Proposed Registration Decision PRD2018-13

Thiamethoxam and Mainspring X Insecticide

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Overview

Background

Thiamethoxam Technical (Reg. No. 26665) is fully registered in Canada for use in gel bait insecticides for ant control (USC[1] 20, Structures). Other uses of Thiamethoxam Technical, and its associated end-use products, are conditionally registered in Canada for use as seed treatments, foliar and soil applications.[2] In 2013, the major new use of greenhouse non-food crops (USC 6) was added to Thiamethoxam Technical (Reg. No. 26665), with conditions of registration required under section 12 of the *Pest Control Products Act*. The end-use product associated with this use is Mainspring X Insecticide (Reg. No. 30901). The additional information for Mainspring X Insecticide has now been received and reviewed under an application to fulfil the conditions of registration, and consultation on this major new use is required, following the procedure under the former conditional registration regulations.[3]

List of Data Previously Required as a Condition of Registration under section 12 for Mainspring X Insecticide

DACO:	8.5
Title:	Fate of thiamethoxam and the transformation product clothianidin in plants, including concentrations in nectar and pollen.
Required data:	A study which determines the concentration of thiamethoxam and clothianidin in nectar and pollen of plants (plant fate study).
DACO:	9.2.4.3
Title:	Hive Study (field)
Required data:	The new study must follow currently accepted guidelines and address concerns regarding toxicity of thiamethoxam and the transformation.

For the outcome of the review of the information provided to fulfil the above conditions of registration, refer to Section 4.2.1 of this document.

The end-use product, Mainspring X Insecticide, contains both thiamethoxam and cyantraniliprole in equal proportions. For further information on cyantraniliprole, please consult the Proposed Registration Decision PRD2013-09, *Cyantraniliprole* and Regulatory Decision RD2013-25, *Cyantraniliprole*.

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1 Use-site Category (USC) details at: https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/registrants-applicants/product-application/use-site-category-daco-tables/definitions-conventional-chemical-pesticides.html

2 Please refer to PRD2017-18, Thiamethoxam for the conditions and proposal associated with the seed treatments uses, and PRD2018-14, *Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products* for the conditions and proposal associated with the foliar and soil treatments.

3 Sections 14, 15 and 16(2) of the Pest Control Products Regulations, repealed on 30 Nov 2017.

Re-evaluation and Special Review of Thiamethoxam

The re-evaluation of thiamethoxam to assess risks to pollinators was announced in 2012 (Re-evaluation Note REV2012-02, *Re-evaluation of Neonicotinoid Insecticides*). This re-evaluation was initiated to assess the potential risk to pollinators in light of international updates to the pollinator risk assessment framework, including information requirements. Data obtained from published literature as well as data received from the registrants, including the information (DACOs 8.5 and 9.2.4.3) that were required to fulfil the conditions of registration under section 12, were considered in the re-evaluation assessment.

In addition, the PMRA announced in 2016 the initiation of a special review to evaluate the impact of thiamethoxam on aquatic invertebrates (Re-evaluation Note REV2016-17, *Initiation of Special Reviews: Potential Environmental Risk to Aquatic Invertebrates Related to the Use of Clothianidin and Thiamethoxam*).

Health Canada has conducted an assessment of pollinator risk for thiamethoxam, as well as a special review to evaluate the impact of thiamethoxam on aquatic invertebrates. A Proposed Re-evaluation Decision and a Proposed Special Review Decision have been published:

- PRVD2017-24, *Thiamethoxam and Its Associated End-use Products: Pollinator Re-Evaluation*, summarizes the science evaluation with regards to the potential risks posed by thiamethoxam to pollinators in Canada, as well as proposes strategies to reduce the risks to these pollinators.

- PSRD2018-02, *Special Review of Thiamethoxam Risk to Aquatic Invertebrates: Proposed Decision for Consultation*, summarizes the science evaluation with regards to the potential risks posed by thiamethoxam to aquatic invertebrates in Canada, as well as proposes strategies to reduce the risks to these organisms.

The use pattern of Mainspring X Insecticide is affected by these re-evaluation and special review proposals, and as a result, some uses are currently proposed for cancellation. The continued registration of Mainspring X Insecticide and of USC 6 of thiamethoxam technical active ingredient will be subject to the outcomes of the final decisions pertaining to the re-evaluation and special review of thiamethoxam.

Proposed Registration Decision for Thiamethoxam

With respect to greenhouse non-food crops uses of thiamethoxam, under the authority of section 8 of the *Pest Control Products Act*, the PMRA is proposing a three-year registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use product Mainspring X Insecticide. This consultation is carried under 28(1)(a) of the *Pest Control Products Act*.

An evaluation of available scientific information found that the product has value and presents an acceptable risk to human health and the environment, when used according to the proposed conditions of registration, which include amendments to the label. To address potential risks to

pollinators and aquatic invertebrates, some uses are currently proposed for cancellation and amendments to the registration of the end-use product have been proposed. The continued registration of Mainspring X Insecticide will be subject to the outcomes of the final decisions pertaining to the re-evaluation and special review of thiamethoxam.

Before making a final registration decision on Thiamethoxam and Mainspring X Insecticide, Health Canada will consider any comments received from the public in response to this consultation document.[4] Health Canada will then publish a Registration Decision[5] on Thiamethoxam and Mainspring X Insecticide, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Heath Canada's response to these comments. In addition, the confidential test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

This Overview describes the key points of the evaluation of thiamethoxam on the original use pattern approved for USC 6, while the Science Evaluation and tables in Appendix I provide detailed technical information on the human health, environmental and value assessments of Thiamethoxam Technical and Mainspring X Insecticide. Health Canada is consulting the public under 28(1)(a) of the *Pest Control Products Act* for the major new use of Greenhouse non-food crops. For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

Validity period of conditional registrations

In order to complete the consultations, the validity period of Mainspring X Insecticide has been extended until 31 December 2020. This extension is also applicable to the USC 6 of Thiamethoxam Technical (Reg. No. 26665). This extension was granted under 14(7)[6] of the former Pest Control Products Regulations, to carry out the consultation on the proposed registration decisions with respect to this product.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions.[7] The Act also requires that products have value[8] when used according to the label directions. Conditions of registration may include special precautionary measures on the product

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

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

6 SOR/2017-91, section 11

7 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

8 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

label to further reduce risk. When special review or re-evaluation decisions affect the registration of a product, the effective date of the amendment or cancellation may also be delayed as long as there is no suitable alternative and the risk is acceptable during that time period.[9]

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

What Is Thiamethoxam?

Thiamethoxam is one of the active ingredients in the commercial class product Mainspring X Insecticide. Mainspring X Insecticide is applied as a foliar spray or as a soil drench, and controls or suppresses listed insect pests of greenhouse ornamentals. Thiamethoxam moves through the leaf surface and the translocation system of the plant, affecting the insects through contact and ingestion. Mainspring X Insecticide also contains the active ingredient cyantraniliprole, which is a Mode of Action Group 28 insecticide.

