non-volatile from moist soil and water surfaces.
Ultraviolet (UV) – visible spectrum	Solvent / λ_{max} (nm) / ϵ (L·mol^{-1}·cm^{-1}) CH_3OH: 245.6 / 9 500; 299.2 / 20 500 CH_3OH + HCl: 240.0 / 9 700; 308.6 / 16 500 CH_3OH + NaOH: 245.6 / 9 400; 299.2 / 20 200 No absorption was observed between 400 and 750 nm.	Pymetrozine has a potential for phototransformation under environmentally relevant conditions.
Solubility in water	pH / Solubility (mg/L) 5.0 / 320 6.5 / 290 7.0 / 270 9.0 / 270	Pymetrozine is very soluble in water under environmentally relevant pH conditions and, therefore, has a potential to leach in soils and be transported in surface runoff water.
Solubility (g/L) in organic solvents	Solvent / Solubility (g/L) *n*-hexane: <0.001 toluene: 0.034 dichloromethane: 1.2 ethanol: 2.4 *n*-octanol: 0.45 acetone: 0.94 ethyl acetate: 0.26	

Property	Result	Comment
n-Octanol–water partition coefficient (K_{ow}) at 25°C	pH / $\log K_{ow}$ Pure water / –0.18 5 / –0.24 7 / –0.19 9 / –0.20	Pymetrozine has a negligible potential for bioconcentration or bioaccumulation in organisms.
Dissociation constant (pK_a)	4.6 (basic, protonation at N on pyridine ring) <1 (basic, protonation at N nearest to methyl group on triazine ring)	maximum dissociation under acid conditions in the environment
Stability (temperature, metals)	Significant decomposition (68–95%) was observed when in contact with copper and zinc at room temperature or at 38°C for 3 d. No decomposition was observed when in contact with carbon steel, tin and aluminum for 6 months.	

Table 1.3 End-use product: Endeavor 50WG/Fulfill 50WG

Property	Value
Colour	Beige
Odour	Weak indeterminate odour
Physical state	Solid
Formulation type	Granules
Guarantee	50% nominal (limits: 48.5–51.5%)
Formulants	The product contains U.S. EPA Inert List 3 and List 4B formulants only.
Container material and description	Soluble packs (70 g)
Specific gravity	0.48 g/cm^3 at 25°C
pH	9.4 (1% dispersion in water at 25°C)
Oxidizing or reducing action	The product does not contain oxidizing or reducing agents.
Storage stability	Stable for 2 years at 20°C in box with inner bag (paper–polyethylene laminate with additional barrier material (aluminium))
Explodability	Product is not explosive.

1.3 Details of uses

Endeavor 50WG, a wettable granule formulation containing 50% pymetrozine, is proposed as a foliar spray for the control of aphids and whiteflies on ornamental plants in greenhouses. The product is to be diluted in water at a rate of 10–20 g product/100 L, and applied uniformly to all plant surfaces, particularly the undersides of stems and leaves, to the point of runoff. The proposed yearly spray concentration for Endeavor 50WG is up to a maximum of two applications per crop of a 20 g product /100L concentration. The proposed retreatment interval would be determined by pest monitoring data, but would be not less than 7 d.

Fulfill 50WG, an identical formulation to Endeavor 50WG, is proposed as a foliar spray (ground application only) for the control of certain aphids (buckthorn, foxglove, green peach, potato) in potatoes. Fulfill 50WG is to be applied as a foliar spray, at a dosage of 193 g product (96.5 g a.i.) per hectare, in sufficient water to ensure good coverage of all plant surfaces (at least 100 L/ha). It is to be applied not more than twice per crop per season, with a minimum interval of 7 d between applications and preharvest interval (PHI) of 14 d.

Both end-use products have been registered in the U.S. since 2000. Endeavor 50WG (EPA Reg. No. 100-913) is registered for control of aphids and whiteflies on ornamental plants in landscapes, fields, greenhouses and interior plantscapes, as well as on Christmas trees and nonbearing fruit and nut trees in nurseries. The dilution rate on the U.S. label is equivalent to 18.75–37.5 g product/100 L water, and the maximum dosage for indoor use is equivalent to 7 kg product/ha/year, except in the State of California, where the maximum is 3.36 kg product/ha/year. Fulfill 50WG (EPA Reg. No. 100-912) is registered for control of aphids and whitefly, or aphids only, on 11 cucurbit vegetables (including cucumber, squash, muskmelon, pumpkin and watermelon), 10 fruiting vegetables (including tomato, peppers and eggplant), potatoes and 17 other tuber and corm vegetables (including sweet potato, yams, artichokes, cassava and ginger) and tobacco. The U.S. label permits aerial application.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Table 2.1 Method for analysis of the active substance as manufactured

Product	Analyte	Method ID	Method type	Linearity range	Recovery (%)	RSD (%)	Method
Technical	Pymetrozine	AW-178/2	High performance liquid chromatography (LC) – UV at 250 nm	50–150%	N/R	0.25	Acceptable
Technical	Major impurities	AK-178/2	HPLC–UV at 250 nm	0.5–2.5 µg/mL	85–107	0.1–4.45	Acceptable

2.2 Method for formulation analysis

Table 2.2 Method for formulation analysis

Product	Analyte	Method ID	Method	Linearity range	Recovery range (%)	SD (%)	Method
Endeavor 50WG / Fulfill 50WG	Pymetrozine	AF-1227/1	Liquid chromatography (LC) – UV	100–300 µg/mL	100.0–100.2 (n = 3)	0.24 (n = 5)	Acceptable

Table 2.3 Methods for environmental residue analysis

Matrix	Method code	Method type	Analyte	LOQ	Mean recovery (%) (n)	Mean RSD (%)	Method
Soil	AG-660	HPLC–UV	CGA 180777	10 ppb	77.3–84.5 (13)	8	Acceptable
	AG-641	HPLC – mass spectrometry (MS) – MS	CGA 249257	10 ppb	80–88.2 (30)	6.88	Acceptable
			2U	10 ppb	78–87 (30)	7.1	Acceptable
			CGA 215944	10 ppb	79–88 (30)	7.3	Acceptable
	AG-666	HPLC–UV	GS 23199	10 ppb	84–91 (36)	13	Acceptable
			CGA 294849	10 ppb	83–89 (40)	7.3	Acceptable
Sediment	The methods for soil were acceptable for use for sediments as EAD (R. Gangaraju) stated at the team meeting held on April 12, 2001 that: 1. The transformation products in soil and in sediments are identical. 1.2 The percent extractable in soil and in sediments are similar.						Acceptable

Matrix	Method code	Method type	Analyte	LOQ	Mean recovery (%) (*n*)	Mean RSD (%)	Method
Water	The methods for soil were extended to water as EAD (R. Gangaraju) stated in a team meeting held on April 12, 2001 that there are no new transformation products formed in water.						Acceptable
Crops*	AG-647	HPLC–UV, 2-column switch	GS 23199	0.02 mg/kg	85 (56)	26	Acceptability to be determined by HED.
Meat and milk	AG-658	HPLC–UV	CGA 313124	0.01 mg/kg	Not provided	Not provided	
Fat	AG-644	HPLC–UV, 2-column switch	CGA 215944	0.01 mg/kg	83 (9)	13	

* Refers to cucumber, cantaloupe, pepper, tobacco, tomato (fruit and process fractions)

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

Existing multiresidue methods of analysis that are currently in common usage were not found to be suitable for the determination of pymetrozine residues.

2.3.2 Methods for residue analysis of plants and plant products

The residue of concern (ROC) for enforcement purposes is defined as pymetrozine and the ROC for risk assessment includes pymetrozine and metabolites GS 23199, CGA 294849, CGA 215525 and CGA 249257. The petitioner is proposing two analytical methods for the analysis of residues in plant matrices. Method AG-643 analyses for parent residues only and method AG-647 analyses for metabolite GS 23199 residues only.

Method AG-643: Samples are extracted with sodium borate and methanol, filtered, concentrated and cleaned up using an Extrelut® Column eluted with ethyl acetate. The eluate is collected, evaporated to dryness and the residue reconstituted in acetone. Further purification is achieved using a silica solid-phase extraction (SPE) cartridge with methanol as the eluant. The sample is collected, evaporated to dryness, redissolved in the mobile phase (PIC B7:acetonitrile) and analysed by HPLC with UV detection at 300 nm. The reported limit of quantitation (LOQ) is 0.02 ppm for pymetrozine. The method validation recoveries were adequate in plant matrices, ranging from 63 to 122% with standard deviations ranging from 5.4 to 24%, when spiked at levels of 0.02–0.20 ppm. Concurrent recoveries of pymetrozine in potatoes from supervised residue trials were acceptable with standard deviations not exceeding 20%. The detector response was linear (correlation coefficient, $r = 0.997\ 27$) within the range of 0.01–0.2 µg/mL. The chromatographic peaks were well defined and symmetrical with no apparent carryover to

the following chromatograms in the area of analytical interest for both control and spiked samples.

Method AG-647: Samples are extracted with sodium borate and methanol, filtered and evaporated to dryness following the addition of 2 drops of diethylene glycol diethyl ether. The residues are reconstituted in methanol and water, acidified (pH 4.5), partitioned with ethyl acetate, filtered and evaporated to dryness following the addition of 2 drops of decane:diethylene glycol diethyl ether. The residues are redissolved in the mobile phase and analysed by HPLC with UV detection at 260 nm, using a column switching system from a cyanopropyl column to an aminopropyl column. The reported LOQ is 0.02 ppm for GS 23199. The method validation recoveries were adequate in plant matrices, ranging from 65 to 134% with standard deviations ranging from 5.9 to 28%, when spiked at levels of 0.02–0.20 ppm. Concurrent recoveries of the metabolite GS 23199 in potatoes from supervised residue trials were acceptable with standard deviations not exceeding 20%, when samples were spiked at levels of 0.02–0.4 ppm. The detector response was linear (r = 0.999 78) within the range of 0.01–0.2 µg/mL. Representative chromatograms of control and spiked samples of various plant matrices showed no background interferences.

2.3.3 Methods for residue analysis of food of animal origin

For animal matrices, the ROC for enforcement purposes is defined as pymetrozine. The ROC for risk assessments includes pymetrozine, metabolite CGA 313124 and the CGA 313124 phosphate conjugate for milk. In animal tissues, the ROC is pymetrozine and the metabolite CGA 313124. The petitioner has proposed two methods for the analysis of residues in animal matrices. Method AG-644 analyses for parent residues only and method AG-658 analyses for metabolite CGA 313124 residues only.

Method AG-644: Samples of meat, milk, poultry and eggs were extracted with acetonitrile:water (90:10, v:v), filtered and cleaned up using C18 SPE cartridge eluted with acetonitrile. The eluate is collected, buffered with sodium borate, evaporated to an aqueous remainder and purified using an Extrelut® column with ethyl acetate as the eluant. The eluate is evaporated to dryness, redissolved in acetone and cleaned up using a silica SPE cartridge eluted with methanol. The residues are concentrated, redissolved in methanol:water (1:9, v:v) and further purified using a C18 SPE cartridge eluted with methanol:water (30:70, v:v). The eluate is evaporated to dryness, redissolved in the mobile phase and analysed by HPLC with UV detection at 300 nm, using a column switching system with a cyano column for the initial separation to a C-18 column for the final separation. The reported LOQ is 0.01 ppm for pymetrozine. The method validation recoveries were acceptable in beef (meat, fat, liver, kidney and milk) and poultry (meat, fat, liver and eggs) ranging from 68 to 94% and 61 to 94%, respectively, with standard deviations no greater than 9.5% when spiked at levels of 0.01–0.5 ppm. In goat tissues and milk, the recoveries at a spiking level of 0.01 ppm ranged from 80 to 97%; however, at higher spiking levels, recoveries decreased in liver (48–68%), muscle (58–63%) and kidney (56–60%). The detector response was linear (r = 0.999 53)

within the range of 0.01–0.2 µg/mL. Representative chromatograms of control and spiked samples of various tissues and milk showed no background or matrix interferences.

Method AG-658: The method is intended for data gathering for dietary risk assessment; it is not proposed for enforcement purposes. Samples of animal tissues and milk are homogenized and extracted with methanol:water (90:10, v:v). The extracts are filtered, purified on a C18 SPE cartridge and evaporated. Milk extracts are hydrolyzed in an oven (60°C, 30 min) to release conjugated CGA 313124. The aqueous fraction is further purified using a phenyl SPE cartridge with methanol:water as the eluant. The eluant is purified using a C18 SPE cartridge eluted with methanol, concentrated, redissolved in methylene chloride:methanol (90:10, v:v) and analysed by HPLC with UV detection at 300 nm. The reported LOQ is 0.01 ppm for CGA 313124. The method validation recoveries were adequate in goat (muscle and kidney) and beef (muscle and kidney), ranging from 61 to 125%, when spiked at levels of 0.01–0.20 ppm. At spiking levels of 0.01–0.20 ppm, the recoveries in liver ranged from 99 to 141% (beef) and 87 to 136% (goat), and in fat, recoveries ranged from 73 to 131% (beef) and 22 to 56% (goat). Recoveries in the milk ranged from 61 to 102% (goat) and 57 to 65% (cattle), when spiked at levels of 0.01–0.5 ppm. The detector response was linear (r = 0.999 09) within the range of 0.015–0.15 µg/mL. The control chromatograms had no peaks above the chromatographic background and spiked sample chromatograms contained only the analyte peak.

3.0 Impact on human and animal health

The PMRA's evaluation of the toxicology database on pymetrozine was based on U.S. EPA Data Evaluation Reports (DERs)/California EPA reviews. The toxicology database for pymetrozine is considered adequate for hazard characterization.

3.1 Integrated toxicological summary

Absorption, distribution, metabolism and excretion

The toxicokinetics and metabolism of pymetrozine (CGA 215944) was evaluated in rats and mice. Following oral administration to rats, technical pymetrozine was readily absorbed from the gastrointestinal (GI) tract into the general circulation and extensively metabolized before it was eliminated in both urine and bile. The metabolic pathways in the rat or mouse were independent of sex, pretreatment and dose level. The predominant route of elimination was via the kidneys. Rats eliminated higher administered dose through urine compared with mice (74 versus 59%) and lower administered dose in feces (19 versus 29%) compared with mice. The preferential renal elimination of significant amount of unchanged CGA 215944 at the high dose level (~15% of the dose) compared with the low dose level (~1% of the dose) suggested saturation of the metabolic processes. The identified metabolites including unchanged CGA 215944 (approximately 20%) represented nearly two thirds of the administered dose. Three metabolic pathways were identified.

Acute toxicity
In general, pymetrozine technical was of low toxicity by the oral and dermal routes, and slightly toxic via inhalation. It was not a skin irritant, but was slightly irritating to the eyes. CGA 215944 was considered to be a potential dermal sensitizer by the Maurer Optimization Test.

The end-use products, Endeavor 50WG and Fulfill 50WG (containing 49.8% technical), were considered to be of low acute toxicity by the oral, dermal and inhalation routes in rats. They were slight skin irritants and were minimally irritating to the eye. Both end-use products were considered potential dermal sensitizers. The formulants were on the EPA List 3, 4A or 4B, and (or) the Canadian Registered Products List, and were of no toxicological concern.

Short-term toxicity
In a 28-d dermal toxicity study, rats receiving up to 1000 mg/kg body weight (bw)/d pymetrozine on the shaved skin under occlusive dressing for 6 h/d and 5 d/week, exhibited no systemic toxicity or dermal irritation. The no observed adverse effect level (NOAEL) was 1000 mg/kg bw/d, the highest dose tested.

A 28-d oral gavage study in the rat identified liver, thymus, spleen, testes and kidney as the target organs in the rat. Hepatocellular hypertrophy, atrophy of the thymus and hyperplasia of the splenic white pulp seen in animals treated at 100 mg/kg bw/d resulted in a NOAEL of 10 mg/kg bw/d.

In the 3-month dietary subchronic toxicity studies in the mouse, rat and dog, findings in liver and spleen were seen in all three species. The dog was the most sensitive species, with the lowest NOAEL established at 100 ppm (3 mg/kg bw/d) based on effects in these organs, and skeletal myopathy as well as anemia and biochemical changes in the blood occurring at higher doses.

Blood biochemistry and hematology parameters were affected also in the rat: leucocytosis, increased plasma bilirubin, cholesterol and alkaline phosphatase (ALK). Liver and spleen weights were elevated, and thymus weight was decreased. Hypertrophy of centrilobular hepatocytes, focal calcification of the kidneys in some males and atrophy of the thymus were also noted. The NOAEL was 500 ppm (33 mg/kg bw/d) and the lowest observable adverse effect level (LOAEL) was 5000 ppm (365 mg/kg bw/d) based on liver pathology. After a 4-week recovery period, decreased body weights in both high-dose males and females and leucocytosis in high-dose females still persisted. In the 3-month range-finding toxicity study in the mouse, liver lesions including dose-related hypertrophy of centrilobular hepatocytes, increased focal single cell necrosis in hepatic parenchyma and centrilobular perivascular follicle-like aggregations of hepatocytes were observed at 1000 ppm, the lowest dose level tested.

Long-term toxicity
Beagle dogs given pymetrozine at the highest dose, 1000 ppm (28 mg/kg bw/d) in diet for 12 months suffered hemolytic anemia with macrocytosis and hypochromasia of red blood cells, increased inflammatory cell infiltration in the liver and myopathy in the small and large intestine and skeletal muscle. The NOAEL was 200 ppm (5.33 mg/kg bw/d), and the LOAEL was 1000 ppm based primarily on myopathy and presence of anemia. It appeared that prolonged treatment of pymetrozine to dogs did not substantially increase toxicity.

In the mouse, the NOAEL for chronic toxicity was 100 ppm (11 mg/kg bw/d) and the LOAEL was 2000 ppm (254 and 243 mg/kg bw/d for males and females, respectively) based on increased liver and adrenal weights and increased incidences of hepatic hypertrophy and extramedullary hematopoiesis in the spleen at this dose and next higher dose levels. The NOAEL for chronic toxicity in rats was 100 ppm (3.8 and 4.5 mg/kg bw/d for males and females, respectively) based on decreased body weight gains, increased relative organ to body weight ratio (liver, kidneys and spleen), increased hepatocellular hypertrophy and follicular epithelium hyperplasia in the thyroid noted at the LOAEL of 1000 ppm (39.3 and 47.1 mg/kg bw/d for males and females, respectively) and higher. Long-term studies in both rats and mice provided evidence of treatment-related tumors in the liver at the highest dose level tested, 5000 ppm (675 mg/kg bw/d) in mice and 3000 ppm (154 mg/kg bw/d) in rats. A slightly increased incidence in benign hepatoma or carcinoma or combined hepatoma and carcinoma was also seen at the second highest dose level (1000 ppm in rats, females only; and 2000 ppm in male mice only). Prolonged treatment of pymetrozine to rodents did substantially increase toxicity.

Several mechanistic type studies were conducted in rats and (or) mice (e.g., hepatic cell proliferation, liver and thyroid biochemical and morphology, promotional effects). The information obtained from these non-guideline studies was treated as supplemental since the relevancy of the data in delineating a mechanism of carcinogenicity was not clearly established.

Genotoxicity
Five mutagenicity studies were submitted. No evidence of mutagenic potential of technical pymetrozine (CGA 215944) was observed in vitro in the Ames bacterial mutation test, or in a gene mutation assay with mammalian cells (Chinese hamster lung cells). It was also negative in an unscheduled deoxyribonucleic acid (DNA) synthesis assay with rat hepatocytes. Pymetrozine was not clastogenic in a mammalian cytogenetic assay with or without metabolic activator at any dose level tested. Technical pymetrozine did not induce micronuclei in a mouse micronucleus assay.

Based on the data presented, technical pymetrozine was not considered to be genotoxic.

Developmental and reproductive toxicity

Rat and rabbit developmental toxicity studies and a 2-generation rat reproduction study indicated that pymetrozine did not affect reproduction, or cause birth defects. Fetotoxicity, including increased skeletal anomalies, variations and reduced ossification, was seen only at maternally toxic doses. Between the two species, rabbits appeared to be more sensitive than rats with a much lower NOAEL for both maternal toxicity and fetotoxicity (10 mg/kg bw/d versus 30 mg/kg bw/d for rats) and more serious toxicity end-points (mortality, ↑ post-implantation loss, abortion and total resorptions). Pymetrozine did not exhibit teratogenic potential in either species at the doses tested. In the reproduction study, the adverse effects in parental animals were consistent with other toxicity studies and included increased liver weights and hepatocyte hypertrophy, and more severe liver changes as the dose increased. Toxicity in offspring included decreased pup weights and delayed eye opening. The NOAEL for parental toxicity in the rat reproduction study was 20 ppm (1–4 mg/kg bw/d), for offspring toxicity was 200 ppm (15–18 mg/kg bw/d). Pymetrozine did not affect reproductive parameters at the doses tested, even at the highest dose, 2000 ppm (159/186 mg/kg bw/d, for F_1 and F_2 generations).