Health Considerations

Can Approved Uses of Thiamethoxam Affect Human Health?

Mainspring X Insecticide, containing thiamethoxam, is unlikely to affect your health when used according to label directions.

Potential exposure to thiamethoxam may occur through the diet (food and water) or when handling and applying the products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using pesticide-containing products according to label directions.

In laboratory animals, the technical grade active ingredient thiamethoxam was moderately acutely toxic via the oral route and of low toxicity via the dermal and inhalation routes of

[9] Subsection 21(3) of the *Pest Control Products Act*.

exposure. It was minimally irritating to eyes, non-irritating to skin, and it did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statement "WARNING POISON" are required on the label.

Mainspring X Insecticide was of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was minimally irritating to the eyes, non-irritating to the skin, and did not cause an allergic skin reaction.

Health effects in animals given repeat doses of thiamethoxam over long periods of time included effects on the liver, kidneys, testes and nervous system. There was no evidence to suggest that thiamethoxam damaged genetic material, and it did not cause cancer in rats. Thiamethoxam did produce liver tumours in mice; however, the process of tumour formation is not expected to occur in humans due to differences in metabolism. In animal reproductive toxicity tests, adverse effects on the sperm and testes of offspring were observed at dose levels that did not have health effects in the mother, indicating that the young were more sensitive to thiamethoxam than the adult animal. In additional studies in which pregnant animals were given thiamethoxam, reduced brain weight and changes in brain measurements were observed in offspring at dose levels which produced minimal effects on the mother, again suggesting sensitivity of the young. The risk assessment protects against the effects of thiamethoxam by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Occupational Risks From Handling Mainspring X Insecticide

Occupational risks are not of concern when Mainspring X Insecticide is used according to the proposed label directions, which include protective measures.

Workers who mix and load Mainspring X Insecticide and apply as a foliar or soil treatment and workers re-entering treated greenhouses and nurseries can come in direct contact with thiamethoxam residues on the skin and/or through inhalation. Therefore, the label specifies that anyone mixing and loading thiamethoxam must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and boots and safety glasses or goggles, and when applying, workers must wear a long-sleeved shirt, long pants, socks and boots. Chemical-resistant gloves must also be worn when applying this product using hand-held equipment. Taking into consideration these label statements, precautionary measures, and the exposure duration for handlers, it was determined that the risks to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Thiamethoxam Is Introduced into the Environment?

The risks to pollinators from greenhouse uses of thiamethoxam have not been shown to be acceptable for bee attractive plants that will be planted outside. As such, mitigation, including cancellation of some uses, has been proposed. The risk to aquatic invertebrates from greenhouse uses of thiamethoxam have been shown to be acceptable, with appropriate mitigation measures restricting the discharge of wastewater into aquatic habitats.

Information for fate and ecotoxicity of thiamethoxam can be found under PRVD2017-24 (*Thiamethoxam and Its Associated End-use Products: Pollinator Re-evaluation*), PSRD2018-02, (*Special Review of Thiamethoxam Risk to Aquatic Invertebrates: Proposed Decision for Consultation*) and ERC2007-01 (*Thiamethoxam),* which include relevant tables.

The end-use product, Mainspring X Insecticide, containing thiamethoxam was conditionally registered for greenhouse non-food crops (such as ornamentals). Although most non-target outdoor terrestrial organisms are not expected to be exposed to thiamethoxam from a greenhouse use, there is potential exposure for pollinators and other beneficial arthropods. For pollinators, there is potential exposure when plants are treated in the greenhouse, and bees are used in greenhouse production. There is also potential for oral exposure to bees if bee attractive plants are treated with thiamethoxam in the greenhouse and then planted outside, since residues may remain in pollen and/or nectar. For other beneficial arthropods, the main route of exposure would be for insects that are used in greenhouse production. Thus, potential risk from Mainspring X Insecticide for these exposure scenarios was assessed.

The PMRA recently completed a re-evaluation of the potential risks posed by thiamethoxam to pollinators (PRVD2017-24). That re-evaluation was conducted considering the current use pattern for thiamethoxam (including Mainspring X insecticide) and current risk assessment methods. Therefore, throughout this consultation document, the potential effects and proposed mitigation for pollinators will reference PRVD2017-24. In addition, information related to the toxicity of thiamethoxam to other beneficial arthropods will reference ERC2007-01.

Thiamethoxam presents a potential risk to bees and other beneficial insects. Please refer to the most recent assessment (in PRVD2017-24) of the potential risk to pollinators from use of Mainspring X Insecticide, and proposed mitigation. Mitigation for greenhouse use, including cancellation of some uses where bee-attractive crops will be planted outdoors, has been proposed in PRVD2017-24. For other beneficial arthropods, in order to inform users of the potential risk, label statements are required on the label.

Although there is some potential for exposure to aquatic organisms from greenhouse effluent, appropriate mitigation measures restricting the discharge of wastewater into aquatic habitats would mitigate the potential risk (PSRD2018-02).

Value Considerations

What Is the Value of Mainspring X Insecticide?

Mainspring X Insecticide controls or suppresses a variety of insect pests of greenhouse ornamentals.

Mainspring X Insecticide controls or suppresses aphids, mealybugs, soft scales and whiteflies when applied to the foliage of greenhouse ornamentals. When applied as a soil drench to greenhouse ornamentals, it targets these pests, as well as dipteran leafminers and thrips. These insects are widespread pests in the greenhouse ornamental industry. Thiamethoxam represents a new mode of action for use against dipteran leafminers, mealybugs and thrips on greenhouse ornamentals. Therefore, Mainspring X Insecticide aids in resistance management of these crop-pest combinations and is a new management tool for use on greenhouse ornamentals.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Key Risk-Reduction Measures

Human Health

As workers could come into direct contact with thiamethoxam on the skin or through inhalation of spray mists, anyone mixing and loading thiamethoxam and performing cleaning and repair activities must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks, boots and safety glasses or goggles. During application, workers must wear long-sleeved shirt, long pants, socks and boots. Chemical-resistant gloves must also be worn when applying this product using hand-held equipment. Foliar application of Mainspring X Insecticide to greenhouse cut flowers is not permitted.

Environment

As a result of the pollinator re-evaluation of thiamethoxam and the special review on aquatic invertebrates, further risk mitigation measures for product labels are being proposed. See the documents below for more information.[10]

- Measures to Protect Pollinators, as found in PRVD2017-24, *Thiamethoxam and Its Associated End-Use Products: Pollinator Re-Evaluation*.

[10] https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/public/consultations.html

- Measures to Protect Aquatic Invertebrates, as found in PSRD2018-02, *Special Review* of *Thiamethoxam Risk to Aquatic Invertebrates: Proposed Decision for Consultation*.

The risk-reduction measures and other conditions of registration being proposed as a result of the re-evaluation review of the risk to pollinators and of the special review will apply to the end-use product Mainspring X Insecticide. For other beneficial arthropods used in greenhouse production, in order to inform users of the potential risk, label statements are required on the label.

Conclusion

The conditions of registration relating to the submission of additional information required under section 12 of the *Pest Control Products Act* for thiamethoxam and Mainspring X Insecticide have been met. To address potential risks to pollinators and aquatic invertebrates, amendments to the registrations of the end-use products have been proposed, including cancellation of some uses.

Health Canada's PMRA, under the authority of section 8 of the *Pest Control Products Act* is proposing a three-year registration for the sale and use of Thiamethoxam Technical (Reg. No. 27445) and the end-use product Mainspring X Insecticide (Reg. No. 30901). The continued registration of USC 6 of thiamethoxam is subject to the final outcome of the special review on aquatic invertebrates, and of the final decision on the pollinator re-evaluation.

Next Steps

Before making a final registration decision on Thiamethoxam and Mainspring X Insecticide, Health Canada will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision on Thiamethoxam and Mainspring X Insecticide, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Heath Canada's response to these comments.

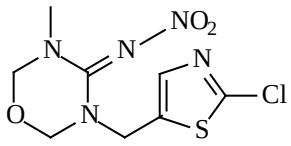
In addition, the confidential test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Thiamethoxam

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Thiamethoxam
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*(EZ)*-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine
2. Chemical Abstracts Service (CAS)	3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine
CAS number	153719-23-4
Molecular formula	$C_8H_{10}ClN_5O_3S$
Molecular weight	291.7
Structural formula	
Purity of the active ingredient	99.1 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Thiamethoxam Technical

Property	Result
Colour and physical state	Off white fine powder
Odour	Odourless
Melting range	139.1°C
Boiling point or range	Not applicable. The product is a solid
Density	1.57 × x 10^3 kg/m^3
Vapour pressure at 20°C	2.7 × 10^{-9} Pa

Property	Result
Ultraviolet (UV)-visible spectrum	No significant absorption at wavelengths over 300 nm in neutral, acidic and basic solutions
Solubility in water at 20°C	4.1 g/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/100 mL) dichloromethane — 11 acetone — 4.8 methanol — 1.3 ethyl acetate — 0.7 toluene — 0.068 octanol — 0.062 hexane — < 0.0001
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = -0.13 ± 0.0017 at 25°C
Dissociation constant (pK_a)	No dissociation within the pH range 2 to 12
Stability (temperature, metal)	No thermal effect (peak) found between room temperature and the melting point of the substance. The technical grade active ingredient is not changed by contact with metals (stainless steel, cast steel, tin & aluminum) and with metal ions (Zn^{+2}, Al^{+3}, Cu^{+2} and Fe^{+2}).

End-Use Product—Mainspring X Insecticide

Property	Result
Colour	Beige brown
Odour	Weak loamy
Physical state	Solid
Formulation type	Wettable Granules
Label concentration	20% Thiamethoxam 20% Cyantraniliprole
Container material and description	HDPE plastic jug or tote, paper bags
Density	0.557 g/mL (bulk density)
pH of 1% dispersion in water	9.5
Oxidizing or reducing action	Not an oxidizing substance
Storage stability	Stable on storage in HDPE or PE containers, and laminated paper/plastic bags at 54°C for fourteen days; and in HDPE at 20°C for one year.
Corrosion characteristics	Not corrosive to HDPE containers, stainless steel, sheet steel, galvanized sheet metal or tin plate
Explodability	Not explosive

1.3 Directions for Use

Foliar applications of Mainspring X Insecticide to greenhouse ornamentals control aphids, mealybugs and soft scales, and suppress whiteflies at a concentration of 37.5–75 g product/100 L of water, with a maximum spray volume of 1000 L/ha, a maximum of two applications and a minimum 14-day reapplication interval.

Drench applications to greenhouse ornamentals control aphids (including root aphids), dipteran leafminer larvae, mealybugs, soft scale and whiteflies, and suppress thrips with a maximum of one application at 50–75 g product/100 L of water.

1.4 Mode of Action

Thiamethoxam is a neonicotinoid insecticide in the Insecticide Resistance Action Committee's Mode of Action Group 4A. It affects insect nerves and acts as a nicotinic acetylcholine receptor agonist. Thiamethoxam is most active through ingestion. It is mobile in the xylem of plants, showing systemic activity by root uptake but is only translaminar active by foliar application.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Thiamethoxam is a broad spectrum nitroguanidine insecticide which belongs to the neonicotinoid pesticidal class. It exerts its pesticidal mode of action by interfering with the nicotinic acetylcholine receptors of the insect's nervous system. Thiamethoxam has a lower affinity for vertebrate nicotinic receptors than those of insects. A detailed review of the toxicology database for thiamethoxam was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, a suite of special studies were conducted to investigate the etiology of liver tumours in the mouse oncogenicity study. The studies in the database were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with thiamethoxam.

Toxicokinetic investigations were conducted in rats and mice with thiamethoxam, radiolabelled with ^{14}C in either the oxadiazine or thiazole ring, administered primarily via the diet or gavage at various dose levels for different durations. These investigations also included comparative metabolism studies in rats and mice which examined blood metabolite profiles in both species following extended dietary dosing.

Absorption, distribution, metabolism and excretion of thiamethoxam were independent of sex, dose level, pre-treatment and radiolabel position. In both rats and mice, thiamethoxam was rapidly absorbed and eliminated. Blood concentrations of radioactivity peaked between one and six hours post-dosing in rats and at 0.5 hours in mice. The half-lives of elimination of radioactivity in blood were three and four hours for rats and mice, respectively. In mice, approximately 72% of the administered dose (AD) was excreted in the urine and 19% was excreted in the feces. In rats, > 84% of the AD was excreted in the urine and ≤ 6% was excreted in the feces. Elimination via expired air was negligible in both species.

Radioactivity was widely distributed to tissues, with the highest concentrations in rats detected in skeletal muscle within eight hours of dosing. Tissue residues in rats seven days post-dosing were very low (less than 1% of the AD), with the highest amounts detected in liver. In mice, the highest tissue residues at 72 hours post-dosing were found in liver, with total body radioactivity less than 1% of the AD.