3.2 Determination of acceptable daily intake

The acceptable daily intake (ADI) was calculated on the basis of the NOAEL of 100 ppm (3.8 mg/kg bw/d) from the 24-month combined chronic and carcinogenicity study in the rat. At the next higher dose of 1000 ppm (39 and 46 mg/kg bw/d for males and females, respectively), decreased body weight and body weight gain, increased relative liver, kidney and spleen weights as well as follicular epithelial hyperplasia of the thyroid were noted. A margin of safety (MOS) of 100 (10× for intraspecies and 10× for interspecies variability) is considered adequate.

3.3 Acute reference dose

For females 13+, an acute reference dose (ARfD) was determined to be 0.25 mg/kg bw. The dose level of 75 mg/kg bw/d from the rabbit teratology study was chosen for calculation with a 3× extra safety factor, considering the seriousness of the toxicity end-point observed at the next higher dose of 125 mg/kg bw/d.

For the general population, an ARfD of 0.42 mg/kg bw was obtained, based on the LOAEL of 125 mg/kg bw from the acute neurotoxicity study with a 3× uncertainty factor added to account for use of a LOAEL.

3.4 Toxicological end point selection: occupational and bystander risk assessment

Endeavor 50WG is proposed for application to ornamentals in greenhouses at a maximum application rate of 0.2 kg a.i./ha using handwand equipment. Based on the maximum application rate and the maximum yearly application of 2.0 kg a.i./ha/year, the product could be applied 10 times per greenhouse per year. Application is expected to occur on a year-round basis. Typically, only one person is involved in mixing, loading, and application activities. Applicators typically treat approximately one hectare of ornamentals per day. In most greenhouses, Endeavor 50WG would be applied in 1 d, while for larger greenhouses application may occur over a period of 2 d. Assuming 2 d per application, the mixer/loader applicator could potentially be exposed for 20 d per year. Exposure of greenhouse workers mixing/loading/applying Endeavor 50WG is therefore expected to be short-term (1–30 d) in duration. However, in rare instances where Endeavor 50WG is applied on a per crop basis (with up to 6 crops produced/year) Endeavor 50WG could be applied up to 120 d/year (60 applications at 2 d/application). Exposure in this instance would be intermediate-term (30–180 d) in duration. For post-application or re-entry activities (e.g., scouting, irrigation, thinning, hand weeding, pruning, pinching, hand harvesting), exposure is expected to be intermediate-term (30–180 d) to long-term (180 d or longer) in duration. Based on information obtained from the Ontario Ministry of Agriculture, Food and Rural Affairs (OMAFRA), application of pesticides is conducted exclusively by trained personnel; personnel involved in application activities are unlikely to conduct post-application activities. Consequently, application and post-application exposures are not cumulative.

Fulfill 50WG is proposed for application to field potatoes at a maximum application rate of 0.0965 kg a.i./ha using groundboom application equipment only. Farmers can potentially treat 65 ha of potatoes/d while custom applicators can potentially treat 400 ha of potatoes per day. Exposure for both farmers and custom applicators as a consequence of mixing, loading, and application activities is expected to be short-term (1–30 d) in duration; no intermediate-term or long-term exposures are anticipated. For post-application or re-entry activities (e.g., scouting) exposure is anticipated to be short-term only; no intermediate-term or long-term exposures are anticipated. Total cumulative exposure from mixing/loading/application plus post-application activities for both farmers and custom applicators is expected to be of short-term duration only.

From the toxicology data package, toxicologically significant effects were observed in the liver, spleen, kidney and thyroid in subchronic and chronic oral studies. Although the in vitro and in vivo genotoxicity studies gave negative results, rodents fed pymetrozine at higher doses developed hepatic tumors. Pymetrozine is extensively and rapidly metabolised with no significant tissue accumulation. There is no evidence for a significant increase in toxicity with increased duration of exposure in the dog, but in rats, prolonged exposure appeared to increase toxicity. The dog was the most sensitive test species. Pymetrozine was not a reproductive toxicant. In both rats and rabbits, developmental effects were seen only at maternally toxic levels. No increased

susceptibility of fetuses to in utero exposure or of the young to postnatal exposure through nursing was demonstrated.

For the short-term occupational risk assessment, the 28-d dermal toxicity in rats (NOAEL of 1000 mg/kg bw/d) is considered the most relevant study for the toxicology end point selection. The 28-d dermal toxicity study was well conducted (standard parameters were measured) and no local or systemic toxic effects were observed at the highest dose of 1000 mg/kg bw/d.

For intermediate-term occupational risk assessment, a combined NOAEL of 5.33 mg/kg bw/d from the 90-d and 12-month dog studies was considered to be appropriate. The dog was the most sensitive species among the tested animals. A wide spectrum of toxicity end points were identified in the 90-d study. Prolonged exposure to pymetrozine (from 13 to 52 weeks) did not appear to increase toxicity in this species.

For the long-term occupational risk assessment, the NOAEL of 3.8 mg/kg bw/d from the combined chronic/oncogenicity study was considered appropriate; this NOAEL was the lowest NOAEL in the data package.

A margin of exposure (MOE) of 100 is considered to be protective of all workers for above exposure scenarios.

For the cancer risk assessment, in view of the uncertainty regarding the mode of action leading to the observed tumor response, it was considered appropriate to use a quantitative approach. Unit risks for pymetrozine, denoted by Q_1^* (representing the upper 95% confidence limit on the slope of the dose–response curve in the low-dose region) were calculated on the basis of the total tumor data (combined benign hepatomas and carcinomas) from the mouse oncogenicity study. The unit risk was calculated to be 1.19×10^{-2}, and this value was used for the cancer risk assessment for occupational as well as dietary uses.

3.5 Drinking water limit

This section is addressed in Section 4.2.

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

3.6.1 Operator exposure assessment

Endeavor 50WG is proposed for application to ornamentals in greenhouses, and Fulfill 50WG is proposed for application to field potatoes. Both end-use products contain the active ingredient pymetrozine at a guaranteed concentration of 50% and have identical water dispersible granular formulations.

Endeavor 50WG would be applied as a foliar spray at a maximum application rate of 0.2 kg a.i./ha using hand held equipment (high and low pressure handwand, and backpack equipment). The product is packaged in 70.9 g water soluble packets. Application is every 14 d under normal insect pressure and every 7 d under severe insect pressure, up to a maximum of 2 kg a.i./ha per year. Up to 2 ha of ornamentals could be treated per day. Based on the maximum application rate of 0.2 kg a.i./ha and the maximum yearly application of 2.0 kg/ha/year as specified on the proposed label, the product could be applied 10 times per year. Assuming 2 d per application, the mixer/loader/applicator could potentially be exposed for a total of 20 d per year (intermittent, short-term duration). If growers find that one-half the recommended application rate provides acceptable aphid and whitefly control (e.g, 0.1 kg a.i./ha), up to 20 applications could be made per year before the maximum yearly amount (2.0 kg a.i./ha/year) is achieved. Assuming 2 d/application, the mixer/loader applicator could be potentially exposed for a total of 40 d/year (intermittent, intermediate-term duration). The proposed label recommends that growers practice resistance management strategies when using this product. This would involve rotating pesticides with different modes of action. The proposed label recommends that applicators and other handlers wear long-sleeved shirt, long pants, waterproof gloves, and shoes plus socks.

Fulfill 50WG would be applied to field potatoes at a maximum application rate of 0.0965 kg a.i./ha using open or closed cab groundboom application equipment only. A maximum of two applications can be made per season. Farmers could treat up to 65 ha of potatoes per day, while custom applicators could treat up to 400 ha of potatoes per day. Farmers would be exposed 2 d/season and custom applicators could be exposed 30 d/season. Exposures resulting from mixing, loading and applying Fulfill 50WG to potatoes are expected to be intermittent and short-term in duration. The proposed label recommends that growers practice resistance management strategies when using this product. This would involve rotating pesticides with different modes of action. The proposed label recommends that applicators and other handlers wear long-sleeved shirt, long pants, waterproof gloves, and shoes plus socks.

Dermal absorption

Potential dermal absorption of pymetrozine was investigated in an in vivo rat study. Male rats were treated dermally with a surrogate pymetrozine formulation at three dose levels: 0.00672 mg/cm^2, 0.0402 mg/cm^2, 0.375 mg/cm^2. The control group received only the vehicle. Sacrifices were made at 0.5, 1 h, 2 h, 4 h, 10 h, and 24 h after application of the dose. The application site was washed just prior to sacrifice. The mean total recovery of radioactivity among the treated groups ranged from 89.8% to 101%.

The amount retained in or on the skin at the application site ranged from 0.18% to 8.84%. Absorption did not appear to increase or decrease with time or dose. Maximal absorption (including radioactivity in the carcass and excretia) was recorded at 4 h post dose in the low dose group (8.86%). However, after 0.5 h exposure, most of the applied radioactivity had already been absorbed. The 10-h time point was used, since a 10-h exposure is most representative of a typical working day, and workers typically shower after each shift. The

low dose was used since it was most representative of the dermal deposition that is expected for greenhouse and agricultural workers. A dermal absorption value 7.38%, based on the sum of the mean percent directly absorbed (0.01%) including the mean percent retained in the skin (7.37%), is recommended for the risk assessment.

Non-cancer end points: exposure and risk assessment

Chemical-specific data for assessing exposures during the handling of Endeavor 50WG and Fulfill 50WG were not submitted. Exposures from mixing, loading and application activities associated with handling Endeavor 50WG and Fulfill 50WG were estimated using the Pesticide Handlers Exposure Database (PHED). PHED is a database of generic mixer/loader/applicator passive dosimetry data that facilitates the generation of scenario specific exposure estimates. With the exception of the handwand and backpack subsets, the PHED subsets meet criteria for data quality, specificity, and quantity as outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. The data quality for handwand and backpack (for greenhouse use) were of low confidence due to the use of A,B, and C grade data, and low number of replicates.

Endeavor 50WG

For Endeavor 50WG (greenhouse use), PHED estimates were based on handlers wearing a long sleeved shirt, long pants and gloves during mixing, loading, and application activities for the following three scenarios:

- Mixer/loader/applicator: liquid, open pour, low pressure handwand
- Mixer/loader/applicator: liquid, open pour, high pressure handwand
- Mixer/loader/applicator: liquid, open pour, backpack sprayer (low pressure handwand)

Data for liquid formulation were used due to the lack of data for water dispersible granular formulations packaged in water soluble bags. This could lead to an overestimate of exposure. The daily exposure estimates and MOEs for Endeavor 50WG are summarized in Table 3.6.1.

Table 3.6.1 Operator exposure estimates and MOEs for greenhouse workers during mixing, loading and application activities associated with application of Endeavor 50WG to ornamentals in greenhouses. PHED estimates are based on workers wearing long-sleeved shirt, long pants and gloves.

Scenario	PHED[a] unit exposure (µg/kg a.i.)	Area treated (ha/d)	Rate (kg a.i./ha)	Daily exposure (kg a.i./d)	Daily dose (µg/kg bw/d)[b]	MOE[c]
Low pressure handwand						
Short-term duration	9.4×10^2	2	0.2	0.4	5.4	1.9×10^5
Intermediate-term duration	1.2×10^2	2	0.1	0.2	0.33	1.6×10^4
High pressure handwand						
Short-term duration	5.6×10^3	2	0.2	0.4	32	3.1×10^4
Intermediate-term duration	5.6×10^2	2	0.1	0.2	1.6	3.3×10^3
Backpack sprayer						
Short-term duration	5.4×10^3	2	0.2	0.4	31	3.2×10^4
Intermediate-term duration	4.6×10^2	2	0.1	0.2	1.3	4.0×10^3

[a] For short-term exposure, since the MOE is based on a dermal toxicity study, exposure estimates are based on dermal deposition only (inhalation exposure is considered negligible compared with dermal deposition); for intermediate-term exposure an oral toxicity study is used, and exposure estimates are corrected for dermal absorption and inhalation absorption was assumed to be 100%.

[b] Calculated as: (PHED unit exposure [µg/kg a.i.]) × (daily exposure [kg a.i./d])/body weight [70 kg]

[c] MOE for short-term exposure based on a NOAEL of 1000 mg/kg bw/d (from 28-d rat dermal study), MOE for intermediate-term exposure based on a NOAEL of 5.33 mg/kg bw/d (combined 9- and 12-month dog feeding study).

The MOEs for greenhouse workers mixing/loading/applying Endeavor 50WG to ornamentals in greenhouses are acceptable.

Fulfill 50WG

For Fulfill 50WG (for potato use), PHED estimates were based on handlers wearing long-sleeved shirt, long pants and gloves during mix/load activities, and long-sleeved shirt, long pants and no gloves during application activities for the following three scenarios:

- Mixer/loader: dry flowable (including water dispersible granule, or wettable granule formulations): farmer and custom applicator
- Applicator: open cab groundboom: farmer and custom applicator
- Applicator: closed cab groundboom: farmer and custom applicator

The daily exposure estimates and MOEs for Fulfill 50WG are summarized in Table 3.6.2. The MOEs for farmers and custom applicators mixing/loading/applying Fulfill 50WG to field potatoes are acceptable.

Table 3.6.2 Exposure estimates for farmers and custom applicators during mixing, loading and application activities associated with the application of Fulfill 50WG to field potatoes. All workers wearing one layer of clothing; mixer/loader wearing gloves; applicator wearing no gloves.

Exposure scenario	PHED[a] unit exposure (µg/kg a.i.)	Area treated (ha/d)	Rate (kg a.i./ha)	Daily exposure (kg a.i./d)	Daily dose[b] (µg/kg bw/d)	MOE[c]
Farmers						
Open cab	2.0×10^2	65	0.0965	6.3	18	5.6×10^4
Closed cab	1.8×10^2	65	0.0965	6.3	16	6.3×10^4
Custom applicators						
Open cab	2.0×10^2	400	0.0965	39	1.1×10^2	9.1×10^3
Closed cab	1.8×10^2	400	0.0965	39	97	1.0×10^4

[a] Since the MOE is based on a dermal toxicity study, the exposure estimates are based on dermal deposition only (inhalation exposure is considered negligible compared with dermal deposition).

[b] Calculated as: (PHED unit exposure [µg/kg a.i.]) × (daily exposure [kg a.i./d])/body weight [70 kg]

[c] MOEs based on NOAEL of 1000 mg/kg bw/d from a 28-d rat dermal toxicity study.

An MOE of 100 is acceptable. For the non-cancer risk assessment, all MOEs for operators handling pymetrozine (Endeavor 50WG and Fulfill 50WG) are acceptable.

Cancer end points: exposure and risk assessment

Endeavor 50WG

For the cancer risk assessment, lifetime average daily exposure estimates and the unit risk were used to estimate risk levels. For Endeavor 50WG, the lifetime average daily dose (LADD) was calculated based on an exposure frequency of 20 d/year (if applied at the recommended application rate of 0.2 kg a.i./ha), or 40 d per year (if applied at one half the recommended application rate), a working tenure of 40 years, and a 75-year lifespan. The LADD and cancer estimates for Endeavor 50WG are summarized in Table 3.6.3.

Table 3.6.3 LADD and cancer risk estimates for greenhouse workers mixing/loading and applying Endeavor 50WG on ornamentals grown in greenhouses

Scenario	LADD[a] (mg/kg bw/d)	Q_1*[b] (mg/kg bw/d)	Cancer risk
Low pressure handwand			
Maximum application rate, 20 d/year	1.9×10^{-5}	1.2×10^{-2}	2.3×10^{-7}
½ Maximum application rate, 40 d/year	1.9×10^{-5}	1.2×10^{-2}	2.3×10^{-7}
High pressure handwand			
Maximum application rate, 20 d/year	9.4×10^{-5}	1.2×10^{-2}	1.1×10^{-6}
½ Maximum application rate, 40 d/year	9.4×10^{-5}	1.2×10^{-2}	1.1×10^{-6}
Backpack sprayer			
Maximum application rate, 20 d/year	7.7×10^{-5}	1.2×10^{-2}	9.2×10^{-7}
½ Maximum application rate, 40 d/year	7.7×10^{-5}	1.2×10^{-2}	9.2×10^{-7}

[a] Based on application rate of 0.2 kg a.i./ha and an exposure frequency of 20 d/year, or application rate of 0.1 kg a.i./ha and an exposure frequency 40 d/year, 40-year working tenure and a lifetime of 75 years. LADD based on workers wearing long-sleeved shirt, long pants and gloves.

[b] Q_1* value is based on formation of liver tumours in male mice.

The cancer risk for greenhouse workers mixing, loading and applying Endeavor 50WG are acceptable.

Fulfill 50WG

For the cancer risk assessment, lifetime average daily exposure estimates and the unit risk were used to estimate risk levels. For Fulfill 50WG, the LADD was calculated based on an exposure frequency of 2 d per season for farmers and 30 d per season for custom applicators, a working tenure of 40 years and a 75-year lifespan. The LADD and cancer estimates for Fulfill 50WG are summarized in Table 3.6.4. The total cancer risk estimate for Fulfill 50WG (operator exposure plus post-application exposure) is provided in Section 3.6.6, Cancer end points.

Table 3.6.4 LADD and cancer risk estimates for farmers and custom applicators: mixing/loading/application activities for Fulfill 50WG on field potatoes

Scenario	LADD[a] (mg/kg bw/d)	Q_1*[b] (mg/kg bw/d)	Cancer risk
Farmers			
Open cab	4.5×10^{-6}	1.2×10^{-2}	5.3×10^{-8}
Closed cab	3.8×10^{-6}	1.2×10^{-2}	4.5×10^{-8}
Custom applicators			
Open cab	4.1×10^{-4}	1.2×10^{-2}	4.9×10^{-6}
Closed cab	3.5×10^{-4}	1.2×10^{-2}	4.2×10^{-6}

[a] Based on application rate of 0.0965 kg a.i./ha, exposure frequency of 2 d/year for farmers and 30 d/year for custom applicators, 40-year working tenure and a lifetime of 75 years. LADD based on mixers/loaders wearing long-sleeved shirt and long pants plus gloves, and applicators wearing long-sleeved shirt, long pants and no gloves.

[b] Q_1* value is based on formation of liver tumours in male mice.

The risk levels for farmers are considered acceptable. The risk levels for custom applicators are considered conservative, as some of the inputs to the exposure assessment (e.g., exposure frequency) are conservative, and the risk levels are therefore considered acceptable.

For all operators handling pymetrozine (Endeavor 50WG and Fulfill 50WG), the cancer risk is considered acceptable.

3.6.2 Bystander exposure

For the proposed agricultural use scenario, bystander exposure during and after application was considered minimal compared with mixer/loader/applicator and re-entry worker scenarios and, therefore, not quantified.

3.6.3 Post-application exposure

Non-cancer end points: exposure and risk assessment

Endeavor 50WG

Cultivation of ornamentals in general can involve a number of re-entry activities ranging from low to high potential for post-application exposure. Re-entry activities considered to have high post-application exposure potential include pruning, pinching, thinning and hand harvesting. Cut flowers would also involve bunching and bundling. Other factors affecting post-application exposure include the height and the degree of foliage of the plant. Since the timing of re-entry activities may be coincident with the timing of Endeavor WG application, an assessment of post-application worker exposure was conducted. A critical parameter for the exposure assessment is the transfer coefficient for

each type of re-entry activity (i.e., rate at which pesticide residues are transferred from the foliage to the body of the worker). There is no data to determine the transfer coefficients for ornamentals other than cut flowers. Consequently, the transfer coefficient for cut flowers was used to conduct a quantitative exposure and risk assessment.

A dislodgeable foliar residue (DFR) study was submitted to estimate post-application exposure. This study was designed to collect data to calculate DFR dissipation curves for pymetrozine on the foliage of roses cultivated in a greenhouse. Although the application method was similar to the proposed use, the rate and frequency of application, and monitoring times were not relevant to the use pattern proposed. The application rate in the study was approximately double the rate supported by the efficacy section (i.e., 386 g a.i./ha versus 200 g a.i./ha); see Section 7.1.4 in this document. The product was applied only once whereas the product is proposed for multiple applications at 7- to 14-d intervals. Also, DFRs were only sampled for up to 24 h, whereas re-entry activities would continue to occur several days after application. The greenhouse scenario is relevant to the proposed use of the product in Canada, and the rose is a representative plant for ornamentals grown in Canadian greenhouses. However, a limitation of the study is the extrapolation of the rose DFR data to all types of ornamental foliage.