The major pathways of thiamethoxam metabolism in rats and mice involve either oxidative loss of the oxadiazine ring to form CGA322704 (also known as clothianidin), or alternatively, oxidative N-demethylation to form CGA330050. Further metabolism of both of these metabolites results in the formation of the other major metabolite, CGA265307. Unchanged thiamethoxam was the major component in blood extracts (78% mice, 82% rats). In mice, CGA322704, CGA265307 and CGA330050 were detected in blood at comparable levels (10–15%). In rats, CGA322704 was detected in blood (16%) with only trace amounts of CGA265307 (0.3%). CGA330050 was not detected in blood in rats. Only three urinary metabolites accounted for greater than 1% of the AD in rats. Unchanged thiamethoxam accounted for 69–83% of the AD in rats (31–44% in mice); CGA322704 was the major urinary metabolite in rats (5–13% of the AD) and mice (8–12%). CGA265307 accounted for ≤ 2% of the AD in rats and 9–18% of the AD in mice. The identification of the major metabolites in rats and mice is presented in Appendix I, Table 1.

Concentrations of the metabolite CGA265307 were approximately 22-fold greater in mouse plasma than in rat plasma after one week of dietary administration of thiamethoxam. After ten weeks of dietary administration, the concentration of CGA265307 in mouse plasma had increased approximately 3.6-fold compared to that recorded after one week of dietary administration, suggesting induction of metabolic pathways, whereas that in rat plasma had lessened with extended administration. As a result, plasma concentrations of CGA265307 were up to 140-fold greater in mice than rats. The difference between the plasma levels of CGA330050 in rats and mice was up to 15-fold over the 10-week dosing duration with higher amounts in mouse plasma. The major difference between metabolism in rats and mice may contribute to differences in long term toxicity.

In vitro investigations with liver fractions obtained from rat, mouse and human tissue preparations revealed that, depending on the metabolism pathway involved (either via oxidative loss of the oxadiazine ring to form CGA322704 or via oxidative N-demethylation to form CGA330050), metabolic rates in mouse liver were 54-fold (via CGA322704) and 87-fold (via CGA330050) higher than those in rat liver and 371-fold and 238-fold higher, respectively, than those in human liver.

In acute toxicity studies, technical thiamethoxam was slightly toxic to rats and moderately toxic to mice via the oral route and of low toxicity to rats via the dermal and inhalation routes of exposure. Thiamethoxam was minimally irritating to rabbit eyes and non-irritating to rabbit skin. It was non-sensitizing in a maximization test in guinea pigs. The metabolite CGA322704 was of low acute toxicity in rats via the oral route of administration.

Mainspring X Insecticide was of low acute toxicity in rats via the oral, dermal, and inhalations routes of exposure. They were minimally irritating to the eye and non-irritating to the skin of rabbits, and they are not expected to be dermal sensitizers, based on tests performed in guinea pigs using the Buehler method.

In the guideline repeat-dose dietary toxicity studies of short-term to long-term duration, the primary target organs of toxicity for thiamethoxam were the kidney (rats), liver (rats, mice, dogs), and testes (dogs). Male rats were more sensitive than female rats to the effects of thiamethoxam on the kidneys. Effects in this organ included hyaline change of renal tubular epithelium, basophilic proliferation of renal tubules, dilatation of renal pelvis and increased organ weight. The observed hyaline change in the proximal convoluted tubules of the male rat kidneys was attributed to the accumulation of alpha 2u-globulin, a protein that is unique to male rats. The results of immunohistochemical assessment of renal tissue in rats following short-term to long-term dietary dosing revealed an increased accumulation of renal alpha 2u-globulin in male rats receiving thiamethoxam. Similar findings were not observed in thiamethoxam-treated females or control animals of either sex. It should be noted, however, that hyaline change, consisting of eosinophilic droplets within the cytoplasm of the proximal convoluted tubules, was observed in one high-dose F_1 generation female in one of the two-generation dietary rat reproductive toxicity studies. In addition, other kidney toxicity was observed in female rats in the repeat-dose dietary studies, including chronic tubular lesions and nephrocalcinosis.

Liver toxicity, in the form of hepatocellular hypertrophy, increased liver weights and associated changes in clinical biochemical parameters, was also observed in rats but these alterations were noted at higher dose levels than those producing kidney toxicity. In mice, liver pathology included hepatocellular hypertrophy, necrosis of single hepatocytes, lymphocytic infiltration and Kupffer cell pigmentation, and hyperplasia. Male mice were slightly more sensitive than females to liver toxicity. In dogs, accumulation of pigment within hepatic Kupffer cells, as well as changes in liver clinical biochemical parameters were noted.

In dogs, testicular effects were a noteworthy finding following repeated dietary dosing. In the 90-day toxicity study, severely decreased food consumption and concomitant body weight loss at the highest dose level necessitated cessation of treatment for seven days and resumption of dosing with a lower dose level. Animals from this group had decreased testis weights, reduced

spermatogenesis and minimal to moderate occurrence of spermatic giant cells in the testes. Atrophy of the seminiferous tubules was observed in one high-dose male. Atrophy of the seminiferous tubules and decreased testes weight were also observed at a lower dose level in male dogs after exposure to thiamethoxam for 12 months.

In addition to the effects on kidneys, liver and testes noted above, changes in other organs were observed at the higher dose levels following repeated dietary dosing. These included decreased ovarian weights and ovarian atrophy in mice in the 90-day toxicity study and decreased ovary weights associated with delayed maturation of the ovaries in dogs in the 90-day toxicity study. Increased adrenal and thyroid weights were also observed at the higher dose levels in the repeat-dose rat studies.

A rat repeat-dose dermal toxicity study identified systemic toxicity (liver, kidney effects) that was consistent with that observed in rat oral toxicity studies. At the highest dose level, there was evidence of chronic tubular lesions in kidneys in females, whereas in males, the kidney findings consisted of renal tubule hyaline change. At the next lower dose level, liver toxicity was observed in females only. These results demonstrated that females were more sensitive than males following dermal dosing.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with thiamethoxam. There was no evidence of oncogenicity after long-term repeated dietary dosing in rats. However, body weight was unaffected in thiamethoxam-treated males in the long-term rat study, suggesting that animals could have tolerated higher dose levels. Despite this, there was evidence of systemic toxicity in males which included chronic nephropathy and lymphocytic infiltration in the kidneys. Decreased body weight gain, chronic tubular lesions in the kidneys and foci of cellular alteration in the liver were observed in females at a higher dose level.

In mice, long-term dietary dosing resulted in an increased incidence of benign and malignant liver tumours in both males and females. The incidence of hepatocellular adenomas was increased ($p<0.01$ pair-wise) in both sexes at the two highest dose levels. An increase ($p<0.05$) was also observed in females at the next lower dose level. At this same dose level, the incidence of adenomas in males was higher than concurrent controls; however, it was not statistically significantly different from that of the concurrent controls and it fell within the range of the historical control data. With regards to hepatocellular carcinomas, the incidence was increased ($p<0.01$) in both sexes at the highest dose level. At the next lower dose level, the incidence of carcinomas was increased ($p<0.05$) in males but fell within the range of the historical controls whereas the incidence in females at this dose level, although not statistically significantly different from that of the concurrent control, fell outside the upper range of the historical control data. The combined incidences of hepatocellular adenomas and carcinomas in both sexes was significantly ($p<0.01$) elevated at the two highest dose levels. Historical control data for combined incidences were not available. At the next lower dose level, the combined incidence in females was significantly ($p<0.05$) increased; the incidence in males at this dose level was slightly higher than concurrent controls, but it was not statistically significant. In females, the increase was largely driven by the adenomas since no carcinomas were observed at this dose level. Treatment with thiamethoxam resulted in an increase in the number of animals with

multiple liver tumours; however, the tumours did not have an impact on group survival. The results of this study indicated that thiamethoxam produced liver tumours only at dose levels producing overt indications of liver toxicity.