The results indicated that transferable residues of pymetrozine did not rapidly dissipate over 24 h. Based on the assumption that DFR residues are a function of the application rate and that DFR residues would decrease linearly with decreasing application rate, the DFR residues for the proposed application rate were estimated by multiplying the DFR residues from the study by 0.52. Since the product was applied only once and since DFR residues were only sampled within 24 h after application, major uncertainties include the long-term dissipation of pymetrozine and whether pymetrozine residues would be cumulative with multiple applications, particularly at application frequencies of 7–14 d. Within 24 h, the degree of pymetrozine dissipation was approximately 8% but this was highly variable. In the absence of good quality data to estimate the dissipation of pymetrozine, and in consideration of the average study dissipation of approximately 8% in 24 h, a dissipation rate of 5% per day was assumed to estimate potential exposure to workers on subsequent days. In addition, for multiple applications, residues were assumed to cumulative (i.e., any residue remaining before the next application was added and each application was assumed to add the same DFR residue as the first application in the study).

Since concurrent passive dosimetry monitoring of workers re-entering treated areas was not conducted, the above dislodgeable residue data was coupled with generic transfer coefficients appropriate for reentry activities conducted on cut flowers. The maximum transfer coefficient for cut flowers is 7000 cm^2/h (for hand harvesting, pruning, pinching and thinning). Dermal deposition was estimated based on an 8-h work day and body weight of 70 kg. To estimate the dermally absorbed exposure, a dermal absorption factor of 7.38% was applied. For each scenario, the time-weighted average daily exposure was calculated; that is, the average of the daily exposures for the entire exposure duration.

The durations of exposure, exposure estimates and MOEs for each of the exposure scenarios are presented in Table 3.6.5.

Table 3.6.5 MOEs from post-application exposure to pymetrozine

Exposure scenario	Duration	Exposure[a] (mg/kg bw/d)	NOAEL[b] (mg/kg bw/d)	MOE
Continual use at high frequency (*a*) The product would be applied at the maximum rate every 7 d for 10 weeks (maximum 10 applications/year at the maximum rate)	Intermediate Term	0.0257	5.3	206
Continual use at high frequency (*b*) The product would be applied at the maximum rate every 14 d for 20 weeks (maximum 10 applications/year at the maximum rate)	Long-term	0.0193	3.8	197
Continual use at high frequency (*c*) The product would be applied at the half the label rate every 7 d for 20 weeks (maximum 20 applications/year at half the label rate)	Long-term	0.019	3.8	201
Continual use at high frequency (*d*) The product would be applied at the half the label rate every 14 d for 40 weeks (maximum 20 applications/year at half the label rate)	Long-term	0.0121	3.8	314
Best case The product would be applied at the maximum rate approximately every 36 d (10 applications/year at the maximum label rate)	Long-term	0.0111	3.8	344
Most likely The product would be applied 2–3 times in quick succession, followed by an interval of several months, before re-application again 2–3 times in quick succession (maximum 10 applications/year)	Long-term	0.0112	3.8	338

[a] Time-weighted average daily exposures

[b] See Section 3.4, Toxicological end point selection: occupational and bystander risk assessment.

For all exposure scenarios, MOEs are greater than 100 and are considered to be acceptable.

Fulfill 50WG

Since no post-application data were submitted for Fulfill 50WG, post-application exposures were estimated using default assumptions. For potatoes, a range of re-entry activities take place at difference stages of cultivation. Scouting was identified as a frequent activity that involved foliar contact. In general, scouting is not performed by farmers or custom applicators, rather it is typically conducted by professional scouters. Re-entry exposure estimates were calculated using the following assumptions: a transfer coefficient (TC) of 1500 cm^2/h; an application rate of 0.965 µg a.i./cm^2; a DFR of 20% of the application rate; residue dissipation at a rate of 10% per day; 8 h of exposure per day; and a 70-kg body weight.

The following equations were used to calculate risks for workers performing post-application activities:

(A) $$\mathbf{DFR_t\ (\mu g\ a.i./cm^2) = AR\ (\mu g\ a.i./cm^2) \times F \times (1–D)^t}$$

Where

DFRt = dislodgeable foliage residue at time "t" (µg a.i./cm^2); t = number of days after application
AR = application rate (0.965 µg/cm^2)
F = fraction of a.i. retained on foliage (20%)
D = fraction of residue that dissipates daily (10% for outdoor crops)

And

(B) $$\mathbf{DDD_t = \frac{DFR_t\ (\mu g\ a.i./cm^2) \times TC\ (cm^2/h) \times DA \times ET\ (h)}{bw\ (kg)}}$$

Where

DDD_t = daily dermal dose at time "t" (µg/kg bw/d); t = number of days after application
DFR_t = dislodgeable foliage residue at time "t" (µg/cm^2)
TC = transfer coefficient (1500 cm^2/h for scouting potatoes)
DA = Since the MOE is based on a dermal toxicity study, dermal deposition is assumed to be 100%
ET = exposure time (8 h/d)
bw = body weight (70 kg for adult male)

Based on the nature of the re-entry activities, and the proposed application rates, re-entry exposure is expected to be intermittent and short-term. The highest daily exposure of re-entry workers occurring on day 0 after the second application is 48.9 µg/kg bw/d. The MOE on day 0 of the second application is 2.0×10^4. The MOE is based on a NOAEL of 1000 mg/kg bw/d from the rat 28-d dermal exposure study. The MOE for agricultural workers re-entering potato fields treated with Fulfill 50WG is acceptable.

An MOE of 100 is considered acceptable in these scenarios. For the non-cancer risk assessment, all MOEs for re-entry workers handling pymetrozine (Endeavor 50WG and Fulfill 50WG) are acceptable.

Cancer end points: exposure and risk assessment

Endeavor 50WG

The LADD from post-application exposure to greenhouse workers was estimated assuming varying numbers of applications and default values for life expectancy (75 years) and working tenure (40 years). Risk levels were unacceptable when application rates greater than 0.6 kg a.i./ha/year were assessed. Following an application rate of 0.6 kg a.i./ha/year, the LADD was 1.8×10^{-3} mg/kg bw/d resulting in a risk of 2×10^{-5}. This risk is acceptable in light of the conservatisms in the exposure assessment, including the assumptions that re-entry exposure would occur every day, the same plant would be treated throughout the year and the highest transfer co-efficient for cut flowers was used. This assessment is considered to be applicable to ornamentals grown for cut flower production or those requiring significant foliar contact during cultivation (e.g., pinching, pruning, hand harvesting).

The Efficacy and Sustainability Assessment Division (ESAD) has recommended that Endeavor 50WG be prepared as a dilution of 10–20 g product/100 L water and applied at a maximum rate of 2000 L/ha. This is equivalent to 400 g product/ha per crop cycle, or 200 g a.i./ha per crop cycle. In addition, ESAD has recommended that the application of Endeavor 50WG not exceed two applications (2 × 20 g product/100 L) per crop cycle. This is equivalent to a maximum yearly rate of 800 g product per greenhouse per year, or 400 g a.i. per greenhouse per year. Based on the ESAD recommendations, Endeavor 50WG can be applied twice per crop cycle per greenhouse per year.

For ornamentals grown for cut flower production (e.g., roses, chrysanthemums, gerbera) or those requiring significant foliar contact during cultivation (e.g., pinching, pruning, hand harvesting), Occupational Exposure Assessment Section (OEAS) can support a maximum application rate of 0.6 kg a.i. per hectare per greenhouse per year. This is equivalent to a maximum of three applications per greenhouse per year. However, to adhere to the ESAD and OEAS use restrictions for ornamentals that have one crop cycle per year, Endeavor 50WG may be applied twice per greenhouse only. For other ornamentals that may have two or more crop cycles per year, three applications of Endeavor 50WG may be applied per greenhouse per year.

For ornamentals not requiring significant foliar contact during cultivation (e.g., bedding plants, seasonal plants), the cancer risk from the proposed use is considered acceptable as re-entry activities involve limited foliar contact.

Fulfill 50WG

The LADD was calculated based on an exposure frequency of 2 d per season for farmers and 30 d per season for professional scouts; a working tenure of 40 years, and a 75-year lifespan. The cancer risk for farmers and professional scouts as a result of exposure to Fulfill 50WG during re-entry activities are summarized in Table 3.6.6. Since farmers could be exposed to Fulfill 50WG as a result of both application and re-entry activities, the total cancer risk for farmers from both activities was determined.

Table 3.6.6 LADD and cancer risk estimates for farmers and custom applicators: mixing/loading/application and post-application activities for Fulfill 50WG on field potatoes

Exposure scenario	LADD[a] (mg/kg bw/d)	Q_1*[b] (mg/kg bw/d)	Cancer risk
Post-application activities: scouting			
Farmers	1.06×10^{-5}	1.2×10^{-2}	1.26×10^{-7}
Professional scout	1.58×10^{-4}	1.2×10^{-2}	1.88×10^{-6}
Total cancer risk for mixing/loading/application and re-entry activities for farmers			
Farmers (open cab) + re-entry	1.5×10^{-5}	1.2×10^{-2}	1.79×10^{-7}

[a] Based on an application rate of 96.5 g a.i./ha, exposure frequency of 2 d/year for farmers and 30 d/year for professional scouts, 40-year working tenure and a lifetime of 75 years.

[b] Q_1* value based on formation of liver tumours in male mice

The risk levels for professional scouts are considered conservative as some inputs to the exposure assessment (e.g., exposure frequency) are conservative and the risk levels are therefore acceptable. For agricultural workers (i.e., farmers and professional scouts) exposed to Fulfill 50WG as a result of re-entry activities, the cancer risk is acceptable.

For greenhouse workers exposed to Endeavor 50WG as a result of re-entry activities, the cancer risk is acceptable only when the application rate is restricted to a maximum of three applications per greenhouse per year.

4.0 Residues

4.1 Residue summary

Nature of the residue in plants

[Triazine-6-^{14}C] and [pyridine-5-^{14}C] labelled pymetrozine was applied to foliage of field grown potato plants at a rate of 450 or 3150 g a.i./ha/season. From the triazine label, the predominant metabolites in the raw agricultural commodity (RAC) were the parent, metabolite GS 23199 and the glycoside conjugate of GS 23199. From the pyridine label, the major metabolites in the RAC were CGA 74465 and gly-CGA 180777. The metabolism of pymetrozine in potato plants is well understood and the ROC may be defined as pymetrozine for enforcement purposes. For risk assessment purposes, the ROC should include pymetrozine and metabolites GS 23199, CGA 215525, CGA 249257 and CGA 294849.

Confined accumulation in rotational crops

[Triazine-6-^{14}C] and [pyridine-5-^{14}C] labelled pymetrozine was applied to sandy loam soil at a rate of 420 g a.i./ha. The plots were divided and planted with wheat, radish and mustard as rotational crops at 30, 60, 95, 122 and 361 d after treatment. From the triazine label, the predominant metabolites identified in rotational crops were gly-GS 23199 and GS 23199. From the pyridine label, the major metabolites identified in rotational crops were CGA 74465 and CGA 180778. An additional confined crop rotation study was submitted to support the findings of the above crop rotation study and further identify the total radioactive residues (TRRs) in wheat matrices. Two additional triazine specific metabolites were identified, CGA 359009 and CGA 323584. In general, the metabolic profile of ^{14}C-residues in wheat was qualitatively similar in both confined crop rotational studies.

Field accumulation in rotational crops

Pymetrozine formulated as 50WG was applied to primary crops (tomatoes, peppers, cucumbers and leaf lettuce) at a rate of 405 g a.i./ha/season. Rotational crops (wheat, turnip and leaf lettuce) were planted 30 DAT. Residues of pymetrozine and the metabolite GS 23199 were each below the LOQ of 0.02 ppm in all crop matrices. A plant-back interval of 30 d will be required on the label for all crops.

Nature of the residue in animals

[Triazine-6-^{14}C] and [pyridine-5-^{14}C] labelled pymetrozine was administered intraruminally by gelatine capsule daily to 4 female lactating goats for 4 consecutive days at dose levels of 0.39–0.54 mg/kg bw/d. Urinary and fecal excretion were the predominant routes of elimination. The predominant metabolite from the triazine label was CGA 313124 in muscle, fat, kidney, feces, urine and milk. The major metabolite in liver was 5U and an additional metabolite, the phosphate conjugate of CGA 313124 was identified in milk. From the pyridine label, the major metabolite in muscle, fat, liver and kidney was CGA 180778. In milk, the predominant metabolites were CGA 313124 and the phosphate conjugate of CGA 313124. The metabolite most identified in urine and

feces was CGA 313124 and 5U, respectively. Based on the lactating goat metabolism study, the ROC may be identified as pymetrozine for enforcement purposes. The ROC for risk assessment should include pymetrozine, metabolite CGA 313124 and the phosphate conjugate of CGA 313124 for milk and, pymetrozine and metabolite CGA 313124 for animal tissues.

Methods for residue analysis of plants and plant products
Analytical methods (HPLC–UV; AG-643 and AG-647) were proposed for data gathering and (or) enforcement purposes. The method LOQ for pymetrozine and the metabolite GS 23199 was reported as 0.02 ppm. These methods were found to give acceptable recoveries in the range of 63–134%. The detector response was linear within the range of 0.01–0.2 µg/mL. The interlaboratory validation (ILV) of methods AG-643 and AG-647 supported the reliability and reproducibility of the methods for the determination of pymetrozine and the metabolite GS 23199 residues in plant matrices, respectively.

Methods for residue analysis of food of animal origin
Analytical methods (HPLC–UV; AG-644 and AG-658) were proposed for data gathering and (or) enforcement purposes. The method LOQ for pymetrozine and the metabolite CGA 313124 was reported as 0.01 ppm. These methods were found to give acceptable recoveries in the range of 68–125% for the analysis of beef matrices. The detector response was linear within the range of 0.01–0.2 µg/mL. The ILV of method AG-644 supported the reliability and reproducibility of the method for the determination of pymetrozine residues in animal matrices.

Storage stability data: plants and animals
The data presented in the freezer storage stability study indicated that residues of pymetrozine were stable at –20°C for 2 months in cucumber, 6 months in potatoes and tomato paste, 14 months in tomatoes and 24 months in cottonseed and cottonseed oil. Freezer storage stability on incurred pymetrozine residues indicated that residues were stable for 10 months in spinach, 13 months in leaf lettuce, 15 months in broccoli, celery and mustard green and 18 months in cabbage. Residues of the metabolite GS 23199 were stable up to 24 months in cucumbers, cottonseed, cottonseed oil, tomatoes and tomato paste. In animal matrices, residues of pymetrozine and the metabolite CGA 313124 were stable for 18 months in milk and 6 months in beef muscle and liver. Freezer storage stability on incurred pymetrozine and metabolite residues indicated that residues were stable from 20 to 32 months in goat liver and milk.

Crop field trials
Supervised crop field trial studies on potatoes were conducted in the U.S. and Canada. Results indicated that the maximum residues of pymetrozine and the metabolite GS 23199 in tubers were each below the LOQ of 0.02 ppm when plants were treated twice with pymetrozine formulated as WP or WG at a rate of 192 g a.i./ha/season (proposed good agricultural practice (GAP)). Based on the Canadian trials, the supervised trial median residue values for pymetrozine and the metabolite were 0.005 ppm.

Consequently, an MRL of 0.02 ppm is recommended to cover residues of pymetrozine in potatoes.

Processed food and feed

Pymetrozine (50% a.i.) was applied to potatoes at rates ranging from 200 to 1000 g a.i./ha/season equivalent to 1× to 5× the proposed GAP. The potatoes were processed into granules and chips. A comparison of the residues in the RAC with those in each processed fraction showed no residue concentration in any processed fractions. MRLs will not need to be established to cover residues of pymetrozine in potato processed fractions.

Meat, milk, poultry and eggs

Encapsulated pymetrozine was administered orally by a balling gun following the evening milking to 9 dairy cattle for 28–30 consecutive days. The dosages were equivalent to 1 ppm (1×), 3 ppm (3×) and 10 ppm (10×). The feeding study indicated that no measurable residues of pymetrozine and the metabolite CGA 313124 were detected in tissues at the highest feeding level of 10 ppm. Residues of pymetrozine in milk were below the LOQ of 0.01 ppm at all feeding levels. Residues of the metabolite CGA 313124 in milk were less than the LOQ (0.01 ppm) at 1× and ranged from <0.01 ppm to 0.02 ppm (3×) and <0.01 ppm to 0.05 ppm (10×). Residues of pymetrozine and the metabolite GS 23199 are not expected to be quantifiable (less than the LOQ) in milk and tissues when livestock are exposed to treated potato waste. Therefore, no MRL will be established to cover residues of pymetrozine in animal matrices.

Dietary risk assessment

The proposed domestic use of pymetrozine on potatoes does not pose an unacceptable chronic, acute or cancer dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors. Using all available refinements (processing factors, supervised trial median residues (STMdRs) for potatoes and imported commodities and estimated percent crop treated information), the potential daily intake (PDI) was equal to or less than 0.2% of the chronic ADI for all population subgroups. For acute dietary intake at the 95th percentile, exposure to residues of pymetrozine represented approximately 0.09 and 0.06% of the ARfD for females 13+ and the general population, respectively. The lifetime cancer risk from dietary exposure to pymetrozine from food and water was estimated to be 6.39E–07 and 1.00E–06 for the general population and all infants less than 1 year old, respectively. It is expected that further refinement would result in a lifetime risk less than the level of concern of 1.00E–06.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

Physical and chemical properties of pymetrozine relevant to the environment are presented in Appendix III, Table 1. Pymetrozine is very soluble in water (270–320 mg/L) under environmentally relevant pH conditions and, therefore, has a potential to leach in soils and be transported in surface runoff water. Low values of vapour pressure ($<4 \times 10^{-6}$ Pa at 25°C) and Henry's Law Constant ($<3.0 \times 10^{-6}$ Pa/m^3/mol) indicate that pymetrozine is non-volatile under field conditions and also from moist soil and water surfaces. Pymetrozine has a negligible potential for bioconcentration/ bioaccumulation in organisms (log K_{ow} = –0.18). Pymetrozine dissociates under acid conditions in the environment (pK_{a1} = 4.06) and has a potential for phototransformation under environmentally relevant conditions (UV–visible absorption λmax = 299–308 nm).

5.2 Abiotic transformation

Pymetrozine was stable to hydrolysis in sterile aqueous pH 7 and 9 buffer solutions, but hydrolysed in pH 5 solution, with half lives of 5–13.2 d. Hydrolysis is, therefore, a major route of transformation in the environment under acid conditions. The hydrolysis of pyridine ring-labelled pymetrozine was biphasic in pH 5 buffer solutions. Pyridine-3-carbaldehyde (CGA 300407) and 4-amino-6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 215525) were the major transformation products of the pyridine ring-labelled and triazine ring-labelled studies, respectively.

In soil, parent compound phototransformed with half-lives of 1.6–4.3 d. Biphasic phototransformation was observed in both the pyridine ring-labelled and triazine ring-labelled pymetrozine studies. One major transformation product, 4,5-dihydro-5-hydroxy-6-methyl-4-[(3-pyridinylmethylene)amino]-1,2,4-triazine-3-(2H)-one (CGA 359009) (28.6–33.5%) and two minor transformation products, 3-pyridine carboxaldehyde (CGA 300407) and 4-amino-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (CGA 294849) were observed.

In water, parent compound phototransformed with half-lives of 1.9–6.2 d. With pyridine ring-labelled study, one major transformation product, pyridine-3-carbaldehyde (CGA 300407) and one minor transformation product, nicotinic acid (CGA 180777) were identified. With the triazine ring-labelled studies, three major transformation products, 4-amino-5-hydroxy-6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 215525), 6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 249257), hydroxy CGA 215525 and two minor transformation products (4-amino-6-methyl-2H-(1,2,4)-triazine-3,5-dione (CGA 294849) and unidentified were observed.

5.3 Biotransformation

Under aerobic conditions, pymetrozine biotransformed in soil with a strong biphasic pattern: a rapid initial breakdown (0–30 d), followed by a much slower transformation. The half-lives were 2.3–5.5 d and 305–405 d, for the primary and secondary phases, respectively. Half-life values of 2.3–5.5 d indicate that pymetrozine is non-persistent in soils under aerobic conditions. Second phase half-life values of 305–405 d indicate, however, a potential residue carry over to the following season. One major transformation product, CGA 180777 (nicotinic acid) was detected under aerobic conditions Pymetrozine transformed slowly in soil under anaerobic flooded conditions, with half-lives of 69–103 d. These values indicate that pymetrozine is moderately persistent in soil under anaerobic conditions. Five major transformation products, CGA 180777, CGA 249257, GS23199, Unknown I and Unknown III were detected.

5.4 Mobility

Adsorption and desorption studies indicated that pymetrozine is immobile in sandy loam and Bosket loam, slightly mobile in silt clay, and low mobility in sandy and Ashkum-Elliot loam soils. The Freundlich soil adsorption coefficient (K_{ads}) values were 6.6, 14.0, 18.9, 27.1 and 30.9 for the sandy soil, sandy loam, Bosket loam soil, silty clay loam soil and Ashkum-Elliott loam soil, respectively; corresponding organic carbon adsorption coefficient (K_{oc}) values were 1394, 5833, 7875, 3080 and 1500 mL/g.

During the 24-h adsorption equilibration period, 10.5–36.5%, 23.6–61.6%, 36.2–66.5%, 45.0–77.3% and 51.4–75.7% of the applied radioactivity was adsorbed to the sandy soil, sandy loam soil, Bosket loam soil, silty clay loam soil and Ashkum-Elliott loam soil, respectively. Following a single 24–h desorption equilibration period, 49.7–64.5%, 36.6–49.0%, 17.2–31.7%, 16.5–32.4% and 15.3–29.3% of the previously adsorbed radioactivity was desorbed from the sand soil, sandy loam soil, Bosket loam soil, silty clay loam soil and Ashkum-Elliott loam soil, respectively. Adsorption K_{oc} values indicated that the transformation product,CGA 359009 (K_{oc} = 284–436 mL/g) is moderately mobile in soils, whereas CGA 249257 (K_{oc} = 9–30 mL/g), CGA 180777 (K_{oc} = 5–49 mL/g) and GS23199 (K_{oc} = 31–48 mL/g) are very highly mobile in soils.

Soil column leaching studies treated with unaged and aged (30 d) pymetrozine indicated very little to no mobility in sand, sandy loam, loam, and silty clay loam soil columns. These results are in agreement with those of adsorption studies. Most of the applied parent compound and its transformation products were retained in application layer and did not leach beyond a 12-cm depth. No significant quantities of parent and transformation products (maximum of 4.3% of applied radioactivity) were detected in the leachates.

5.5 Dissipation and accumulation under field conditions

Dissipation of pymetrozine (Fulfill 50WG) was biphasic under field conditions with half-lives of 3 (1st phase) and 30 d (2nd phase) in a bareground plot of loam soil (New York). Pymetrozine was not detected below the 6-inch depth, indicating that the parent compound did not leach under field conditions. Five major transformation products were detected: CGA 359009, CGA 249257, CGA 180777 (3-pyridinecarboxylic acid or niacin), CGA 294849 and GS 23199. All the transformation products were detected in the 0–12″ soil depth, except CGA 180777, which was detected in one replicate in the 12–18″ depth. None of the transformation products was detected at the end of the study period, which indicates that the transformations products are not persistent under field conditions. These results indicate that the parent compound and transformation products have a low potential to leach under field conditions.

Studies conducted in California and Georgia indicated that pymetrozine is non-persistent to moderately persistent and both parent compound and transformation products did not leach under field conditions.

5.6 Bioaccumulation

No data were submitted on bioaccumulation in organisms. The log K_{ow} of –0.18, however, indicates that pymetrozine has a negligible potential for bioaccumulation and, therefore, these data are not required. The log K_{ow} values for the transformation products, CGA 300407, CGA 249257 and CGA 215525 were 0.31, –0.95 and –0.13, respectively. These transformation products have, therefore, a negligible potential for bioaccumulation in organisms.

5.7 Summary of fate and behaviour in the terrestrial environment

Summary of fate and behaviour in the terrestrial environment is presented in Appendix III, Tables 2 and 3. Pymetrozine is non-persistent to slightly persistent in soils under aerobic conditions (lab DT_{50} = 2.3–5.5 d and field DT_{50} = 30 d). Under anaerobic conditions, it is moderately persistent with combined soil and water half-lives of 69–103 d. It is rapidly transformed in the terrestrial environment by three major transformation routes, acid hydrolysis ($t_{1/2}$ = 5–13 d at pH 5), photolysis ($t_{1/2}$ = 1.6–4.3 d) and biotransformation (1st phase $t_{1/2}$ = 2.3–5.5 d). It exhibits a strong biphasic transformation pattern in all the three transformation processes: a rapid initial breakdown of the available pymetrozine, followed by a much slower transformation process. Adsorption (K_{oc} = 1394–7875 mL/g), soil column leaching (no significant residues in the leachates) and field dissipation studies (no residues below 6″ soil depth) indicate that pymetrozine is slightly mobile to immobile in soils and has, therefore, a low potential to leach and contaminate groundwater.

Nine major and eleven minor transformation products were detected in both laboratory and field studies (Table 3). These products were, however, not persistent under field conditions, as no residues were detected in soils at the end of the study period. Adsorption and desorption studies indicated that transformation products, CGA 359009 (K_{oc} = 278–406 mL/g) and CGA 249257 (K_{oc} = 9–30 mL/g) are moderately mobile and CGA 180777 (K_{oc} = 5–50 mL/g) and GS23199 (K_{oc} = 31–48 mL/g) are very highly mobile in soils. Soil column and field dissipation studies indicated, however, no significant residues in the leachates and beyond 12″ soil depth and, therefore, these transformation products have a low potential to leach and contaminate groundwater.

5.8 Summary of fate and behaviour in the aquatic environment

Summary of fate and behaviour in the aquatic environment is presented in Appendix III, Tables 4 and 5. Pymetrozine transforms rapidly in water by acid hydrolysis ($t_{1/2}$ = 5–13 d at pH 5) and photolysis ($t_{1/2}$ = 1.9–6.2 d). Photolysis is a principal route of transformation in the aquatic environment. In aquatic systems, four major (CGA 300407, CGA 215525, CGA 249257 and hydroxy CGA 215525) and three minor (CGA 180777,CGA 294849 and unidentified) transformation products were detected. No data were submitted on biotransformation in aerobic and anaerobic aquatic systems.

5.9 Summary of fate and behaviour in air

Pymetrozine has a very low vapour pressure ($<4 \times 10^{-6}$ Pa at 25°C) and a low Henry's Law Constant ($<3 \times 10^{-6}$ Pa/m^3/mol at 25°C; 1/H = 8.3×10^8). These values indicate that CGA 215944 is essentially non-volatile and no significant volatilization is expected. Atmospheric contamination is, therefore, not considered to be a route of exposure with the proposed use.

5.10 Expected environmental concentrations

5.10.1 Endeavor 50WG

Endeavor 50WG is proposed for indoor use (greenhouses) on non-food flowering and ornamental plants. As environmental exposure of pymetrozine through treated vegetation, soil and water is limited with the proposed indoor use, the expected environmental concentrations (EECs) were not calculated.

5.10.2 Fulfill 50WG

Maximum EECs in soil, water and diets of birds and mammals are presented in Appendix III, Table 6.

Drinking water: The estimated environmental concentrations in drinking water as a result of leaching or runoff are summarized in Appendix III, Table 7.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

Summary of toxicity of pymetrozine to terrestrial organisms is presented in Appendix IV, Table 1. Pymetrozine has no adverse effects on earthworms up to 12.3 mg a.i./kg soil and on predatory and parasitic arthropods up to 1200 g a.i./ha. Pymetrozine is non-toxic to bees on an acute basis, and to wild birds and mammals on an acute and shot-term dietary basis. No adverse effects on reproductive performance of birds and mammals were observed up to 100 mg a.i./kg diet.

6.2 Effects on aquatic organisms

Summary of toxicity of pymetrozine to aquatic organisms is presented in Appendix IV, Table 2. Pymetrozine is slightly toxic to daphnids on an acute basis and will adversely affect its reproductive performance at concentrations greater than 0.0251 mg a.i./L. It is slightly to moderately toxic to marine invertebrates on an acute basis. Pymetrozine is non-toxic to freshwater and marine fish on an acute basis and has no adverse affects on their reproductive performance up to 11.7mg a.i./L. Pymetrozine will inhibit the algal growth at concentrations greater than 6.28 mg a.i./L water. The log K_{ow} of –0.18 indicates that pymetrozine has a negligible potential for bioaccumulation in organisms.

6.3 Effects on biological methods of sewage treatment

Data are not currently required by the PMRA.

6.4 Risk characterization

6.4.1 Environmental behaviour

Pymetrozine is non-persistent to slightly persistent in soils under aerobic conditions and moderately persistent under anaerobic conditions. Pymetrozine is slightly mobile to immobile in soils and has a low potential to leach and contaminate groundwater.

Nine major and eleven minor transformation products were detected in both laboratory and field studies. These products were, however, not persistent under field conditions. Transformation products, CGA 359009 and CGA 249257, are moderately mobile and CGA 180777 and GS23199 are very highly mobile in soils. These transformation products have, however, a low potential to leach and contaminate groundwater under field conditions. Parent compound and the transformation products have also a negligible potential for bioaccumulation in organisms.

6.4.2 Endeavor 50WG

Terrestrial organisms
Pymetrozine is non-toxic to bees, earthworms, predatory and parasitic arthropods, wild birds and mammals on an acute basis and also on short term dietary basis to birds and mammals. Reproductive performance of birds and mammals may, however, be adversely affected, if the concentration of the treated foliage exceeds 100 mg a.i./kg diet. With the proposed indoor use, however, the birds and mammals are not exposed to the treated foliage and therefore, the risk to these organisms is limited.

Aquatic organisms
Pymetrozine is non-toxic to fish and slightly to moderately toxic to aquatic invertebrates on an acute basis. Reproductive performance and general health (chronic effects) of young fish and invertebrates will be adversely affected if the concentration of pymetrozine in water exceeds 11.7 and 0.0251 mg a.i./L, respectively.

Pymetrozine is, however, practically immobile in soils and will not contaminate aquatic systems due to runoff with the proposed indoor use. Exposure to aquatic organisms such as fish, invertebrates, algae and plants is, therefore, limited and pymetrozine will not pose a risk to these organisms. A label statement is, however, required not to contaminate the aquatic systems with effluents, drainage or waste water from the treated greenhouses.

6.4.3 Fulfill 50WG

Terrestrial organisms
Risk to terrestrial organisms was assessed using the NOEL or NOEC values of the most sensitive species. The proposed use of Fulfill 50WG suggests that exposure is likely to occur through the consumption of treated foliage and food sources, with the greatest risk arising from oral ingestion of treated foliage or diet. Dietary intake (DI) was estimated from the information on the food consumption (FC) and the EEC of CGA 215944 in the diet (DI = FC × EEC). Assessment of acute risk to wild birds and mammals was based on the number of days of intake of treated foliage that will result in observable effects. Dietary and reproductive risk to birds and mammals, and acute risk to bees and soil organisms were assessed using MOS (NOEC and EEC) values.

Assessment of risk to terrestrial organisms (Appendix IV, Table 3*a*) indicated that the proposed use of Fulfill 50WG will not pose a risk to earthworms, bees, wild birds and mammals on an acute basis. Fulfill 50WG also will not pose a dietary risk to wild birds and reproductive risk to wild mammals. Proposed use of Fulfill 50WG will, however, pose a low risk to the reproductive performance of birds, a low risk to mammals on a dietary basis and a low acute risk to predators and parasites.

Aquatic organisms

Risk to aquatic organisms was assessed using MOS, i.e., EEC in water in a conservative scenario of direct overspray (100% deposition) of Fulfill 50WG and NOEC of most sensitive species (Appendix IV, Table 3*b*). The MOS values indicated that the proposed use of Fulfill 50WG will not pose a risk to freshwater and marine fish on acute and chronic basis. Also, it will not pose an acute risk to aquatic invertebrates and algae. Fulfill 50WG will, however, pose a risk to aquatic invertebrates such as daphnids on a chronic basis.

6.5 Data gaps

No data were submitted on biotransformation in aquatic systems.

Based on anaerobic soil biotransformation data, pymetrozine is expected to be at least moderately persistent in aquatic system. Calculation of the MOS, based on a direct over spray scenario, indicated a chronic risk to aquatic invertebrates. In reality, less than 7% of the label rate would be deposited on aquatic systems from ground boom spray drift. Consequently, the calculated buffer zone was <1 m, indicating that aquatic exposure to pymetrozine would not be significant. Therefore, data on biotransformation in aquatic systems are not required for the proposed use of Fulfill 50WG, in accordance with the URMUR regulatory directive (DIR99-05, *User Requested Minor Use Registration (URMUR)*).

The data, however, may be required for any additional Fulfill uses, where there is an increase in application rate or number of applications.

6.6 Environmental concerns

Endeavor 50WG: An assessment of the environmental safety indicated that the proposed use of Endeavor 50WG will not pose a risk to the environment.

Fulfill 50WG: An assessment of the environmental safety from the use of Fulfill 50WG has identified the following concerns:

- Fulfill 50WG will pose a low acute risk to predators and parasites, a low reproductive risk to wild birds and a low dietary risk to wild mammals.
- Fulfill 50WG will pose a chronic risk to freshwater invertebrates such as water fleas.

6.7 Risk mitigation

Endeavor 50WG: The following label statement is required to protect the aquatic systems from the contamination of greenhouse effluents and drainage water.

> "This product is moderately toxic to aquatic organisms. Do not discharge effluent, waste and drainage water containing this product into water bodies, such as lakes, streams, ponds, rivers, and estuaries."

Fulfill 50WG: Wild birds and mammals: Dietary risk to wild mammals and reproductive risk to wild birds were assessed using a conservative scenario of over spray of maximum cumulative application rate on foliage and associated food sources. Photolysis studies, however, indicated that phototransformation of pymetrozine is a principal route of dissipation in the environment. The level of exposure to birds and mammals through treated foliage and diet is, therefore, expected to be much lower than that under direct over spray scenario. Further, as the level of risk is low even in a conservative scenario of over spray of maximum application rate, it is acceptable.

Predators and parasites: Proposed use of Fulfill 50WG poses only a low risk, which is acceptable.

Aquatic invertebrates: As spray drift will not likely pose a significant risk, buffer zones are not required for the aquatic systems. The following label statement is, however, required to protect the aquatic invertebrates such as daphnids from the injury of pymetrozine:

> "This product is injurious to aquatic organisms such as water fleas. Do not over spray aquatic systems including sloughs, coulees, ponds, prairie potholes, lakes, rivers, streams, and wetlands. Do not contaminate these habitats when cleaning and rinsing spray equipment or containers."

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Endeavor 50WG was proposed as a Commercial class insecticide for control of the green peach aphid (*Myzus persicae* (Sulzer)), melon aphid (*Aphis gossypii* Glover), greenhouse whitefly (*Trialeurodes vaporariorum* (Westwood)) and silverleaf whitefly (*Bemisia argentifolii* Bellows & Perring) on flowering and ornamental plants in greenhouses (USC 6).

On greenhouse ornamentals, important aphid pests include the green peach aphid, melon aphid, chrysanthemum aphid (*Macrosiphoniella sanborni* (Gill)), rose aphid (*Macrosiphum rosae* (L.)), foxglove aphid (*Aulacorthum solani* Kaltenbach) and potato aphid (*Macrosiphum euphorbiae* (Thomas)). Aphids can deform new growth by feeding near the growing points, and further spoil the appearance of plants by covering the foliage with shed skins and honeydew, which also provide a growth medium for sooty mould. The major whitefly pests on greenhouse ornamentals are the greenhouse whitefly, silverleaf whitefly and sweet potato whitefly (*Bemisia tabaci* (Gennadius)). Whiteflies excrete large amounts of honeydew, and the infested plants may lack vigour, wilt and turn yellow.

Fulfill 50WG is proposed for registration as a foliar spray on potatoes (USC 14) for control of the green peach aphid, potato aphid and buckthorn aphid (*Aphis nasturtii* Kaltenbach) and foxglove aphid. The proposed dosage was 193 g product/ha, applied in sufficient water to ensure good coverage (minimum of 100 L/ha), with not more than two applications per crop per season, a minimum of 7 d between applications, and 14 d between the last application and harvest (PHI).

Aphids on potatoes may reduce plant vigour if populations are high, but their main threat to potato plants is through their ability to vector viruses. This is especially of concern in seed potato fields, where increased virus levels can lead to reclassification of a field to a lower seed class or decertification to table stock, resulting in substantial revenue loss to the grower. In fields grown for tablestock or processing markets, viruses can decrease yields and plants infected with Potato Leaf Roll Virus (PLRV) can exhibit reduced tuber quality due to the development of net necrosis in susceptible cultivars.

The aphid species most commonly found colonizing potato plants in Canada include the potato aphid, green peach aphid, buckthorn aphid and foxglove aphid.

7.1.2 Mode of action

Pymetrozine belongs to a new chemical class known as pyridine azomethines. When applied as a systemic insecticide to plants, pymetrozine causes neural inhibition of feeding by Homoptera (sap-sucking bugs such as aphids and whiteflies). Feeding usually stops within a few hours of exposure, but mortality due to starvation or desiccation may take several days.

7.1.3 Crops

Endeavor 50WG is proposed for use on non-food greenhouse flowering and ornamental plants (USC 6: Greenhouse non-food crops). Fulfill is proposed for used on potato plants (USC 14: Terrestrial food crops)

7.1.4 Effectiveness against pests

Endeavor 50WG (Submission No. 2000-3412)
Forty-eight greenhouse trials were conducted in various locations in the U.S. to test the efficacy of Endeavor 50WG in controlling aphids and whiteflies on greenhouse ornamentals. Thirty-three trials involved aphids and 15 involved whiteflies. Twelve of the trials included data on phytotoxicity and four trials included data on plant vigour.

Results from the submitted trials indicate that Endeavor 50WG is effective in controlling aphids on greenhouse ornamentals at all dilution rates tested (2.14–40 g a.i./100 L; 89–100% mortality). Only one trial was carried out at each of the three lowest dilution rates (2.14, 2.67 and 4.28 g a.i./ha), therefore a lowest effective dilution rate could not be established. The submitted data support the use of Endeavor 50WG at a dilution rate of 10–20 g product/100 L (5–10 g a.i./100 L) for control of aphids on greenhouse ornamentals.

It is normal to express rates of products for greenhouse use as dilution rates (g product/100 L), rather than the rates per unit area (g/ha) used for field crops. The rates in the Endeavor efficacy data package were all shown in g/hL (g/100 L). The volume of spray per hectare was stated for only 16 of the 43 Endeavor trials, and ranged from 100 to 3739 L/ha, with a mean of 1484 L/ha. The wide range of spray volumes could be related to the forms of the plants (tests were conducted on 10 species), and (or) their growth stages at the time of the trials. The efficacy data have been reanalysed in terms of grams of active ingredient per hectare (g a.i./ha) for the 11 aphid and 6 whitefly trials where the volume of spray per hectare was stated. According to the results of this analysis, 101–200 g a.i./ha gave adequate control of aphids (average 93% after one application). Dosages of 1–100 g a.i./ha might also be enough (average 94% control after one application), but there are few data for these dosages. To keep the rate as a dilution, which is the usual way for greenhouse applications, and to allow for some types of ornamentals requiring more spray per unit area than others, the label directions are amended as follows:

> "Use 10–20 g of Endeavor/100 L of water, and spray to the point of runoff, but do not exceed 20 g product/100 L per application, or two applications (2 × 20 g product/100 L) per crop cycle."

Since greenhouse ornamentals can be planted and harvested at any time of year, it is more realistic to set the limit per crop cycle, rather than per calendar year.

The submitted efficacy data included 5 trials against the greenhouse whitefly, 10 against the silverleaf whitefly and 1 against the sweet potato whitefly. When the efficacy data based on dilution rates were analysed, it appeared that Endeavor was only partially effective against whiteflies, with no clear relation between efficacy and rate. With 10 g a.i./100 L there was only a mean reduction in numbers of 33% after one application and 68% after three applications of Endeavor 50WG, while with 40 g a.i./100 L the

reductions were 35% after one application and 67% after three applications. When the efficacy data were reanalysed in terms of grams a.i./ha for the 6 whitefly trials where the volume of spray per hectare was stated, the results were similar to what they had been when considered on a grams per 100 L basis, with 52 and 54% reductions in numbers after one and two applications, respectively, at 51–200 g a.i./ha, and 52% and 78% reductions after one and two applications, respectively, at 201–400 g a.i./ha. High levels of control (90–98%) were achieved by two applications at dosages of 401–1500 g a.i./ha, but these results are from only four trials, and are not sufficient to justify raising the upper limit to, say, 700 g a.i./ha for whitefly control.

These results are not sufficient to support a claim that Endeavor 50WG controls whiteflies if used on its own, but this product could still be useful because it is compatible with biocontrol agents. In view of the potential contribution of Endeavor to whitefly integrated pest management (IPM) programs on ornamentals, and the fact that the efficacy data support its use against aphids on ornamentals, the following statement is added to the label:

> "Greenhouse whitefly (*Trialeurodes vaporariorum*) and silverleaf whitefly (*Bemisia argentifolii*): Application at the recommended rate can contribute to whitefly IPM programs by reducing whitefly infestation levels."

Six of the efficacy trials (five aphid, one whitefly) included some treatments with and others without adjuvants, and another three trials (one aphid, two whitefly) had treatments with adjuvants, but none without them. Mean reductions in insect counts on treated plants at 6–21 (usually 7) d after treatment were 95% for aphids and 58% for whiteflies in plots with adjuvant, compared with 92% for aphids and 49% for whiteflies in plots without adjuvant. These results, and those for Fulfill 50WG against aphids on potatoes (see below) show a slight advantage in using an adjuvant with this formulation (Endeavor 50WG and Fulfill 50WG identical). An adjuvant is not necessary for liquid formulations of contact pesticides under good conditions, but may be required for dry formulations of systemic pesticides such as Endeavor 50WG, especially for use on plants with a thick waxy layer on the leaves that reduces wetting and absorption. It is therefore recommended that a statement on the use of spray adjuvants be allowed on the label. The applicant has also been asked to amend the label statement on the use of spray adjuvants to include examples of hard-to-wet plants, and examples of recommended registered adjuvant products.