Thiamethoxam was proposed to produce liver tumours in mice as a result of cytotoxicity and cell death, followed by increased cell replication rates, and ultimately, the production of tumours. A series of special studies were conducted to investigate the etiology of the mouse liver tumours. The special studies included investigation of differential metabolism in mice and rats, as well as in vitro comparison of thiamethoxam metabolism by microsomal preparations from mouse, rat and human liver (discussed previously). The studies also addressed histological and biochemical changes in mice and rats. The investigative studies included dietary administration to rats and mice for various study durations of up to 50 weeks, employing dose levels consistent with mouse tumourigenic dose levels. In mice, decreased cholesterol was identified as an early indicator of liver perturbation, occurring as early as seven days, on the basis of these dietary studies. In light of this finding, a comparative hepatotoxicity study in weanling and adult mice following seven days of dietary exposure was also provided, which investigated the sensitivity of weanling and adult mice to the cholesterol-lowering effects of thiamethoxam. The comparative hepatotoxicity of the major metabolites, CGA322704, CGA265307, and CGA330050, with thiamethoxam was also investigated in dietary feeding studies in rats and mice.

The findings in this suite of special studies showed a clear effect of both dose and duration of thiamethoxam treatment on hepatic changes in mice, supporting a sequence of events, from disturbance of cellular homeostasis to hepatotoxicity, hepatocellular lethality, and compensatory cell proliferation. Effects in mice noted early on in treatment included reduced cholesterol and serum protein (after one week of dietary administration) and increased alanine aminotransferase (after 10 weeks of dietary administration). Hepatocellular hypertrophy, necrosis, and apoptosis were noted in mice from week 10 onwards, whereas inflammatory cell infiltration and increased aspartate aminotransferase were noted at week 20. Increased mitotic index was observed in mice after 40 weeks of dietary administration. At higher dose levels in mice, increases in the mean hepatic concentration of reduced and oxidized glutathione were observed. Treatment with thiamethoxam in mice caused an increase in hepatic γ-glutamylcysteine synthetase and hepatic glutathione S-transferase activity. Thus, thiamethoxam can be considered a moderate inducer of liver phase II xenobiotic metabolizing enzymes in mice. Liver effects were noted in two mouse strains (Tif:MAGf and CD-1), suggesting that the toxicity noted was not strain-specific. The temporal and dose relationship for liver toxicity in mice was not observed in rats; similar testing did not identify adverse effects on biochemistry and histopathology parameters, nor was there an increase in enzyme induction or cell replication rates. These differences in liver toxicity between rats and mice suggested a differential metabolism of thiamethoxam in these species.

This differential metabolism between rats and mice was confirmed in previously-mentioned studies that demonstrated a species difference in production of metabolites CGA265307 and CGA330050; over time, mice showed induction of metabolism with high levels of CGA265307 and CGA330050, whereas rats showed a reduction in metabolism. The in vitro data demonstrated a similar difference, as rate conversions in mouse liver were much higher than those in rat liver fractions. The rate conversions in human liver were even lower than in rat liver,

suggesting that metabolism of thiamethoxam to the major metabolites would be much lower in humans.

The metabolites CGA322704 and CGA265307 did not produce evidence of hepatotoxicity in mice or rats. CGA330050 produced a spectrum of hepatotoxicity similar to thiamethoxam following repeated dietary dosing in mice, with evidence of decreased cholesterol and serum protein, increased hepatocellular hypertrophy, necrosis, apoptosis, and inflammatory cell infiltration. Hepatic effects in rats fed the metabolite CGA330050 were limited to increased liver enzymes, suggesting a lack of liver toxicity in rats. These findings, combined with the evidence of differential metabolism summarized above, suggest that the metabolite CGA330050 is a major contributor to the thiamethoxam-induced hepatotoxicity observed in mice. Another possible contributor to the development of hepatotoxicity in thiamethoxam-treated mice is CGA265307. Although this metabolite was not hepatotoxic in rats or mice, it did inhibit inducible nitric oxide synthase. Nitric oxide produced by these enzymes is known to have a regulatory role in the liver in modulating the adverse effects of Tumour Necrosis Factor alpha (TNFα) released from endothelial cells during chemically induced hepatotoxicity. Thus, inhibition of these enzymes may have exacerbated the liver toxicity resulting from the hepatotoxic metabolite, CGA330050. Results of the comparative study in weanling and adult mice indicated that plasma levels of thiamethoxam and metabolites CGA322704, CGA265307, and CGA330050 were up to two-fold higher in weanlings than in adults. The pattern of metabolism and ratio of metabolites to each other and to thiamethoxam was the same in both age groups. Despite the higher plasma levels in weanling mice compared to adult mice, the reductions in plasma cholesterol and the changes in liver morphology (increased centrilobular vacuolation and decreased eosinophilia) in weanlings were significantly less than in adults. Weanlings were at least two-fold less susceptible to cholesterol reduction than adults across the dose levels tested.

Based on the overall evidence, the increase in mouse liver tumour response appears to be linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite. As a result, it was determined that a threshold approach to the cancer risk assessment could be taken.

There was no evidence of sensitivity of the young in gavage developmental toxicity studies in rats and rabbits conducted with thiamethoxam. In rats, reduced fetal body weights and an increase in skeletal variations (asymmetrically shaped 6th sternebrae and irregular ossification of occipital bone) were observed at a dose level that produced reductions in body weight as well as clinical signs of toxicity in dams. In the rabbit study, the findings were similar in that there was a reduction in fetal body weight and a slightly increased incidence of fetal skeletal findings (fused or asymmetrically shaped sternebrae). The skeletal findings in rabbits were increased on a fetal basis only, and the incidences were only slightly outside the upper end of the historical control values. Maternal toxicity was also observed at the same dose level, consisting of reduced body weight and food consumption, uterine hemorrhage, post-implantation loss, and death in the dams.