Fulfill 50WG (Submission No. 2000-3413)

Twenty-five field trials were conducted in various areas of the U.S. to test the efficacy of foliar- applied Fulfill 50WG or related formulations in controlling three potato-colonizing aphid species: the potato aphid, green peach aphid and buckthorn aphid.

The results indicated that Fulfill 50WG was effective in controlling potato, green peach, and buckthorn aphids on potato. Furthermore, the scientific rationale provided by Syngenta was sufficient to allow inclusion of foxglove aphids on the Fulfill 50WG label.

In 12 plots where Fulfill 50WG was applied at rates ranging from 49 to 56 g a.i./ha, control of aphids was 68% when compared with the check plot. However, the 30 plots receiving from 99 to 112 g a.i./ha of Fulfill exhibited an average of 81% control of aphids, suggesting that a rate of 96.5 g a.i./ha is the lowest effective rate. This was also supported by plots receiving 150 or 200g a.i./ha, which showed control similar to that in plots receiving 96.5 g a.i./ha. Therefore, registration is supported at the rate of 96.5 g a.i./ha (193 g product/ha).

Sufficient data were also provided to support a second application of Fulfill 50WG if aphid populations build up following the initial application.

The efficacy submitted for Fulfill 50WG include five trials that had some treatments with and others without adjuvants. The results suggest a slight advantage in using an adjuvant (80% control for treatments with and 71% control for treatments without adjuvants). An adjuvant is not necessary for liquid formulations of contact pesticides under good conditions, but may be required for dry formulations of systemic pesticides such as Fulfill 50WG, especially under drought conditions, when the waxy layer on the leaves of plants thickens, reducing absorption.

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

Endeavor 50WG (Submission No. 2000-3412)
Endeavor 50WG at dilutions of 7.5–40.0 g product/100 L was sprayed 1–6 times on plants of 21 species or varieties, which were observed for 7–61 d after the last treatment. No adverse effects were noted on any of the plants tested. In four trials that assessed plant vigour, plants treated with Endeavor 50WG were all healthy and had much higher vigour ratings than the untreated controls, due to insect damage to the controls. The label includes the following precautionary statement:

> "…While many species and cultivars have been tested, a small group of each species and cultivar should be evaluated for phytotoxicity two weeks prior to making applications to the entire crop. Applications should not be made to poinsettia after bract formation."

Fulfill 50WG (Submission No. 2000-3413)
In six studies to investigate crop tolerance, Fulfill 50WG was sprayed on potato plants (Russet Burbank, Newleaf Russet Burbank, Katahdin) 1–4 times at dosages of 192–224 g product/ha (96–112 g a.i./ha) in 187–840 L water/ha. No signs of phytotoxicity were noted in any of the six trials, at 7–105 d after application. In addition, four of the field trials to measure the efficacy of Fulfill 50WG at 192–224 g/ha included observations on phytotoxicity, but none was found.

7.3 Observations on undesirable or unintended side effects, e.g., on beneficial and other non-target organisms, on succeeding crops, other plants or parts of treated plants used for propagating purposes (e.g., seed, cutting, runners) (OECD 7.5)

See Section 7.5.2 for a discussion of effects on non-target beneficials.

7.4 Economics

Endeavor 50WG (Submission No. 2000-3412)
Insects on greenhouse ornamental plants for sale are not tolerated. The Canadian Food Inspection Agency's Greenhouse Certification Program for the export of greenhouse-grown plants to the U.S. requires that all the plants exported be both insect and disease free.

Fulfill 50WG (Submission No. 2000-3413)
Control of aphids on potatoes is necessary for prevention of PLRV and other viruses that aphids transmit. Virus infection can cause seed potatoes to be decertified, which could reduce their market value by 72%.

7.5 Sustainability

7.5.1 Survey of alternatives

7.5.1.1 Non-chemical control practices

Non-food greenhouse flowering and ornamental plants
Methods for preventing aphid and whitefly infestations in greenhouses include: removing weeds from inside the greenhouses and keeping a 3-m band around the outside of the greenhouse weed-free; inspecting all incoming plants for infestations; screening air vents and other possible routes of entry; and using yellow sticky traps to survey for any dispersing adults.

Several invertebrate biological control agents are commercially available for greenhouse use. For aphids, they include the parasitoid wasp *Aphidius colemani* Viereck and the predatory gall midge *Aphidoletes aphidimyza* (Rondani). For whiteflies, they include the parasitoid wasps *Encarsia formosa* (Gahan) and *Eretmocerus eremicus* Rose & Zolnerowich and the predatory beetle *Delphastus pusillus* Le Conte.

Potatoes
On potato plants, a number of natural controls can keep aphid populations below damaging levels. These include environmental stresses (e.g., high winds, heavy rains, extreme temperatures) and natural enemies like predators (e.g., lady beetles, lacewings, damsel bugs) and parasites (e.g., parasitoid wasps and entomophagous fungi). However, natural enemies develop much more slowly than aphids and are susceptible to a number of the insecticides and fungicides used in potato production. The spraying of broad

spectrum insecticides to control Colorado potato beetles and leafhoppers, and fungicides to control blight and other fungal diseases, kills these natural aphid enemies and can lead to dramatic increases in aphid populations.

7.5.1.2 Chemical control practices

Many different insecticides, which display several different modes of action, are already registered for all of the proposed uses (Table 7.5.1).

Table 7.5.1 Insecticides registered for control of aphids on potatoes, and for control of aphids and whiteflies on greenhouse non-food crops

Insecticide group	Potatoes	Greenhouse non-food crops	
	Aphids	Aphids	Whiteflies
Carbamates	methomyl oxamyl pirimicarb	bendiocarb pirimicarb	bendiocarb
Neonicotinoids	imidacloprid	imidacloprid	imidacloprid
Organochlorines	endosulfan	endosulfan	endosulfan
Organophosphates	acephate diazinon dimethoate malathion methamidophos phorate phosmet	acephate chlorpyrifos diazinon dichlorvos malathion naled oxydemeton-methyl parathion sulfotep	acephate chlorpyrifos diazinon dichlorvos malathion naled parathion sulfotep
Synthetic pyrethroids	deltamethrin		permethrin
Others		insecticidal soap nicotine kinoprene pyrethrins	insecticidal soap kinoprene pyridaben

7.5.2 Compatibility with current management practices including IPM

Since pymetrozine is a systemic feeding inhibitor for sap-sucking insects, it is unlikely to harm predators and parasites of aphids and whiteflies directly. Environmental toxicology data indicate that Fulfill 50WG (which is identical to Endeavor 50WG) at dosages up to 1200 g a.i./ha caused little or no mortality of predatory ground beetles (*Poecilus cupreus* Linnaeus), green lacewings (*Chrysoperla carnea* (Stephens)), predatory mites (*Typhlodromus pyri* Scheuten) and parasitoid wasps (*Aphidius rhophalosiphi* DeStefani) that are used to control aphids (see Section 6.1.1.3). It is unfortunate that these tests did not include the parasitoid wasps *Encarsia formosa* and *Eretmocerus eremicus* or the

predatory beetle *Delphastus pusillus* that are actually used for whitefly control, but *Encarsia* is considered to be susceptible to insecticides to the same extent as *Aphidius*. Other tests have shown that pymetrozine is not acutely toxic to honeybees (Section 6.1.1.2).

The labels for both Endeavor 50WG and Fulfill 50WG bear the following statement:

> "**Suitability for Integrated Pest Management Programs**
> Endeavor/Fulfill is suitable for Integrated Pest Management (IPM) programs, as it has a low toxicity to beneficial insect (including honeybees and bumblebees) and mite populations."

7.5.3 Contribution to risk reduction

Pymetrozine and associated end-use products were registered as reduced risk products in the U.S. and are potential alternatives to the organophosphate insecticides listed in Table 7.5.1 for control of aphids and whiteflies. Organophosphate insecticides are currently under re-evaluation, both by the PMRA and the U.S. EPA.

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

In the mode of action classification of the Insecticide Resistance Action Committee (IRAC), issued in September 2001 and published on the IRAC website (http://www.plantprotection.org/IRAC/IRACMOA2001Dec01.pdf), pymetrozine is in Group 9, "Compounds of unknown or non specific mode of action (selective feeding blockers)," and the only member of Subgroup 9B, with a footnote that "Not all members of this class have been shown to be cross-resistant. Different mechanisms that are not linked to target site of action, such as enhanced metabolism, are common for this group of chemicals." According to other documents on the IRAC website (consulted in April 2002), both the greenhouse whitefly and the sweet potato whitefly have developed resistance to a wide range of insecticides, including carbamates, organophosphates and pyrethroids. In southern Spain, the sweet potato whitefly is developing resistance to the neonicotinoid insecticide imidacloprid, and imidacloprid-resistant individuals show decreases in susceptibility to several other insecticides, including pymetrozine.

The labels for both Endeavor 50WG and Fulfill 50WG are amended to include the following:

> "**Resistance Management**
> For resistance management, please note that Endeavor/Fulfill 50WG Insecticide contains a Group 9B insecticide. Any insect population may contain individuals naturally resistant to Endeavor/Fulfill 50WG Insecticide and other Group 9B insecticides. The resistant individuals may dominate the insect population if this group of insecticides are used

repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but are specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed. To delay insecticide resistance:

- Where possible, rotate the use of Endeavor/Fulfill 50WG Insecticide or other Group 9B insecticides with different groups that control the same pests in a field.

- Insecticide use should be based on an IPM program that includes scouting, record keeping, and considers cultural, biological and other chemical control practices.

- Monitor treated pest populations for resistance development.

- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and (or) IPM recommendations for the specific site and pest problems in your area.

- For further information or to report suspected resistance, contact Syngenta company representatives at 1-800-459-2422 (in Eastern Canada) or 1-800-665-9250 (in Western Canada) or at www.syngenta.ca."

The following site of action identification symbol is on the primary panels of the labels:

GROUP	9B	INSECTICIDE

7.6 Conclusions

The following conclusions are based on full reviews of the submitted efficacy and value data.

Endeavor 50WG (Submission No. 2000-3412)

- The results of 33 trials against aphids support the proposed use of Endeavor 50WG to control the green peach aphid and melon aphid on greenhouse ornamentals at dilution rates of 10–20 g product/100 L (5–10 g a.i./100 L), which represents a dosage of 100–200 g product/ha (50–100 g a.i./ha) at a spray rate of 1000 L/ha.

- In 14 trials against the greenhouse whitefly and the silverleaf whitefly, Endeavor 50WG at 100–400 g product/ha (50–200 g a.i./ha) gave, on average, only 52% and 54% control after one and two applications, respectively. High levels of control (90–98%) were achieved after two applications at dosages of 401–1500 g a.i./ha, but these results are from only four trials, and are not sufficient to justify raising the recommended rate (e.g., to 700 g a.i./ha) for whitefly control. These results are not sufficient to support a claim that Endeavor 50WG controls whiteflies if used on its own, but support a label claim that application at the recommended rate would contribute to whitefly IPM programs by reducing whitefly infestation levels.

- The results of six trials show that there may be a slight advantage in using an adjuvant with Endeavor 50WG. A statement on the use of spray adjuvants when treating hard-to-wet plants is on the label, with examples of hard-to-wet plants, and examples of the recommended registered adjuvant products.

- In phytotoxicity and plant vigour tests on plants of 21 species, no adverse effects on any of the plants were noted by up to 61 d after the last of up to 6 applications of Endeavor 50WG at dilutions of 7.5–40.0 g product/100 L (3.75–20.0 g a.i./100 L). Plants treated with Endeavor 50WG had much higher vigour ratings than untreated controls, due to insect damage to the controls.

Fulfill 50WG (Submission No. 2000-3413)

- The results of twenty-five field trials in various areas of the U.S. support the proposed use of Fulfill 50WG as a foliar spray on potato plants at a dosage of 193 g product/ha (96.5 g a.i./ha) to control aphids including potato aphid, green peach aphid and buckthorn aphid. Furthermore, a scientific rationale provided by the applicant supports the use of Fulfill 50WG against the foxglove aphid.

- Sufficient data were also provided to support a second application of Fulfill 50WG if aphid populations increase following the initial application, making a maximum seasonal rate of 386 g product/ha (193 g a.i./ha).

- The results of five trials that compared the efficacy of Fulfill 50WG with and without spray adjuvants suggest a slight advantage in using an adjuvant (80% control for treatments with and 71% control for treatments without adjuvants).

- In six trials to investigate crop tolerance, Fulfill 50WG was sprayed on potato plants of three varieties between one and four times at dosages of 192–224 g product/ha (96–112 g a.i./ha). No signs of phytotoxicity were noted in any of the trials, at 7–105 d after application.

7.6.1 Summary

The results of trials against aphids support the proposed use of Endeavor 50WG (50% pymetrozine, a feeding inhibitor for sapsucking insects) to control aphids including green peach aphid and melon aphid on non-food greenhouse ornamentals and flowering plants, at dilution rates of 10–20 g product/100 L, with a maximum of two applications per crop cycle. At these rates, Endeavor 50WG gave only partial control of whitefly including greenhouse whitefly and the silverleaf whitefly. This supports a claim that its use at the recommended rate would contribute to whitefly IPM programs by reducing whitefly infestation levels, without harming whitefly parasitoids and predators.

The results of six trials show a slight advantage in using an adjuvant with Endeavor 50WG. A statement pertaining to the use of spray adjuvants when treating hard-to-wet plants is on the label.

In phytotoxicity tests on plants of 21 species, no adverse effects on any of the plants were noted for up to six applications of Endeavor 50WG. Plants treated with Endeavor 50WG had much higher vigour ratings than untreated controls due to insect damage to the controls.

The results of 25 field trials support the proposed use of Fulfill 50WG (which is identical in composition to Endeavor 50WG) as a foliar spray on potato plants at a dosage of 193 g product/ha (96.5 g a.i./ha) to control the potato aphid, green peach aphid, buckthorn aphid and foxglove aphid.

The results of five trials that compared the efficacy of Fulfill 50WG with and without spray adjuvants suggest a slight advantage in using an adjuvant. A statement on the use of spray adjuvants is on the label.

Fulfill 50WG performed equally well by itself or when tank-mixed with any one of five fungicides tested, but no data were submitted to show if tank mixing of Fulfill 50WG with the fungicides had any effect on efficacy of the fungicides.

In six trials to investigate crop tolerance, Fulfill 50WG was sprayed on potato plants of three varieties between one and four times at dosages at or above those proposed. No signs of phytotoxicity were noted in any of the trials, at 7–105 d after application.

A summary of the proposed and revised label directions is shown in Appendix I, Table 2.

8.0 Toxic Substances Management Policy considerations

During the review of pymetrozine, the PMRA has taken into account the federal Toxic Substances Management Policy[1] (TSMP) and has followed DIR99-03[2]. It has been determined that this product does not meet TSMP Track-1 criteria because of the following.

- Pymetrozine does not meet the criteria for persistence. Its values for half-life in soil under aerobic (5.5 d) and anaerobic conditions (103 d) are below the TSMP Track-1 cut-off criteria for soil ($\geq$182 d).

- Pymetrozine is not bioaccumulative. Studies have shown that the octanol–water partition coefficient (log K_{ow}) is –0.18, which is below the TSMP Track-1 cut-off criterion of $\geq$5.0.

- Pymetrozine does not meet the criteria for CEPA-toxic or CEPA-toxic equivalent under the TSMP (see Sections 3.6, 4.7 and 6.4).

- Pymetrozine does not form any major transformation products that meet the TSMP Track-1 criteria.

By-products or microcontaminants: Pymetrozine does not contain any byproducts or microcontaminants that meet the TSMP Track-1 criteria. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

Formulants: The formulation products, Endeavor 50WG and Fulfill 50WG, do not contain any formulants that are known to contain TSMP Track-1 substances or EPA List 1 or 2 formulants.

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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.

9.0 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations and has found it sufficient pursuant to Section 18.b, to allow a determination of the safety, merit and value of pymetrozine and associated end-use products, Endeavour 50WG and Fulfill 50WG. The PMRA has concluded that the use of pymetrozine and associated end-use products, Endeavour 50WG and Fulfill 50WG in accordance with their labels have merit and value consistent with Section 18.c of the PCP Regulations and do not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of pymetrozine and associated end-use products, Endeavour 50WG for the control of aphids, including green peach aphid and melon aphid, and whiteflies, including greenhouse whitefly and silverleaf whitefly, on non-food greenhouse uses on flowering and ornamental plants, and Fulfill 50WG for the control of aphids, including buckthorn, foxglove, green peach and potato aphids, on potatoes, are proposed for full registration under Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ALK	alkaline phosphatase
ARfD	acute reference dose
AST	aspartate aminotransferase
bw	body weight
bwg	body weight gain
CMC	carboxymethylcellulose
d	day
DEEM™	Dietary Exposure Evaluation Model™
DI	dietary intake
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DT_{50}	time required for non first-order dissipation (50%)
EC_{50}	median effective concentration
EEC	expected environmental concentration
EPA	Environmental Protection Agency
F_0	parental generation
F_1	first generation offspring
F_2	second generation offspring
FC	food consumption
GAP	good agricultural practice
GD	gestation days
GI	gastrointestinal
h	hour
ha	hectare
HPLC	high performance liquid chromatography
ILV	interlaboratory validation
IPM	integrated pest management
K_{ads}	Freundlich soil adsorption coefficient
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol–water partition coefficient
LADD	lifetime average daily dose
LC	liquid chromatography
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MIS	maximum irritation score
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue limit
MS	mass spectrometry

NOAEL	no observed adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect level
NZW	New Zealand White
PCP	Pest Control Products
PDI	potential daily intake
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PLRV	Potato Leaf Roll Virus
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
Q_1*	cancer unit risk
r	correlation coefficient
RAC	raw agricultural commodity
ROC	residue of concern
SPE	solid-phase extraction
STMdR	supervised trial median residue
TC	transfer coefficient
TRR	total radioactive residue
U.S.	United States
UV	ultraviolet
µ	micro
♂	male
♀	female

Appendix I Summary tables

Table 1 Toxicology summary table

Note: Effects reported were observed in both sexes unless otherwise indicated.

METABOLISM
CGA 215944 (with pyridine- or triazine-labelled material) was readily absorbed from the GI tract of rats and rapidly eliminated via urine (principal route, accounted for 56–80% of the dose) and bile (10–37%) after oral gavage administration. Maximum concentrations in the blood were reached 15 minutes or 1 h for males and females, respectively at low dose (0.5 mg/kg bw) and 4 or 8 h for males and females, respectively at high dose (100 mg/kg bw). For both labels, the calculated elimination half life was 1–2 h for the low dose and 2–11 h for the high dose. Derivatives from the pyridine label persisted longer in tissues and organs than those from the triazine label. After 7 d post-dosing, only 0.2–1.4% of the given radioactivity was detected in expired air and 0.2–0.7% in cage washing. The relatively high urinary level of unchanged test material (15–18%) suggests metabolic saturation at 100 mg/kg bw. The highest residue levels were in the liver and kidney at all time points irrespective of the dose or labelling site. Tissue retention was low, accounting for only 0.3–3.8% of the given dose 7 d post-dosing. The skeletal muscle had the highest percent of the administered dose (7–8%) of the low dose at 1 h and 19–21% of the high dose at 8 h. Metabolism of CGA 215944 was extensive and the metabolic pathways were independent of sex, species, pretreatment and dose level. The metabolite patterns were qualitatively similar among both sexes, doses and labels. The identified metabolites, including unchanged CGA 215944 (approximately 20%) were estimated to represent nearly two thirds of the administered high dose. Three metabolic pathways were identified. The first involves an oxidation of the methyl substituent at the triazine ring to yield metabolite 3U (18–20% of the dose) some of which is further oxidized to the corresponding carboxylic acid, 5U (5–7% of the dose). Another oxidation at the methylene group within the triazine ring yields metabolite 2U (4–10% of the dose). The third involves cleavage of the bridge between the two rings in CGA 215944 and in 2U (both estimated at >20% of the dose) to give rise to several single ring metabolites, nine of which were identified (each below 1%). There was no indication that conjugated metabolites were formed. In a comparative metabolism study, rats and mice received repeated dietary concentrations of CGA 215944 followed by a pulse gavage dose of radiolabelled CGA 215944. Rats rapidly excreted the test material (80% within 24 h) irrespective of test diet concentration. In the mouse, excretion was also rapid, however, excretion within the first 24 h decreased slightly as dietary concentration increased (from 82 to 75%). Total carcass retention was low in both species (approximately 2%). Mice and rats showed similar excretion patterns but rats had increased urinary excretion (>70%) relative to mice (43–60%). Metabolite fractions in urine and feces were similar; both contained unchanged test substance (higher in rat urine than mouse urine), and the amount in the rat urine was higher than in the feces. Metabolite 3U was the major metabolite in the urine of both species, the amount of this metabolite in the feces was slightly less than that in urine. Metabolites identified in fractions 2 and 3 in urine and feces were similar. There were numerous small metabolites of unknown structure.

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	LD_{50} OR LC_{50} (mg/kg bw) or (mg/L)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
ACUTE STUDIES: Technical			
Oral	Sprague-Dawley rats (5/sex/dose level) (4000, 5000, 6000, 6500, 7000 mg/kg bw)	5693 in males	At ≥5000: clinical signs (hypo-activity, dyspnea, staggered gait to prostration) At ≥6000: mortality **Low toxicity**
Dermal	Sprague-Dawley rats (5/sex)	LD_{50} > 2000 mg/kg bw (limit test)	No mortality or clinical signs **Low toxicity**
Inhalation	(TIF:RAI f (SPF), hybrids of RII/1 × RII/2) albino rats (5/sex)	LC_{50} = > 1.8 mg/L (maximum achieved dose)	No mortality or clinical signs **Slightly toxic [CAUTION]**
Skin irritation	New Zealand White (NZW) rabbit (3/sex)	No signs of irritation	**Non-irritating to skin**
Eye irritation	NZW rabbit (3/sex)	maximum average score = 3.13; maximum irritation score (MIS) = 12.8	**Conjunctival and iridial effects; minimally irritating to eyes**
Skin sensitization (Maurer Optimization)	Pirbright White guinea pig (10/sex)		**Potential dermal sensitizer**
Acute neurotoxicity	Crl:CD(SD)BR rats (10/sex/dose) 0, 125, 500, 2000 mg/kg bw	NOAEL < 125 mg/kg bw (the lowest dose level)	≥**125:** ↓ body temperature;↓ number of rears and motor activity (♂); ↓ tail pinch response (♀) ≥**500:** tremors (♂); ↓ number rears and motor activity (♀); clinical signs (chromodacryorrhea, chromorhinorrhea, discoloured urine, infrequent stool, stained extremities, head and ventral body) **2000:** mortality, ↓ bw (♂); tremors (♀) No treatment-related neuropathological findings

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	LD_{50} OR LC_{50} (mg/kg bw) or (mg/L)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
ACUTE STUDIES: Formulation products, containing 49.8% a.i.			
Oral	Crl:CD (SD) rats (5/sex) (5000 mg/kg bw)	LD_{50} > 5000 mg/kg bw (Limit test)	**At 5000**: red-stained face and uro-genital area, soft stool, urination of red liquid, thin appearance **Low toxicity**
Dermal	Sprague-Dawley rats (5/sex)	LD_{50} > 2000 mg/kg bw (limit test)	Dermal irritation in all animals clearing by the end of the study **Low toxicity**
Inhalation	HSD:SD rats (5/sex)	LC_{50} > 3.09 mg/L (gravimetric concentration)	No mortality; ↓ activity, piloerection **Low toxicity**
Skin irritation	NZW rabbit (4 ♂ and 2 ♀)	PDI = 1.3	Very slight erythema and edema **Slight dermal irritant**
Eye irritation	NZW rabbit (6 animals)	MIS = 5.7	**Conjunctival irritation; slight eye irritant**
Skin sensitization (closed patch technique, Magnusson and Kligman Test)	Crl:(HA)BR guinea pig (20 test animals, 10 controls)	Two studies indicate a positive result and one indicates a negative result	**Potential dermal sensitizer**
STUDY	**SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)**	**NOEL OR NOAEL AND LOAEL (mg/kg bw/d)**	**TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS**
SHORT-TERM: Technical			
28-d **dermal** (6 h/d, 5 d/week for 4 weeks) (98% a.i.)	Tif: RAIF (SPF) Sprague-Dawley rat (10/sex/dose) 0, 10, 100 and 1000 mg/kg bw/d	NOAEL = 1000 mg/kg bw/d the highest dose tested, for both systemic toxicity and dermal irritation	No treatment-related effects

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
28-d oral **gavage** (98% a.i.)	Tif: RAIF (SPF) Sprague-Dawley rat (10/sex/dose) 0, 10, 100 and 600 mg/kg bw/d	NOAEL = 10 mg/kg bw/d LOAEL = 100 mg/kg bw/d	≥**100:** ↑ cholesterol, platelet, hepatic hypertrophy; hyperplasia of splenic white pulp; ↑ relative liver weight, thymic atrophy (♂) **600:** ↓ bw and FC, anemia (↓ red blood cells, hyperchromasia), ↑ water consumption (WC), ↑ white blood cells, reticulocyte, bilirubinuria, protein, ALK, spleen weights, ↓ glucose, potassium, chloride, ↑ hepatic hypertrophy; ↑ urine density, ↓ spermatozoa (♂)
3-month **dietary** (98% a.i.)	Tif:MAGf(SPF) mice (10/sex/dose) 0, 1000, 3000 and 7000 ppm	NOAEL or LOAEL not established, since the study was a range-finding study to determine the dose levels for the definitive carcinogenicity study.	≥**1000:** ↑ relative liver weights, ↑ hepatocyte hypertrophy and centrilobular perivascular-like aggregates of lymphocytes, necrosis of liver ≥**3000:** ↑ relative spleen weights **7000:** ↓ bw (♂ only) **Note**: **This study was not submitted to the PMRA; reported results taken from 18-month oncogenicity study.**

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
90-d **dietary** (with 4-week recovery) (98% a.i.)	TiF:RAIF (SPF) rat (10/sex/dose; extra 10/sex at 0 and 5000 ppm for recovery) 0, 50, 500 and 5000 ppm (equal to 0, 3.42, 32.5 and 360 mg/kg bw/d ♂/♀)	NOAEL = 500 ppm (~32.5 mg/kg bw/d) LOAEL = 5000 ppm (~360 mg/kg bw/d)	**5000 ppm:** ↓ bw, FC and WC; leucocytosis, ↑ creatinine, bilirubin, P, cholesterol, ↑ ALK, ↑ relative liver, spleen, brain weights, atrophy of thymus; ↓ glucose, K and urine volume, ↑ testis and heart weights, ↑ hepatic hypertrophy, ↑ kidney calcification(♂); bilirubinuria (♀) **After 4-week recovery:** Recovery of above effects with the exception of bw; thymus atrophy (♂); leucocytosis (♀) **Control terminal body weight**: ♂ 522.7 g; ♀ 302.7 g **Control terminal daily food consumption:** ♂ 24.1 g; ♀ 16.7 g
90-d **dietary** neurotoxicity (98.2% a.i.)	Crl:CD(SD)BR rat (10/sex/dose) 0, 500, 1000 and 3000 ppm (equal to 0, 36/41, 68/81 and 201/224 mg/kg bw/d ♂/♀)	NOAEL (systemic toxicity and neurotoxity) = 1000 ppm (68/81 mg/kg bw/d ♂/♀) LOAEL = 3000 ppm (210/224 mg/kg bw/d)	**3000 ppm:** ↓ bw; ↑ repetitive movement (“stereotypy”) (♂); tiptoe gait, walking on toes (♀) No treatment-related gross or microscopic findings including neuropathology were observed.

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
3-month **feeding** (98% a.i.)	Beagle dog (4/sex/dose) 0, 100, 500 and 2500 ppm (equal to 0, 3/3, 14/15 and 53/60 mg/kg bw/d (♂/♀))	NOAEL = 100 ppm (3 mg/kg bw/d) LOAEL = 500 ppm (14 mg/kg bw/d for males and 15 mg/kg bw/d for females)	≥**500 ppm:** ↑ absolute and relative liver weights, hepatocellular necrosis, proliferation of intrahepatic bile ducts, perivascular inflammatory cell infiltration, lymphohisiocytic infiltration in various organs, myopathy of the skeletal muscle, inflammation cell infiltration (stomach, thyroid, myocardium, GI wall); splenic hemosiderosis (♂); ↑ spleen and ovary weights, splenic extramedullary hematopoiesis (♀) **2500 ppm:** mortality, anemia, bw loss, ↓ FC, cholestasis, hemosiderosis and extramedullary hematopoiesis and edema of gall bladder wall, ↑ prothrombin time, occurrence of phagocytic cells in the mesenteric lymph nodes; ↑ aspartate aminotransferase (AST) and alanine aminotransferase, gamma glutamyl transpeptidase, creatine kinase, testicular tubular atrophy (♂); ↑ AST and ALK, globulin, protein, atrophic lymphatic follicles in the lymph nodes, hypercellularity of the bone marrow (♀)

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY: Technical			
12-month **feeding** + 4-week recovery (98% a.i.)	Beagle dog (4/sex/dose) 0, 20, 200 and 1000 ppm (equal to 0, 0.57, 5.33 and 27.9 mg/kg bw/d) Satellite group (2/sex) dosed with 0 or 1000 ppm to assess recovery	NOAEL = 200 ppm (5.33 mg/kg bw/d) LOAEL = 1000 ppm (27.8 mg/kg bw/d)	≥**200 ppm:** ↑ absolute and relative liver weights (♂); absolute liver weight (♀) **1000 ppm:** inflammatory liver cell infiltration, myopathy of small and large intestine and skeletal muscle, ↓ testes weight (♂); transient ↓ in bw and FC, anemia (♀) **No remarkable findings in recovery animals, but the number of animals precluded a meaningful evaluation**.
18-month oncogenicity (98% a.i.)	Tif:MAGf(SPF) mice (50/sex/dose) 0, 10, 100, 2000 and 5000 ppm (equal to 0, 1.2, 12, 254 and 678 mg/kg bw/d) Satellite groups (10/sex/dose for hematology)	NOAEL= 100 ppm (12 mg/kg bw/d) LOAEL = 2000 ppm (250 mg/kg bw/d)	≥**2000 ppm**: ↓ bw (9% at 2000 ppm, 24% at 5000 ppm), body weight gain (bwg) (15% at 2000 ppm, 44% at 5000 ppm), ↑ relative liver weight, liver hepatocellular hypertrophy, hypercellularity in the bone marrow; extra medullary hematopoesis in the spleen; ↑ hemosiderosis (♀) **5000 ppm**: ↑ survival and spleen weight, ↑ stomach hyperplasia and chronic inflammation, ↓ thymus weight; ↑ adrenal and kidney weights, hemosiderosis in the spleen (♂); ↓ kidney weight, ↑ ovary weight **Carcinogenicity**: ↑ hepatic carcinomas in ♂ and ♀ at 2000 and 5000 ppm (incidence of 5, 5, 5, 9, 23 ♂ and 0, 0, 0, 0, 4 ♀ for control to high dose, respectively); ↑ adenoma in ♀ at 5000 ppm (incidence 4, 5, 5, 1, 14 in control to high dose, respectively)

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
24-month combined chronic and carcinogenicity (98% a.i.)	TiF:RAIF (SPF) rat (80/sex/dose) 0, 10, 100, 1000 and 3000 ppm (50/sex/dose for carcinogenicity (24 months) assessment, 10/sex/dose sacrificed after 12 months, 10/sex/dose for hematology and 10/sex/dose for biochemistry and urine; blood samples taken at weeks 13, 27, 53, 78 and 105) (equal to 0, 0.38/0.45, 3.8/4.5, 38.5/46.3 and 123.4/148.3 mg/kg bw/d (♂/♀))	NOAEL = 100 ppm (3.8/4.5 mg/kg bw/d ♂/♀) LOAEL =1000 ppm (38.5/46.3 mg/kg bw/d)	≥ **100 ppm:** ↑ hepatocellular hypertrophy at 1-year sacrifice (♂) with no incidence in 100 ppm animals at study termination (adaptation) ≥ **1000 ppm:** ↓ bw and bwg ♀ (at 1000 ppm, bwg approximately 12% less than controls ($p < 0.05$) by the end of the first month, persisting throughout study; at 3000 ppm, bw and bwg approximately 34% less than controls); ↑ relative liver, kidney, spleen weights (♂); ↑ follicular epithelial hyperplasia of thyroid (♂) **3000 ppm:** ↓ bw and bwg ♂ (approximately 19% less than controls); ↓ FC; ↑ bilirubin, albumin (♂); ↑ cholesterol (♀); ↑ phospholipids (week 13 only); ↑ relative liver, kidney, spleen weights (♀); ↑ brain and testis weights; mottled liver appearance, liver cysts, hepatocellular hypertrophy, focus of cellular changes, biliary cysts; ↑ uterus dilatation and follicular epithelial hyperplasia of thyroid (♀) **Carcinogenicity**: ↑ benign hepatoma in 1000 and 3000 ppm females (incidence 0, 0, 0, 2, 7 for control to high dose, respectively), ↑ benign and (or) malignant liver tumours in 1000 and 3000 ppm females (incidence 0, 0, 0, 3, 7 for control to high dose, respectively); no increase in tumour incidence at interim sacrifice

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Multi-generation dietary (98% a.i.)	Tif: RAIf (SPF) rat (30 rats/dose) 0, 20, 200 and 2000 ppm (equal to 0, 1.3/1.6, 13/16 and 128/152 mg/kg bw/d for F_0 ♂/♀; and 1.5/1.8, 15/18 and 159/186 mg/kg bw/d for F_1 ♂/♀)	NOAEL (parental systemic toxicity) = 200 ppm (13–15 mg/kg bw/d F_0 and F_1 ♂, and 16–18 mg/kg bw/d F_0 and F_1 ♀) NOAEL (offspring toxicity) = 200 ppm (15–18 mg/kg bw/d) NOAEL (reproductive toxicity) > 2000 ppm (159/186 mg/kg bw/d) the highest dose tested	**At 200:** ↑hepatocyte hypertrophy (F_0 and F_1 ♂), ↑ relative liver weights (F_1 ♂ and ♀) **At 2000:** ↓ bw and bwg and FC; ↑ relative liver and spleen weights (F_0 ♀; F_1 ♂ and ♀); ↑ hypertrophy of basophilic cells of pituitary (F_1 ♂) "developmental cyst" in pituitary (F_0 ♂ and ♀); hyperplasia of splenic white pulp lymphatic follicles (F_0 ♀); ↑ hepatocyte hypertrophy (F_0 and F_1 ♀); ↓ pup weights (F_0 day 14 and on, F_1 day 7 and on); delayed eye opening
Teratogenicity (98% a.i. in 0.5% carboxymethylcellulose (CMC))	Tif:RAIF (SPF) rat (24 mated rats/dose) at 0, 30, 100 or 300 mg/kg bw/d from gestation days (GDs) 6–15	NOAEL (maternal toxicity) = 30 mg/kg bw/d NOAEL (developmental toxicity) = 30 mg/kg bw/d	≥**100:** ↓ bwg and FC **At 300:** ↑ skeletal anomalies/variations; one dam with total resorptions **Not teratogenic**
Teratogenicity (98% a.i. in 0.5% CMC)	Thomae Russian Chbb:HM rabbit (20 mated rabbits/dose) at 0, 10, 75 and 125 mg/kg bw/d from GDs 7–19	NOAEL (maternal toxicity) = 10 mg/kg bw/d NOAEL (developmental toxicity) = 10 mg/kg bw/d	≥**75:** ↓ bwg and FC; ↑ early resorptions **At 125:** mortality (2 dams), 3 dams at with total resorptions abortion, abortion (1), bw loss (GDs 7–19); ↑ post-implantation loss; ↓ litter size ≥**75:** ↑ skeletal variations and anomalies (additional 13th rib, fused sternebrae, poor ossification) **Not teratogenic**

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
GENOTOXICITY			
STUDY	**TEST SYSTEM**	**POSITIVE CONTROL**	**CONCLUSION**
Salmonella / Ames Test (98% a.i.) in dimethylsulfoxide (DMSO)	*Salmonella typhimurium* strains TA98, 100, 1535, 1537 or *Escherischia coli* WP2uvr at 313, 625, 1250, 2500 or 5000 µg/plate; +/–S9	Positive controls: 2-AA, 2-NF-TA98; 2-AA, NaA - TA100; CP, NaA - TA1535 2-AA, 9-AA - TA1537 2-AA, 4-NQO - WP2urvA	Negative for mutagenic potential
Mammalian cells in culture gene mutation assay (98% a.i.) in DMSO	Chinese hamster lung cells (V79) at 5.21, 20.83, 83.33 and 333.33 µg/mL; +/–S9	Positive controls: Ethylmethane sulphonate 0.3 µL/mL (–S9) Dimethylnitrosamin 0.1 µg/mL (+S9)	Negative for induction of forward gene mutation in HGPRT locus
In vitro unscheduled DNA synthesis (98% a.i.) in DMSO	Primary rat hepatocytes 2.78, 8.33, 25, 75, 150 and 300 µg/mL)	Positive controls: 2-acetoaminofluorene, 45 µM	Negative (no increases in unscheduled DNA synthesis, as determined by nuclear silver grain counts)
Mammalian cytogenetics (in vitro) (98% a.i.) in DMSO	Chinese hamster ovary K1 cells at 2.58, 5.16, 10.31, 20.63, 41.25, 82.5, 165.0 and 330.0 µg/mL	Positive controls: Mitomycin-C, 0.2 µL/mL (–S9) Cyclophosphamide, 40 µg/mL (+S9)	Negative (not clastogenic; no increases in specific or unspecific chromosomal aberrations)
Mammalian cytogenetics (in vivo) (98% a.i.) in arachis oil	Mouse bone marrow micronucleus assays 1. One dose at 4000 mg/kg, killed at 16, 24 and 48 h 2. At 1000, 2000 and 4000 mg/kg bw, killed at 24 h	Positive controls: Cyclophosphamide, 64 µg/mL for both assays	Negative; no increases in micronuclelated polychromatic erythrocytes
Compound-induced mortality: Mortality was seen at 6000 mg/kg bw in an acute oral toxicity study (gavage), at >5000 ppm (~360 mg/kg bw/d) in the 90-d rat dietary study, and 2500 ppm (54/60 mg/kg bw/d ♂/♀) in the 90-d dog feeding study.			

STUDY	SPECIES AND STRAIN AND DOSES (ppm or mg/kg bw/d)	NOEL OR NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS

Recommended ARfD

(1) For females 13+, the NOAEL of 75 mg/kg bw/d for the end points of mortality, total resorptions, abortion, and increased post-implantation loss (from the rabbit developmental toxicity study) was chosen. Due to the seriousness of the toxicity end points (mortality, abortion, ↑ post-implantation loss and total resorptions, an extra 3× safety factor is added to the standard inter- (×10) and intra-species (×10) uncertainty factors.

ARfD=75 mg/kg bw/300 = 0.25 mg/kg bw

(2) For the general population, the LOAEL of 125 mg/kg bw/d from the acute neurotoxicity study was selected. An uncertainty factor of 300 was used to account for the use of a LOAEL.

ARfD = 125 mg/kg bw/300 = 0.42 mg/kg bw

Recommended ADI

The lowest NOAEL of 100 ppm (3.8 mg/kg bw/d) was obtained from the 24-month combined chronic and carcinogenicity study in the rat. At the next higher dose of 1000 ppm (39/46 mg/kg bw/d for males and females, respectively), increased relative liver, spleen and kidney weights in both males and females and reduced body weight gain were seen. Increased hyperplasia of the follicular epithelium of the thyroid was also seen in 1000 ppm males. The standard uncertainty factor of 100 was considered adequate.

ADI = 3.8 mg/kg bw/d/100 = 0.038 mg/kg bw/d

This ADI gives an MOE of >390 for effects in the offspring (NOAEL = 15 mg/kg bw/d), and >100 for a wider spectrum of effects (e.g., blood chemistry, organ weight changes) seen in the subchronic/chronic toxicity study in the dog (NOAEL = 5.33 mg/kg bw/d, which is considered the most sensitive species among the tested animals).