Two two-generation reproductive toxicity studies in which rats were administered thiamethoxam in the diet were available. There were no effects on mating, gestation or fertility in either study. In the first study, which included two litters per generation, kidney toxicity was observed in the

parental males, consistent with the findings in the short-term studies. Kidney hyaline change was observed in one high-dose parental F_1 female which, as mentioned previously, raised some uncertainty regarding the claim that the finding in male rats in numerous other studies in the database was due to α2u-globulin accumulation in the proximal convoluted tubules. In offspring, decreases in body weight and bodyweight gains were observed in the postnatal period at dose levels that were toxic to parental males. With respect to reproductive toxicity, an increase in both the incidence and severity of atrophy of the seminiferous tubules was observed in the F_1 generation in the absence of parental systemic toxicity, suggesting potential sensitivity of the young. This atrophy was not observed in the F_0 generation, nor was it observed in any of the short-term or chronic toxicity studies. In this reproductive toxicity study, there was reduced sperm motility at all dose levels in both generations; however, the findings were equivocal as there was no clear dose-response, the data were highly variable, and there was no effect on sperm count or morphology. A separate, complementary study was conducted to investigate these findings. Although the results indicated that technical error was the likely cause of the reduced sperm motility in the two-generation study, this complementary study was limited to analysis of F_0 animals and thus, no information relevant to the sperm motility finding in F_1 animals was available. For this reason, no definitive conclusion can be made regarding a possible association between the sperm observations and seminiferous tubule atrophy observed in the F_1 animals in this study. It bears noting that atrophy of the seminiferous tubules was observed in adult dogs in both the 90-day and the 12-month toxicity studies.

A second two-generation reproductive toxicity study with similar dose levels as the first study was conducted. Effects in parental animals included reductions in body weight, renal pathology (males), and changes in the weights of various organs, including increased kidney (males) and decreased pituitary (females) weights. Offspring toxicity was observed at a higher dose level and consisted of pup deaths occurring during postnatal weeks 3–4 as well as decreases in litter weights and a slight delay in preputial separation. With respect to reproductive toxicity, testicular effects were again a prominent finding with minimal germ cell loss or disorganization and Sertoli cell vacuolation (F_1) occurring at the highest dose level. With regards to effects on sperm motility, reductions were observed (F_0 and F_1) but only at the highest dose level. At the next lower dose level, which was also toxic to parental animals (kidney effects in males, reduced pituitary weights in females), reduced testes weights (F_1) were observed. Decreased sperm counts occurred in F_1 males at a dose level that was not toxic to parental animals; since these effects were observed only after in utero and postnatal exposure, this study provides evidence of sensitivity of the young.

In an acute neurotoxicity study, rats exposed via gavage to thiamethoxam demonstrated alterations in the functional observation battery and in locomotor activity parameters. These alterations included drooped palpebral closure, increased forelimb grip strength and decreased locomotor activity. A higher dose produced more pronounced signs of toxicity, including death, abnormal body tone, ptosis, impaired respiration, tremors, crouched-over posture, impaired gait, and uncoordinated landing in the righting reflex test. In a repeat-dose dietary neurotoxicity study in rats, there was no evidence of neurotoxicity. There was no neurohistopathology observed in either the acute or repeat-dose neurotoxicity study. A dietary developmental neurotoxicity (DNT) study in rats was available. In this study, treatment-related findings were observed at the highest dose level only. In maternal animals, reductions in food consumption as well as slight reduction

in body weight and weight gain occurred during the gestation and lactation periods. Offspring toxicity at the highest dose level consisted of reduced body weights throughout the pre-weaning and post-weaning periods as well as delayed sexual maturation in males. High variability in the female sexual maturation data precluded a determination of treatment-related changes. High-dose offspring had reduced brain weights (males, postnatal day (PND) 12 and 63; females, PND 12). Changes in brain morphometric measurements were also observed in high-dose animals at PND 12 and at study termination. At PND 12, males had reductions in the molecular layer of the cerebellum and the cerebellum length while females had reduced thalamus width. At PND 63, treatment with thiamethoxam was associated with reduced dorsal cortex thickness as well as decreases in thalamus, hippocampus, and overall thalamus/cortex widths in both sexes. In addition, there was a reduction in thickness of the piriform cortex and corpus callosum and in the thalamus height in males. There was no effect on startle response or on acquisition of learning or memory during performance of the Y water maze. It was noted, however, that the maze design lacked complexity and as such the results of the water maze were of limited utility. The results of this study indicated serious effects in offspring in the presence of slight toxicity in maternal animals.

The identification of the major metabolites in rats and mice is reported in Appendix I, Table 1. The results of the toxicology studies conducted on laboratory animals with thiamethoxam and its metabolites, and the associated end-use product Mainspring X Insecticide are reported inAppendix I, Table 2 and Table 3, respectively. The toxicology reference values for human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports

As of 31 January 2018, there were 32 human incidents and 39 domestic animal incidents reporting the active ingredient thiamethoxam, alone or in combination with other active ingredients.

Human incidents were minor or moderate in nature. In the majority of Canadian incidents, thiamethoxam was a component of a seed treatment product that contained multiple active ingredients. In four cases, individuals reported exposure to a product used as a spray. In more than half of the cases, the route of exposure was skin and/or respiratory (some individuals reported both routes of exposure). Dermal exposures resulted in signs like pruritus, erythema, rash, and paresthesia. Those exposed via the respiratory route reported chest discomfort, malaise, dizziness, and headache. In moderate cases, tremors, difficulty breathing, and more serious skin lesions were reported.

Domestic animal incidents were classified as minor, moderate, major, or death. The majority of cases were related to ingestion of seed treated with thiamethoxam, alone or in combination with other active ingredients. Half of the cases involved livestock and the predominant effects were nervous and muscular signs (ataxia, gait disturbance, and tremor). The remaining cases involved cats and dogs and most signs were gastrointestinal in nature (anorexia, vomiting, diarrhea, and weight decrease).

These incident reports were considered in this evaluation and did not affect the risk assessment.

This exposure scenario is not anticipated with the proposed products because most incidents involved the exposure to small grains treated with thiamethoxam and other active ingredients.

3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for thiamethoxam. The database contains the full complement of required studies including gavage developmental toxicity studies in rats and rabbits, two dietary two-generation reproductive toxicity studies in rats, and a dietary DNT study in rats. In addition, a supplemental comparative hepatotoxicity study in weanling and adult mice following seven days of dietary exposure was provided, which investigated the sensitivity of weanling and adult mice to the cholesterol-lowering effects of thiamethoxam.

With respect to sensitivity of the young animal to liver toxicity, weanling mice were at least two-fold less sensitive than adults to reductions in plasma cholesterol, and also displayed less severe liver pathology compared to adult mice despite having higher plasma levels of thiamethoxam and its major metabolites compared to adults.