Table 2 Summary of label proposals and recommendations

Endeavor 50WG, Submission No. 2000-3412, for use on non-food greenhouse flowering plants and ornamentals (USC 6)		
	Originally proposed	Acceptable revision
Rate of application	18.8–37.5 g/100 L of water Maximum rate 700 g/ha per application, or 7.0 kg/ha per year	10–20 g/100 L water Maximum rate 20 g product/100 L per application, or two applications (2 × 20 g product/100 L) per crop cycle
Spray adjuvants	On hard-to-wet plants, add a non-ionic or organosilicone-based surfactant to improve coverage	On hard-to-wet plants, such as chrysanthemums and roses, add a non-ionic or organosilicone-based surfactant such as AGRAL® 90 at a rate of 250 mL/100 L (0.25% v/v), AG-SURF® at a rate of 250 mL/100 L (0.25% v/v), LI® 700 at a rate of 500 mL/100 L (0.5% v/v) or SYLGARD® 309 at a rate of 250 mL/100 L of water (0.25% v/v) of spray mixture, to improve coverage.
Retreatment interval	7 d Severe insect pressure 14 d Normal insect pressure	Retreat as indicated by pest monitoring data, but not more often than once every 7 d.
Pests controlled	Green peach aphid (*Myzus persicae*) Melon aphid (*Aphis gossypii*) Greenhouse whitefly (*Trialeurodes vaporariorum*) Silverleaf whitefly (*Bemisia argentifolii*)	Aphids including: Green peach aphid (*Myzus persicae*) Melon aphid (*Aphis gossypii*) Application at the recommended rate can contribute to whitefly infestation levels, without harming whitefly parasitoids and predators. Whiteflies including: Greenhouse whitefly (*Trialeurodes vaporariorum*) Silverleaf whitefly (*Bemisia argentifolii*)

Fulfill 50WG, Submission No. 2000-3413, for use on potatoes (USC 14, Terrestrial Food Crops)		
Rate of application	193 g product/ha Apply in sufficient water to ensure good coverage; use a minimum of 100 L/ha. Where a dense canopy exists and (or) aphid infestations are high, use greater water volumes (i.e., at least 200 L/ha). Do not exceed 2 applications (386 g product/ha) per crop per season.	193 g product/ha Apply in sufficient water to ensure good coverage; use a minimum of 100 L/ha. Where a dense canopy exists and (or) aphid infestations are high, use greater water volumes (i.e., at least 200 L/ha). Do not exceed 2 applications (386 g product/ha) per crop per season.
Spray adjuvants	The addition of a penetrating type spray adjuvant at the manufacturer's suggested rate, is recommended to provide optimum coverage and insect control.	The use of a non-ionic adjuvant such as AGRAL® 90 at a rate of 250 mL/100 L (0.25% v/v), AG-SURF® at a rate of 250 mL/100 L (0.25% v/v), LI® 700 at a rate of 500 mL/100 L (0.5% v/v) and SYLGARD® 309 at a rate of 250 mL/100 L of water (0.25% v/v) of spray mixture, is recommended to improve the performance of Fulfill 50WG insecticide under drought stress conditions.
Retreatment interval	Allow a minimum of 7 d between applications and 14 d (PHI) between the last application and harvest.	Allow a minimum of 7 d between applications and 14 d (PHI) between the last application and harvest.
Pests controlled	Aphids of 14 named species, including: green peach aphid (*Myzus persicae*), potato aphid (*Macrosiphum euphorbiae*), buckthorn aphid (*Aphis nasturtii*) and melon aphid (*Aphis gossypii*)	Aphids including: Green peach aphid (*Myzus persicae*), Potato aphid (*Macrosiphum euphorbiae*), Buckthorn aphid (*Aphis nasturtii*), Foxglove aphid (*Aulacorthum solani*)

Appendix II Residue summary tables

Table 1 Food residue chemistry overview of metabolism studies and risk assessment

PLANT STUDIES	
CROPS (*N*=1)	Potatoes
ROC FOR MONITORING	Pymetrozine (CGA 215944)
ROC FOR RISK ASSESSMENT	Pymetrozine (CGA 215944) and metabolites GS 23199, CGA 215525, CGA 249257 and CGA 294849
IS METABOLISM PROFILE IN DIVERSE CROPS SIMILAR?	N/A
ANIMAL STUDIES	
ANIMALS (N=1)	Lactating goat
ROC FOR MONITORING	Pymetrozine (CGA 215944)
ROC FOR RISK ASSESSMENT	Pymetrozine (CGA 215944), metabolite CGA 313124 and the phosphate conjugate of metabolite CGA 313124 for milk and pymetrozine and metabolite CGA 313124 for tissues
IS METABOLISM PROFILE IN RAT AND RUMINANT SIMILAR?	YES
FAT SOLUBLE RESIDUE	NO

DIETARY RISK from food including contribution for drinking water		
Chronic non-cancer dietary risk **ADI =0.038 mg/kg bw/d**	**POPULATION**	**ESTIMATED RISK (% of ADI)**
		Median values; percentcrop treated for U.S. and Canadian commodities; processing factors
	All infants <1 year old	0.2
	Children 1–6	0.2
	Children 7–12	0.1
	Females 13–50 years	0.1
	Males 13–19 years	0.1
	Males 20+ years	0.1
	Seniors 55+	0.1
	Total population	0.1
Acute dietary exposure analysis, 95th percentile	**POPULATION**	**ESTIMATED RISK (% of ARfD)**
ARfD = 0.25 mg/kg bw	**Females 13+**	0.09
ARfD = 0.42 mg/kg bw	**Total population**	0.06
Cancer dietary risk **Q_1^* = 0.0119 $(mg/kg/d)^{-1}$**	**POPULATION**	**ESTIMATED RISK (% of ADI)**
		Median values; percentcrop treated for U.S. and Canadian commodities; processing factors
	All infants <1 year old	0.000001
	Children 1–6	0
	Children 7–12	0
	Females 13–50 years	0
	Males 13–19 years	0
	Males 20+ years	0
	Seniors 55+	0
	Total population	0

Table 2 Food residue chemistry integrated summary table

PARAMETER		PERTINENT INFORMATION				
FULFILL		**Pymetrozine**				
Crop	Formulation and type	Method and timing	Rate (g a.i./ha)	Number per season	Maximum rate (g a.i./ha)	PHI (days)
Potatoes	50WG	Apply when aphids first appear, before populations build to damaging levels. One additional application may be needed to control persistent aphid populations.	96.5	2	193	14
LABEL RESTRICTIONS		• Do not apply by air • Do not use liquid fertilizer as a carrier for Fulfill 50WG • Do not exceed 2 applications (386 g product/ha) per crop per season • Allow a minimum of 7 d between applications • The use of a non-ionic adjuvant such as AGRAL® 90, AG-SURF® and SYLGARD® is recommended to improve the performance of Fulfill 50WG insecticide under drought stress conditions.				
PHYSICOCHEMICAL PROPERTIES		**Value**				
Water solubility, at 25°C		pH: 5.0 — Solubility (mg/L): 320 pH: 6.5 — Solubility (mg/L): 290 pH: 7.0 — Solubility (mg/L): 270 pH: 9.0 — Solubility (mg/L): 270				
		Metabolite: CGA 300407 — pH: 5–9 — Solubility (g/L): >500 Metabolite: CGA 249257 — pH: 5 — Solubility (g/L): 29 pH: 7 — Solubility (g/L): 29 pH: 7.2 — Solubility (g/L): 29 pH: 9 — Solubility (g/L): 27 Metabolite: CGA 215525 — pH: 5.3 — Solubility (g/L): 210 pH: 7.2 — Solubility (g/L): 220 pH: 7.3 — Solubility (g/L): 210 pH: 9.4 — Solubility (g/L): 210				
Solvent solubility at 25°C		Solvent: ethanol — g/L: 2.4 Solvent: dichloromethane — g/L: 1.2 Solvent: acetone — g/L: 0.94 Solvent: *n*-octanol — g/L: 0.45 Solvent: ethyl acetate — g/L: 0.26 Solvent: toluene — g/L: 0.034 Solvent: *n*-hexane — g/L: <0.001				
Octanol–water partition coefficient (K_{ow}) of pymetrozine at 25°C		pH: pure water — log K_{ow}: –0.18 pH: 5 — log K_{ow}: –0.24 pH: 7 — log K_{ow}: –0.19 pH: 9 — log K_{ow}: –0.20				

PARAMETER	PERTINENT INFORMATION
Octanol–water partition coefficient (K_{ow}) of metabolites at 25°C	Analyte / pH / log K_{ow} CGA 300407 / 7.2 / 0.31 CGA 249257 / 7.5 / –0.95 CGA 215525 / 7.4 / –1.3
pK_a	Analyte / pK_a Pymetrozine / 4.06 and <1 at 20°C CGA 300407 / 3.72 (basic) CGA 249257 / <0 (basic) CGA 215525 / 1.55 (basic)
Vapour pressure	Analyte / Vapour pressure (Pa) Pymetrozine / $<4 \times 10^{-6}$ CGA 300407 / 45.9 CGA 249257 / 2.2×10^{-4} CGA 215525 / 1.2×10^{-3}
Specific gravity	0.48 g/cm^3 at 25°C
NATURE OF THE RESIDUE: ANIMALS ***Radiolabelling positions***	***Lactating goats*** [triazine-6-^{14}C] pymetrozine and [pyridine-5-^{14}C] pymetrozine
Proposed metabolic pathway	In the lactating goat metabolism study, radiolabelled pymetrozine was administered intraruminally to female lactating goats (Gemsfarbige Gebirgsziege) for 4 consecutive days at dose levels of 0.39–0.54 mg/kg bw/d, equivalent to 7.57–9.97 mg/kg feed/d. Urinary and fecal excretion were the predominant routes of elimination accounting for an average of 49.7 and 15.7% of the total administered dose, respectively. The metabolite CGA 313124 was the predominant residue in fat, kidney, feces and urine treated with triazine-^{14}C labelled pymetrozine. In milk samples, the major metabolites were the phosphate conjugate of CGA 313124 and metabolite CGA 313124. The most predominant metabolite in muscle was the parent. In liver, the major metabolite was metabolite I_{A2} (5U) from the ACN:water extract and metabolite CGA 249257 after the microwave extraction. The most predominant metabolite in muscle, fat, liver and kidney treated with the pyridine-^{14}C labelled pymetrozine was metabolite CGA 180778. The most predominant metabolites in milk from the pyridine label were the phosphate conjugate of CGA 313124 and metabolite CGA 313124. In urine, the major metabolite was CGA 313124 and in feces, metabolite I_{A2} (5U) was the most predominant. The metabolism of pymetrozine appear to proceed via oxidation, hydrolysis, deamination and conjugation. Cleavage of the parent compound between the triazine and pyridine ring was a major pathway observed in both triazine-^{14}C and pyridine-^{14}C labelled CGA 215944 studies as several metabolites were label specific. The metabolic profile seen in goats was similar to the profile seen in the rat metabolism study.
ROC	For enforcement purposes, the ROC is identified as pymetrozine, however for risk assessment the ROC includes pymetrozine, metabolite CGA 313124 and the phosphate conjugate of CGA 313124 for milk and pymetrozine and the metabolite CGA 313124 for animal tissues.

PARAMETER	PERTINENT INFORMATION	
NATURE OF THE RESIDUE: PLANTS	***Potatoes***	
Radiolabelling positions	[triazine-6-^{14}C] pymetrozine and [pyridine-5-^{14}C] pymetrozine	
Proposed metabolic pathway	In the metabolism study, radiolabelled pymetrozine was applied three times by foliar treatment to field-grown potato plants for a total seasonal rate of 450 g a.i./ha (equivalent to 2.3× the recommended label rate) or 3150 g a.i./ha/season (equivalent to 16× the recommended label rate). Potato tubers and foliage were harvested 7, 14 and 29 d after the last treatment. For both rates and at a 7-d PHI, the parent was the most predominant residue, followed by gly-GS 23199, GS 23199, CGA 249257 and CGA 294849/CGA 215525. At a 14-d PHI, the most predominant metabolite was gly-GS 23199, followed by GS 23199, parent, CGA 294849/CGA 215525 and CGA 249 257. The major metabolites identified in potato tubers treated at both rates were CGA 215944 and the glycoside conjugate of GS 23199. The most predominant metabolite identified in potato tubers treated with pyridine-^{14}C pymetrozine at all PHIs was CGA 74465, followed by the glycoside conjugates of CGA 180777. All other characterised and (or) identified metabolites (CGA 215944, CGA 180777, CGA 180778, CGA 128632 and gly-CGA 128632) accounted for less than 3% of the TRRs. The metabolism of pymetrozine appear to proceed via oxidation, hydrolysis, deamination and conjugation. Cleavage of the parent compound between the triazine and pyridine ring was a major pathway observed in both triazine-^{14}C and pyridine-^{14}C labelled CGA 215944 studies as several metabolites were label specific.	
ROC	The ROC is identified as pymetrozine for enforcement purposes and for risk assessments, the ROC includes pymetrozine and metabolites CGA 249257, CGA 294849, GS 23199 and CGA 215525.	
RESIDUE ANALYTICAL METHOD	**PLANT MATRICES**	
	HPLC–UV Method AG-643 (Enforcement method)	HPLC–UV Method AG-647 (Data gathering)
Method ID	Analytical Method for the Determination of CGA 215944 in Crops by HPLC, Lab project no. 344004, protocol no. 627-95	Analytical Method for the Determination of GS 23199 in Crops by HPLC, Lab project no. 34404, protocol no. 628-95
Analytes	Pymetrozine (CGA 215944)	GS 23199

PARAMETER	PERTINENT INFORMATION	
Method principle	Method used for the analysis of pymetrozine. The analytes are extracted with sodium borate and methanol, concentrated and cleaned up using an SPE cartridge. Quantitation was by HPLC with UV detection at 300 nm. The method detector response was linear within the range of 0.01–0.20 ppm for pymetrozine (r = 0.997 27 and 0.997 55). The mean relative standard deviation at spiking levels of 0.01 and 0.20 ppm for pymetrozine in various plant matrices ranged from 8 to 27%. The relative standard deviations measured with respect to recoveries following spiking at the LOQ (0.02 ppm) were less than 14%. Therefore, the values obtained are indicative of the method having good repeatability.	Method used for the analysis of metabolite GS 23199. The analytes are extracted with sodium borate and methanol and evaporated following the addition of 2 drops of diethylene glycol diethyl ether. Residues are reconstituted in methanol and water, acidified, partitioned with ethyl acetate, filtered and evaporated after the addition of diethylene glycol diethyl ether. Quantitation is by HPLC with UV detection at 300 nm using a column switching system. The detector response was linear within the range of 0.01–0.20 ppm for pymetrozine (r = 0.999 78). The mean relative standard deviation for the metabolite GS 23199 in various plant matrices ranged from 7 to 24%. In most cases, the relative standard deviations measured with respect to recoveries following spiking at the LOQ (0.02 ppm) were less than 18%. Therefore, the values obtained are indicative of the method having good repeatability.
ILV Method	The method validation indicated that acceptable recoveries were obtained for pymetrozine in several crops at spiking levels of 0.02 and 0.20 ppm. Confirms reliability and reproducibility of the method.	The method validation indicated that acceptable recoveries were obtained for GS 23199 in several crops at spiking levels of 0.02 and 0.20 ppm. Confirms reliability and reproducibility of the method.
RESIDUE ANALYTICAL METHOD	**PLANT MATRICES**	
	LC–MS–MS Method AG-643 (Data gathering)	LC–MS–MS Method AG-647 (Data gathering)
Method ID	“Analytical Method for the Determination of CGA 215944 in Crops by HPLC” modified to implement LC–MS–MS instead of column switching HPLC	“Analytical Method for the Determination of GS 23199 in Crops by HPLC” modified to implement LC–MS–MS instead of column switching HPLC
Analytes	Pymetrozine (CGA 215944)	GS 23199

PARAMETER	PERTINENT INFORMATION	
Instrument or detector	Method used for the analysis of pymetrozine residues in potatoes from Canadian trials. Samples extracted with borate, methanol and water. An aliquot was acidified and extracted through an SPE cartridge. Quantitation is by LC–MS–MS. The mean relative standard deviation at spiking levels of 0.02, 0.1 and 0.4 ppm for pymetrozine in potatoes was 11%, indicating good repeatability. The detector response was linear within the range of 0.0005–0.50 ppm for pymetrozine (r = 0.9986). The reported limit of detection (LOD) and LOQ were 0.005 and 0.02 ppm, respectively.	Method used for the analysis of the metabolite GS 23199 residues in potatoes from Canadian trials. Samples extracted with borate, methanol and water. An aliquot was evaporated after addition of 2 drops of diethylene glycol diethyl ether. Residues redissolved in methanol, acidified and partitioned with ethyl acetate, and the ethyl acetate fraction was evaporated to dryness. Quantitation was by LC–MS–MS. The mean relative standard deviation at spiking levels of 0.02, 0.1 and 0.4 ppm for GS 23199 in potatoes was 5%, indicating good repeatability. The detector response was linear within the range of 0.005–0.25 ppm for GS 23199 (r = 0.9938). The reported LOD and LOQ were 0.005 and 0.02 ppm, respectively.
RESIDUE ANALYTICAL METHOD	**ANIMAL MATRICES**	
	HPLC–UV Method AG-644 (Enforcement method)	HPLC–UV Method AG-658 (Data gathering)
Method ID	Analytical method for the determination of residues of CGA 215944 in Meat, Milk and Eggs, Lab project no. 344002, protocol no. 659-95	Analytical Method for the Determination of Residues of CGA 313124 in Meat and Milk, Lab project no. 344001, protocol no. 271-96
Analytes	Pymetrozine (CGA 215944)	CGA 313124 and the phosphate conjugate of CGA 313124

PARAMETER	PERTINENT INFORMATION	
Instrument or detector	Method used for the analysis of pymetrozine residues in animal matrices. Samples were extracted with acetonitrile and water, filtered and cleaned up with an SPE column. The eluate is collected, buffered with sodium borate, evaporated and cleaned up. The eluate is evaporated, redissolved in acetone and cleaned up. Residues were concentrated, redissolved in methanol and water, purified and analysed by HPLC. The UV detector response at 300 nm was linear within the range of 0.01–0.20 ppm for pymetrozine (r = 0.999 53). The mean relative standard deviation at spiking levels of 0.01–0.50 ppm for pymetrozine in various animal matrices ranged from 2 to 31%. In most cases, the relative standard deviations measured with respect to recoveries following spiking at the LOQ (0.01 ppm) were less than 18%. Therefore, the values obtained are indicative of the method having acceptable repeatability.	Method used for the analysis of metabolite CGA 313124 in animal matrices. Samples are extracted with methanol and water, filtered, cleaned up and evaporated. Milk samples are hydrolysed to release conjugated CGA 313124. The aqueous fraction is purified with methanol. The eluate is purified, evaporated to dryness and dissolved in mobile phase for analysis by HPLC. The UV detector response at 300 nm was linear within the range of 0.02–0.2 ppm for CGA 313124 (r = 0.999 09). The mean relative standard deviation at spiking levels of 0.01–0.50 ppm for CGA 313124 in various animal matrices ranged from 7 to 35%. Therefore, the values obtained are indicative of the method having acceptable repeatability. The LOQ is reported as 0.01 ppm.
ILV Method	The method validation indicated that acceptable recoveries were obtained for pymetrozine in several animal matrices at spiking levels of 0.01 and 0.10 ppm, confirming the reproducibility of the method.	The method validation is not required for the data gathering method.
MULTIRESIDUE METHOD	The registrant reported that multi residue methods of analysis that are currently in common usage were not found to be suitable for the determination of pymetrozine residues.	

PARAMETER	PERTINENT INFORMATION
STORAGE STABILITY DATA	***Plant matrices*** Residues of pymetrozine were stable for 2 months in cucumbers, 6 months in potatoes and tomato paste, 14 months in tomatoes and 24 months in cottonseed and cottonseed oil when stored at –18°C to –20°C. In a supplemental storage stability study, pymetrozine were stable at –20°C for 10 months in spinach, 13 months in leaf lettuce, 15 months in broccoli, celery and mustard green and 18 months in cabbage. Residues of the metabolite GS 23199 were stable for up to 24 months in cucumbers, tomatoes, tomato paste, cottonseed and cottonseed oil when stored at –20°C. ***Animal matrices*** Residues of pymetrozine and the metabolite CGA 313124 were found to be stable in beef muscle and liver for 6 months and in milk for 18 months when stored frozen at –20°C. Supplemental freezer storage stability data was provided with the lactating goat metabolism studies. Milk and liver samples from the triazine and pyridine studies were stored at –20°C. Results indicated no qualitative or quantitative differences for residues of pymetrozine and its metabolites in samples stored from 20 to 32 months.
CROP FIELD TRIALS	***Potato*** The results from the supervised crop field trials conducted on potatoes grown in Canada (zones 1A, 5 and 14) and the U.S. (zones 1, 2, 3, 5, 5A, 9, 10 and 11) indicated that the maximum residues of pymetrozine and the metabolite GS 23199 in tubers were each below the LOQ of 0.02 ppm when plants were treated twice with pymetrozine formulated as WP or WG at a rate of 96 g a.i./ha at 7-d intervals for a total seasonal rate of 192 g a.i./ha (equivalent to the proposed GAP). An adjuvant was used for all trials except for one U.S. trial. Residue data from trials conducted at exaggerated rates (3× and 5× the proposed GAP) indicated that residues of pymetrozine and the metabolite GS 23199 were each below the LOQ of 0.02 ppm, when potato tubers were collected 14 d after the last treatment. Although the number of Canadian trials submitted was not representative of all Canadian growing regions, the available residue data demonstrated that there was no variability in the magnitude of residues within a zone and from one zone to another, therefore additional trials are not required.
RESIDUE DECLINE	Residue decline studies were conducted at 1× the proposed Canadian use pattern. Results indicated that residues of pymetrozine and the metabolite GS 23199 were each below the LOQ of 0.02 ppm at 0, 1, 3, 7, 14 and 21 d following the last treatment.
PROCESSED FOOD AND FEED	Potato plants were treated with pymetrozine formulated as 50WG at rates ranging from 200 to 1000 g a.i./ha/season, equivalent to 1.0× to 5.0× the proposed Canadian use pattern. Residues of pymetrozine and the metabolite GS 23199 were each below the LOQ of 0.02 ppm in the RAC and all of its processed fractions. There was no concentration of residues with processing.

PARAMETER	PERTINENT INFORMATION
DAIRY CATTLE FEEDING	Holstein dairy cows were orally dosed with pymetrozine at levels of 1, 3 and 10 ppm in the diet for 28–30 consecutive days. These dosing levels represent circa 11×, 32× and 108× the anticipated dietary burden to dairy cattle using the proposed MRL of 0.02 ppm for potatoes. The animals were sacrificed 20–24 h following the last treatment. There were no measurable residues (<0.01 ppm) of pymetrozine and the metabolite CGA 313124 in tissues at the highest feeding level of 10 ppm. Residues of pymetrozine in milk were also below the LOQ of 0.01 ppm at all feeding levels. However, residues of the metabolite CGA 313124 in milk were less than the LOQ (0.01 ppm) at 1× and ranged from <0.01 to 0.02 ppm (3×) and <0.01 to 0.05 ppm (10×).
CONFINED ROTATIONAL CROPS	Radiolabelled pymetrozine was applied once to sandy loam soil at a rate of 412 g a.i./ha (triazine) or 421 g a.i./ha (pyridine) equivalent to 2× the proposed Canadian GAP. Wheat, radish and mustard were planted 30, 60, 95, 122 and 361 d after the last treatment. Soil samples were collected before and immediately after treatment and at all planting intervals. Wheat samples collected at 25% maturity, 50% maturity and maturity were separated into grain and forage. Mustard, radish tops and roots were collected at maturity. The predominant metabolite identified in radish roots from the triazine labelled pymetrozine for all planting intervals was GS 23199. Metabolite gly-GS 23199 was most predominant in wheat grain (30, 122 and 361 DAT), 25% mature wheat forage (30 and 361 DAT), 50% mature wheat forage (122 and 361 DAT), mature wheat fodder (30 and 361 DAT) and mustard (30 and 361 DAT). Several additional plant metabolites from the triazine label were identified as CGA 266591, glycoside of CGA 266591 and glycoside of 6 carboxy-1,2,4-triazin-3-one resulting from further degradation of the parent molecule. The parent was detected in all rotational crop matrix except in wheat planted (361 DAT), wheat grain (122 DAT) and mustard planted (122 DAT). The major metabolite identified from the pyridine labelled pymetrozine was CGA 74465 for all crops at all planting intervals except for mustard planted (30 and 361 DAT) and radish foliage planted (361 DAT), metabolite CGA 180778 was the most predominant. Pymetrozine was not detected in any rotational crop matrix at any plant-back interval from soil treated with pyridine-^{14}C pymetrozine. The metabolic profile of ^{14}C-residues in rotational crops grown in ^{14}C-pymetrozine treated soil was qualitatively similar among the different crops for each test substance. An additional confined crop rotation study was submitted to further identify the TRRs in wheat matrices. Two additional metabolites from the triazine label were identified as CGA 359009 and CGA 323584. The metabolic profile of ^{14}C-residues in wheat grown in ^{14}C-pymetrozine treated soil confirmed the qualitative similarity to the metabolic profile observed in the rotational study in which wheat, radish and mustard were planted at 30, 60, 95, 122 and 361 d after the last treatment.
FIELD ROTATIONAL CROPS	Pymetrozine formulated as 50WG was applied four times to primary crops (tomatoes, peppers, cucumbers and leaf lettuce) with 7-d intervals at a rate of 101.25 g a.i./ha for a total seasonal rate of 405 g a.i./ha (2× the proposed GAP). Rotational crops (wheat, turnip and leaf lettuce) were planted 30 d after the last treatment. Samples of turnip, leaf lettuce, wheat grain and straw were collected at maturity and samples of wheat forage and hay were collected at appropriate intervals. Residues of pymetrozine and the metabolite GS 23199 were each below the LOQ (0.02 ppm) in all crop matrices. Samples were only collected 30 d after the last treatment; therefore, no decline in residues of pymetrozine or the metabolite GS 23199 were observed. No soil samples were collected. Based on these results, the data supports a minimum plantback interval of 30 d for all crops.

PARAMETER	PERTINENT INFORMATION
PROPOSED MRLs	An MRL of 0.02 ppm is recommended to cover residues of pymetrozine in or on potatoes.
U.S. TOLERANCES	Crop — Tolerance Brassica, head and stem, Subgroup 5A — 0.50 ppm Brassica, leafy greens, Subgroup 5B — 0.25 ppm Cotton, gin by-products — 2.0 ppm Cotton, undelinted seed — 0.30 ppm Hop, dried cones — 6.0 ppm Pecan — 0.02 ppm Turnip greens — 0.25 ppm Vegetable, cucurbit, Group 9 — 0.10 ppm Vegetable, fruiting, Group 8 — 0.20 ppm Vegetable, leafy (except brassica), Group 4 — 0.60 ppm Vegetable, tuberous and corm, Subgroup 1C — 0.02 ppm
CODEX MRLs	No Codex MRLs are currently established.
DIETARY RISK ASSESSMENT (DRA) Dietary Exposure Evaluation Model™ (DEEM™) Version 7.76 1994–1998 Continuing Survey of Food Intake for Individuals	*Acute dietary risk assessment* Using all available refinement data, including processing study data, residue field trial data and estimated percent crop treated information, it was determined that the acute dietary exposure (95th percentile, deterministic) to pymetrozine (food and water) represented approximately 0.09% of the ARfD (0.25 mg/kg bw) for females 13+ and 0.15% of the ARfD (0.42 mg/kg bw) for all infants. *Chronic dietary risk assessment* Using all available refinement data, including processing study data, residue field trial data and estimated percent crop treated information, the chronic dietary exposure to pymetrozine from food and water for the most exposed population subgroups, children 1–6 years old and infants (<1 year), the PDI represented approximately 0.2% of the ADI. The PDI for the remaining population subgroups (including infants, children, adults and seniors) each represented 0.1% of the ADI. *Cancer dietary risk assessment* A Q_1* was established at 0.0119 mg/kg/d^{-1} for pymetrozine. Using this Q_1* value in the DEEM™ Software and all available refinement data (processing factors, STMdRs, percent crop treated), the lifetime cancer risk from dietary exposure (food and water) was estimated to be in the range of 5.53E–07 to 1.00E–06 for all population subgroups.

Appendix III Environmental fate

Table 1 Physical and chemical properties of the active ingredient relevant to the environment

Property	Value	Comments
Water solubility (mg/L water at 25°C)	pH 5.0: 320 pH 6.5: 290 pH 7.0: 270 pH 9.0: 270	Pymetrozine is very soluble in water under environmentally relevant pH conditions and, therefore, has a potential to leach in soils and be transported in surface runoff water.
Vapour pressure at 25°C	$<4 \times 10^{-6}$ Pa	Pymetrozine is considered to be non-volatile under field conditions.
Henry's Law Constant ($Pa/m^3/mol$)	$<3.0 \times 10^{-6}$ (1/H = 8.3E + 8)	Pymetrozine is considered to be non-volatile from moist soil and water surfaces.
log K_{ow}	–0.18	Pymetrozine has a negligible potential for bioconcentration or bioaccumulation in organisms.
pK_{a1} and pK_{a2}	4.06 and <1	Maximum dissociation under acid conditions in the environment
UV–visible absorption (λ_{max})	299–308 nm	Pymetrozine has a potential for phototransformation under environmentally relevant conditions.

Table 2 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	^{14}C pyridine-5-CGA 215944	pH 5: $t_{½}$ = 5 pH 7 and 9: stable	pH dependent; major route of transformation under acid conditions
	^{14}C-triazine-6-CGA 215944	pH 5: $t_{½}$ = 13.2 d pH 7 and 9: stable	
Phototransformation on soil	^{14}C pyridine-5-CGA 215944	$t_{½}$ = 4.3 d	Major route of transformation
	^{14}C-triazine-6-CGA 215944	$t_{½}$ = 1.6 d	
Biotransformation			
Biotransformation in aerobic soil	^{14}C pyridine-5 and ^{14}C-triazine-6-CGA 215944	2.3–5.5 d (1st phase) and 305–405 d (2nd phase)	Non-persistent based on DT_{50} values; however, 2nd phase DT_{50} indicates residue carryover
Biotransformation in anaerobic soil	^{14}C pyridine-5 and ^{14}C-triazine-6-CGA 215944	69–103 d	Moderately persistent under anaerobic conditions

Property	Test substance	Value	Comments
Mobility			
Adsorption or desorption in soil	^{14}C-triazine-6-CGA 215944: aged	sandy soil: K_{oc} = 1394 mL/g	Low mobility
		sandy loam: K_{oc} = 5833 mL/g	Immobile
		Bosket loam: K_{oc} = 7875 mL/g	Immobile
		silty clay loam: K_{oc} = 3080 mL/g	Slightly mobile
		Ashkum-Elliott loam: K_{oc} = 1500 mL/g	Low mobility
Soil column leaching	^{14}C pyridine-5-CGA 215944: aged	no residues beyond 6 cm depth and in the leachate	Little to no mobility in sand, sandy loam, loam and silty clay loam soils; low potential to leach in soils
	^{14}C-triazine-6-CGA 215944: unaged	No residues beyond 6 cm depth and in the leachate	
	^{14}C-triazine-6-CGA 215944: aged	No residues beyond 12 cm depth and in the leachate	
Volatilization		Vapour pressure < 4×10^{-6} Pa at 25°C and Henry's Law Constant < 3.0×10^{-6} Pa/m^3/mol (1/H = 8.3E + 8)	Low potential for volatilization
Field studies			
Field dissipation	Fulfill 50WG	DT_{50}: 30 d	Slightly persistent
Field leaching		No residues below 0–6″ soil depth	Low potential for leaching

Table 3 Transformation products in the terrestrial environment

Property	Test substance	Transformation products	
		Major	Minor
Abiotic transformation			
Hydrolysis	^{14}C pyridine-5-CGA 215944	pyridine-3-carbaldehyde (CGA 300407) (77.1%)	Not reported
	^{14}C-triazine-6-CGA 215944	4-amino-6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 215525) (47.7%)	6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 249257) (2.6%)
Phototransformation on soil	^{14}C pyridine-5-CGA 215944	4,5-dihydro-5-hydroxy-6-methyl-4-[(3-pyridinylmethylene)amino]-1,2,4-triazine-3-(2H)-one (CGA 359009) (28.6%)	3-pyridine carboxaldehyde 9CGA 300407) (7.6%); two unidentified with each at ≤4.1%
	^{14}C-triazine-6-CGA 215944	4,5-dihydro-5-hydroxy-6-methyl-4-[(3-pyridinylmethylene)amino]-1,2,4-triazine-3-(2H)-one (CGA 359009) (33.5%)	4-amino-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione (CGA 294849) (5.7%); two unidentified with each at ≤0.9%
Biotransformation			
Biotransformation in aerobic soil	^{14}C pyridine-5 and ^{14}C-triazine-6-CGA 215944	CGA 180777 (nicotinic acid) (16.5%)	CGA 359009 (7.7%), CGA 319251 (0.5%), CGA 294849 (7.0%), CGA 215525 (3.45), GS 23199 (7.3%), CGA 359009 (3.9%), unknown VI (5.2%), and CGA 249257 (<2%)
Biotransformation in anaerobic soil	^{14}C pyridine-5 and ^{14}C-triazine-6-CGA 215944	CGA 180777(nicotinic acid) (84.4%) Unknown I (11.5%) Unknown III* (20.2%) GS23199 (15.6%) CGA 249257 (13.2%)	CGA 319251, CGA 359009, CGA 294849, CGA 215525, GS23199, CGA 249257, CGA 313124, 16 unidentified
Field studies			
Field dissipation	Fulfill 50WG	CGA 359009, CGA 249257, CGA 180777, CGA 294849 and GS 23199	Not reported

( ) maximum of applied radioactivity

Table 4 Fate and behaviour in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	^{14}C pyridine-5-CGA 215944	pH 5: $t_{½}$ = 5 d pH 7 and 9: stable	pH dependent; major route of transformation under acid conditions
	^{14}C-triazine-6-CGA 215944	pH 5: $t_{½}$ = 13.2 d pH 7 and 9: stable	
Phototransformation in water	^{14}C pyridine-5-CGA 215944	4.3 d	Major route of transformation
	^{14}C-triazine-6-CGA 215944	1.9–6.2 d	
Biotransformation			
Biotransformation in aerobic water systems	No data submitted		
Biotransformation in anaerobic water systems	No data submitted		
Field studies			
Field dissipation	No data submitted		

* (4-amino-4,5-dihydro-5-hydroxy-6-methyl-1,2,4-triazin-3(2H)-one)

Table 5 Transformation products in the aquatic environment

Property	Test substance	Transformation products	
		Major	Minor
Abiotic transformation			
Hydrolysis	^{14}C pyridine-5-CGA 215944	pyridine-3-carbaldehyde (CGA 300407) (77.1%)	
	^{14}C-triazine-6-CGA 215944	4-amino-6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 215525) (47.7%)	6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 249257) (2.6%)
Phototransformation in water	^{14}C pyridine-5-CGA 215944	pyridine-3-carbaldehyde (CGA 300407) (91.8%)	nicotinic acid (CGA 180777) (4.2%)
	^{14}C-triazine-6-CGA 215944	4-amino-5-hydroxy-6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 215525) (78.8%); 6-methyl-4,5-dihydro-2H-(1,2,4)-triazin-3-one (CGA 249257) (38.8%); and hydroxy CGA 215525 (10.2%)	4-amino-6-methyl-2H-(1,2,4)-triazine-3,5-dione (CGA 294849) (5.3%) and unidentified (3.7%)
Biotransformation			
Biotransformation in anaerobic soil and water	No data submitted		
Field studies			
Field dissipation	No data submitted		

(*x*%) maximum concentration of applied radioactivity

Table 6 Maximum EEC in soil, water and diets of birds and mammals

Organism	EEC
Soil (mg a.i./kg soil)	0.079
Water (mg a.i./L water)	0.059
Bobwhite quail diet (mg a.i./kg dw diet)	33.7
Mallard duck diet (mg a.i./kg dw diet)	6.51
Rat diet (mg a.i./kg dw diet)	97.12
Mouse (mg a.i./kg dw diet)	96.53
Rabbit (mg a.i./kg dw diet)	145.21

Table 7 Predicted exposure concentrations of pymetrozine in drinking water sources

Level	Groundwater	Reservoir		Dugout	
	Annual average concentration[a]	Acute[b]	Chronic[c]	Acute[b]	Chronic[c]
Level 1	0.11 µg a.i./L	3.2 µg a.i./L	0.85 µg a.i./L	5.0 µg a.i./L	3.1 µg a.i./L
Level 2		2.4 µg a.i./L	0.52 µg a.i./L	2.7 µg a.i./L	0.95 µg a.i./L

[a] Maximum yearly average for a 20-year simulation
[b] 90th percentile of yearly peaks
[c] 90th percentile of yearly averages

Appendix IV Environmental toxicology and risk assessment

Table 1 Effects on terrestrial organisms

Organism	Exposure	End point value	Degree of toxicity
Invertebrates			
Earthworm	Acute	LC_{50} = 1098 mg a.i./kg NOEC = 12.3 mg a.i./kg soil	
Bee	Oral	NOEC < 4 µg a.i./bee LD_{50} > 117 µg a.i./bee	Non-toxic
	Contact	NOEC = 200 µg a.i./bee LC_{50} > 200 µg a.i./bee	Non-toxic
Predatory and parasitic arthropod	Ground beetle, green lacewing, parasitic wasp and predatory mite	NOEC = 1200 g a.i./ha	
Birds			
Bobwhite quail	Acute	NOEL < 500 mg a.i./kg bw LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic
	Dietary	NOEC = 2550 mg a..i/kg LC_{50} > 5130 mg a.i./kg diet	Practically non-toxic
	Reproduction	NOEC = 100 mg a.i./kg diet	
Mallard duck	Acute	NOEL = 31.25 mg a.i./kg bw	No LD_{50} was reported
	Dietary	NOEC = 315 mg a.i./kg LC_{50} > 5010 mg a.i./kg diet	Practically non-toxic
	Reproduction	NOEC = 300 mg a.i./kg diet	
Mammals			
Rat	Acute	LD_{50} = 5820 mg a.i./kg bw	Practically non-toxic
	Dietary	NOEC = 500 mg a.i./kg diet	LC_{50} not reported
	Reproduction	NOEC < 1000 mg a.i./kg diet	
Mouse	Dietary	NOEC = 7000 mg a.i./kg diet	Practically non-toxic
Vascular Plants			
Vascular plant	Seedling emergence	No effects observed	
	Vegetative vigour		

Table 2 Effects on aquatic organisms

Organism	Exposure	End point value	Degree of toxicity[a]
Freshwater species			
Water flea	Acute	NOEC < 19.2 and LC_{50} = 87 mg a.i./L	Slightly toxic
	Chronic	NOEC = 0.0251 mg a.i./L	
Rainbow trout	Acute	NOEC = 128 and LC_{50} > 128 mg a.i./L	Practically non-toxic
	Chronic	NOEC = 11.7 mg a.i./L	
Bluegill sunfish	Acute	NOEC = 134 and LC_{50} > 134 mg a.i./L	Practically non-toxic
Bioconcentration in fish	No data submitted; not required, as the log K_{ow} of –0.18 indicated a low potential for bioaccumulation		
Freshwater alga:green algae	Acute	NOEC = 6.28 and EC_{50} = 21.6 mg a.i./L	
Marine species			
Crustacean (Mysid shrimp)	Acute	NOEC < 18.7 and LC_{50} = 61.7 mg a.i./L	Slightly toxic
Mollusk (Eastern oyster)	Acute	NOEC = 0.768 and LC_{50} = 3.06 mg a.i./L	Moderately toxic
Sheepshead minnow	Acute	NOEC = 117 and LC_{50} > 117 mg a.i./L	Practically non-toxic

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

Table 3*a*. Risk to terrestrial organisms

Organism	Exposure	End point value	EEC	MOS	Risk
Invertebrates					
Earthworm	Acute	NOEC = 12.3 mg a.i./kg soil	0.079 mg a.i./kg soil	156	No risk
Bee	Oral	NOEC = 4.48 kg a.i./ha	178.59 kg a.i./ha	25.1	No risk
Predatory and parasitic arthropod	Acute	NOEC = 1200 g a.i./ha	178.59 kg a.i./ha	6.72	Low risk
Birds					
Wild birds	Acute: mallard duck*	NOEL = 31.25 mg a.i./kg bw	DI = 0.488 mg a.i./individual/d	69 d to reach NOEL	No risk
	Dietary: mallard duck*	NOEC = 315 mg a.i./kg diet	6.51 mg a.i./kg diet	48.4	No risk
	Reproduction: bobwhite quail*	NOEC = 100 mg a.i./kg diet	33.7 mg a.i./kg diet	3	Low risk
Mammals					
Wild mammals	Acute: rat*	NOEL = 5820 mg a.i./kg bw	DI = 5.83 mg a.i./individual/d	350 d to reach NOEL	No risk
	Dietary: rat*	NOEC = 500 mg a.i./kg diet	97.20 mg a.i./kg diet	5.14	Low risk
	Reproduction*	NOEC < 1000 mg a.i./kg diet	97.20 mg a.i./kg diet	10.3	No risk

* most susceptible species

Table 3*b*. Risk to aquatic organisms

Organism	Exposure	End point value	EEC	MOS	Risk
Freshwater species					
Water flea	Acute	NOEC < 19.2 mg a.i./L	0.059 mg a.i./L	32.5	No risk
	Chronic	NOEC = 0.0251 mg a.i./L	0.059 mg a.i./L	0.45	Risk
Freshwater fish	Acute: rainbow trout*	NOEC = 128 mg a.i./L	0.059 mg a.i./L	2170	No risk
	Chronic: rainbow trout*	NOEC = 11.7 mg a.i./L	0.059 mg a.i./L	198	No risk
Freshwater alga	Acute: green algae	NOEC = 6.8 mg a.i./L	0.059 mg a.i./L	115	No risk
Marine species					
Crustacean	Acute: mysid shrimp	NOEC < 18.7 mg a.i./L	0.059 mg a.i./L	317	No risk
Mollusk	Acute: eastern oyster	NOEC = 0.768 mg a.i./L	0.059 mg a.i./L	13	No risk
Marine fish	Acute: sheepshead minnow	NOEC = 117 mg a.i./L	0.059 mg a.i./L	198	No risk