In developmental toxicity studies in rats and rabbits, reduced fetal weights and skeletal findings were observed in the presence of maternal toxicity. In rabbits, post-implantation losses were noted in the presence of severe maternal toxicity. In the DNT study, reduced brain weights and alterations in brain morphometric parameters were noted at the high-dose level in both male and female offspring in the presence of slight maternal toxicity (minimal body weight effects). Reduced pup body weight and delayed sexual maturation in males were also noted at this dose level.

Thiamethoxam did not affect mating, gestation, or fertility in either reproductive toxicity study or in the DNT study. However, there was evidence in both reproductive toxicity studies that the young may be more sensitive to thiamethoxam toxicity following in utero and postnatal exposure. In the first study, atrophy of the seminiferous tubules was observed in the F_1 generation in the absence of parental systemic toxicity. A reduction in sperm motility in both generations was considered equivocal due to issues that included highly variable data and lack of effect on sperm count or morphology. Additional investigation of this finding was limited in that only F_0 animals were examined; thus no information was available on animals that received in utero and postnatal exposure. This lesion was not observed in the F_0 generation, nor was it observed in any of the repeat-dose, including chronic toxicity, studies in rodents. For this reason, no definitive conclusion can be made regarding a possible association between this observation and seminiferous tubule atrophy observed in the F_1 animals. Atrophy of the seminiferous tubules and reduced testicular weights were observed in adult dogs in both the 90-day and the 12-month

toxicity studies. In the second reproductive toxicity study, with similar dose levels as the first study, offspring toxicity (decreased litter weights, slightly delayed preputial separation, and pup deaths during postnatal weeks 3–4) occurred at the highest dose level which was also toxic to parental animals. Minimal germ cell loss or disorganization and Sertoli cell vacuolation (F_1), as well as reduced sperm motility (F_0 and F_1) also occurred at this dose level. Decreased sperm counts in F_1 males occurred at a lower dose level in the absence of parental systemic toxicity indicating that the young may be more sensitive to thiamethoxam toxicity following in utero and postnatal exposure.

Overall, the toxicology database of thiamethoxam is considered complete and all required studies for assessing risk to infants and children were available. The effects on offspring brain weight and morphology in the DNT study were considered serious although the level of concern was tempered by the presence of maternal toxicity. Concern regarding the effects on offspring testes (seminiferous tubule atrophy, reduced sperm counts) observed in the absence of maternal toxicity in the reproductive toxicity studies was partially tempered by the absence of effect on reproductive indices, recognizing that these indices may be an insensitive measure in rodents in view of their fecundity. Based on the available information, the PCPA factor was reduced to three-fold.

3.2 Determination of Acute Reference Dose

General Population (including females 13 to 49 years of age, infants and children)

To estimate acute dietary risk, the DNT study with a NOAEL of 35 mg/kg bw/day was selected for risk assessment. At the LOAEL of 298 mg/kg bw/day, reduced pup weights, delayed sexual maturation, reduced brain weights and altered brain morphometrics were observed. The brain effects potentially could result from a single exposure and therefore these findings are relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to 3-fold. Accordingly, the composite assessment factor (CAF) is 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{35 \text{ mg/kg bw/day}}{300} = 0.1 \text{ mg/kg bw}$$

3.3 Determination of Acceptable Daily Intake (ADI)

General Population (including females 13 to 49 years of age, infants and children)

To estimate dietary risk following repeated exposure, the combined results of the two reproductive toxicity studies were selected for risk assessment. The highest NOAEL of 1.2 mg/kg bw/day was established based on testicular and sperm effects in F_1 animals occurring at the study LOAELs of 1.8 and 3.0 mg/kg bw/day. These studies provided the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold

for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the PCPA factor was reduced to 3-fold. The resulting CAF is thus 300.

The ADI is calculated according to the following formula:

$$ADI = \frac{NOAEL}{CAF} = \frac{1.2 \text{ mg/kg bw/day}}{300} = 0.004 \text{ mg/kg bw/day}$$

Cancer Assessment

Results of in vitro and in vivo genotoxicity studies indicated that thiamethoxam was not genotoxic. As well, thiamethoxam was not oncogenic in rats. However, a treatment-related increased incidence of liver tumours was observed in mice. The increase in tumour response was linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite. Although the pattern of tumour formation (enzyme changes, hypertrophy, apoptosis, necrosis and cell turn-over) is biologically plausible in humans, a prolonged exposure to high concentrations of thiamethoxam would be required to elicit this effect. As a result, it was determined that a threshold approach to the cancer risk assessment could be taken. The ADI provides a margin of 925 to the NOAEL of 3.7 mg/kg bw/day for liver tumours in female mice and is considered protective of all populations.

Cumulative Assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Thiamethoxam belongs to a group of insecticides commonly known as the neonicotinoids. Upon completion of the re-evaluation of thiamethoxam, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to thiamethoxam is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation route for mixers, loaders, and applicators. For postapplication re-entry workers, the exposure is characterized as long-term for greenhouse scenarios and short- to intermediate-term for outdoor scenarios and predominantly by the dermal route.

Short-, Intermediate- and Long-term Inhalation

Repeat-dose inhalation toxicity studies were not available. For exposures of all durations via the inhalation route, the NOAEL of 1.2 mg/kg bw/day from the combined results of the two reproductive toxicity studies was selected for risk assessment. The combined results of these studies revealed testicular and sperm toxicity in the F_1 generation. These effects were only observed after in utero and postnatal exposure. Worker populations could include pregnant or

lactating women and therefore these endpoints were considered appropriate for the occupational risk assessment. The target Margin of Exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 3-fold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of the NOAEL from the reproductive toxicity studies and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-, Intermediate- and Long-term Dermal

For occupational exposures of all durations via the dermal route, the NOAEL of 1.2 mg/kg bw/day from combined results of the two reproductive toxicity studies was selected for risk assessment. The combined results of these studies identified testicular and sperm toxicity in the F_1 generation. These effects were only observed after in utero and postnatal exposure. Worker populations could include pregnant or lactating women and therefore these endpoints were considered appropriate for the occupational risk assessment. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern, namely, reproductive organ toxicity in pups following prenatal or postnatal exposure. The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of 3-fold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of the NOAEL from the reproductive toxicity studies and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

Based on in vivo rodent dermal absorption studies conducted with various formulations of thiamethoxam, as summarized in Evaluation Report ERC2007-01, *Thiamethoxam*, the dermal absorption value for thiamethoxam was determined to be 2.5%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Exposure to workers mixing, loading and applying thiamethoxam is expected to be short- to intermediate-term in duration and to occur primarily by the dermal and inhalation routes.

Dermal and inhalation exposure estimates were derived for mixers/loaders/applicators applying thiamethoxam to a variety of greenhouse crops, outdoor ornamentals using backpack and hand-held (manually- and mechanically-pressurized) sprayers using unit exposure values from the Pesticide Handler Exposure Database (PHED). All exposure estimates are based on mixers/loaders/applicators wearing PPE that is in keeping with label instructions.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 2.5% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation

absorption. Exposure was normalized to mg/kg bw/day by using a 70 kg adult body weight.

Exposure estimates were compared to the toxicological end points (no observed adverse effects levels (NOAELs)) to obtain the MOE; the target combined MOE is 300.

Dermal and inhalation risks to workers mixing, loading and applying thiamethoxam were not of concern (MOEs were above the target MOE; Appendix I, Table 5).

The endpoints selected for worker risk assessment are also protective of any potential cancer findings and there are no health risks of concern.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with thiamethoxam to perform a variety of tasks, both indoors and outdoors.

Postapplication exposure assessments were only conducted for foliar treatments as exposure was deemed negligible following soil treatments. The duration of exposure is considered to be long-term for greenhouse postapplication activities, and short- to intermediate-term for activities performed in nurseries.

Inhalation risks to postapplication workers were deemed negligible considering the vapour pressure of thiamethoxam and the 12 hour restricted-entry interval (REI). Therefore, since the primary route of exposure for workers re-entering treated areas would be through the dermal exposure, the postapplication risk assessment for thiamethoxam is limited to dermal exposure in greenhouses and for outdoor ornamentals.

Greenhouse application
Dermal exposure to workers entering treated greenhouses is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients and a chemical-specific dermal absorption factor. Chemical-specific dislodgeable foliar residue data were not submitted. As such, the current default assumptions used in the exposure assessment are a deposition value of 25% of the application rate and 0% daily dissipation.

Exposure estimates were compared to the toxicological end point to obtain the MOE; the target MOE is 300.

Dermal risks to workers re-entering greenhouses to perform postapplication activities on potted ornamentals were not of concern. Dermal risks to workers re-entering greenhouses to perform most postapplication activities on cut flowers were not of concern. However, dermal risks to workers re-entering greenhouses to perform postapplication activities such as disbudding, hand pruning and hand harvesting on cut flowers were of concern (See Appendix I, Table 6).

Nursery application
Dermal exposure to workers entering treated areas is estimated by coupling dislodgeable foliar residue values with activity-specific transfer coefficients and a chemical-specific dermal

absorption factor. Chemical-specific dislodgeable foliar residue data were not submitted. As such, for nurseries, the dislodgeable foliar residue value, based on a default deposition value of 25% of the application rate, as well as a standard 10% daily dissipation rate, was used in the exposure assessment.

Dermal risks to workers re-entering nurseries to perform postapplication activities on outdoor ornamentals were not of concern (See Appendix I, Table 6).

The endpoints selected for worker risk assessment are also protective of any potential cancer findings and there are no health risks of concern.

3.4.2.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal for greenhouse uses. For field uses, appropriate label statements will be added to ensure that the products will only be applied when there is low risk of drift when taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.4.3 Residential Exposure and Risk Assessment

The end-use product is a commercial marketing-class product for use in commercial settings. Therefore, residential handler and postapplication exposure assessments are not required.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Information for fate and behaviour of thiamethoxam and its transformation products can be found under PRVD2017-24, PSRD2018-02 and ERC2007-01.

4.2 Environmental Risk Characterization

This consultation document references the information in ERC2007-01, as well as recent risk assessments, PRVD2017-24 (for pollinators) and PSRD2018-02 (for aquatic invertebrates).

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection

at the community, population, or individual level).

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

4.2.1 Risks to Terrestrial Organisms

Information for ecotoxicity of thiamethoxam to terrestrial organisms, relevant for this use pattern, can be found in the previously published risk assessments, PRVD2017-24 and ERC2007-01. There is negligible environmental exposure to most terrestrial organisms from use of thiamethoxam in a greenhouse, with the exception of bees and other beneficial arthropods, such as predators and parasites, which may be used in greenhouse production. Additionally, when bee-attractive crops from the greenhouse are planted outside, there is the possibility that bees may be exposed to any residues present in pollen and/or nectar.

The risk assessment for bee pollinators, as well as the proposed mitigation measures to protect bees, can be found in PRVD2017-24, *Thiamethoxam and Its Associated End-use Products: Pollinator Re-Evaluation.* Refer to PRVD2017-24, *Thiamethoxam and Its Associated End-use Products: Pollinator Re-Evaluation* for the science review of the data listed in the Overview "*List of data previously required as a condition of registration under section 12*" and for the review of public literature relevant to the assessment.

The risk to beneficial arthropods other than pollinators, such as predators and parasites, was assessed under ERC2007-01. The screening level RQs for Mainspring X insecticide were assessed based on the maximum application rate for thiamethoxam (150 g a.i./ha applied once per growing season). The assessment determined that there was potential risk for these beneficial insects following application of thiamethoxam (RQ values up to 1145, Appendix I, Table 7.1). Therefore, toxicity statements indicating potential for harm to beneficial insects other than pollinators used in greenhouse production are required on the label.

4.2.2 Risks to Aquatic Organisms

Information for ecotoxicity of thiamethoxam to aquatic organisms can be found in the previously published risk assessments, ERC2007-01 and in the current consultation document PSRD2018-02. Exposure to aquatic organisms from greenhouse use was considered in the special review focussed on risks to aquatic invertebrates (refer to PSRD2018-02). With appropriate mitigation for greenhouse effluent (or wastewater), negligible environmental exposure to aquatic organisms is expected from the use of thiamethoxam in a greenhouse.

Incident reports/additional considerations

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act*.

For a summary of incident reports related to pollinators and aquatic invertebrates, refer to PRVD2017-24 and PSRD2018-02. There were no incident reports related to other beneficial arthropods from greenhouse application.

5.0 Value

Support for product performance was based on use history from the United States, and on the results of 19 trials conducted on a wide variety of greenhouse ornamental crops. Claims for mealybugs, root aphids and soft scales were supported by use history while claims for aphids, dipteran leafminers, thrips and whiteflies were supported by trials. Phytotoxicity was not observed in any of the trials. However, because it was not practical to test all species and varieties of ornamental plants for tolerance to Mainspring X Insecticide, a statement to test a small number of plants for phytotoxicity before widespread use was included on the product label.

Because thiamethoxam represents a new mode of action for use against dipteran leafminers, mealybugs and thrips on greenhouse ornamentals, Mainspring X Insecticide aids in resistance management of these pests. It is also a management tool for use against all listed pests.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, i.e., those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian*

Environmental Protection Act. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, thiamethoxam and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[11] and evaluated against the Track 1 criteria. Thiamethoxam and its end-use product, Mainspring X insecticide, did not meet TSMP criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical, as well as formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[12] The list is used as described in the PMRA Notice of Intent NOI2005-01[13] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[14] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act,* 1999 (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[14]

7.0 Summary

7.1 Human Health and Safety

The submitted toxicology database is adequate to characterize the potential health hazards associated with thiamethoxam. In short-term and chronic toxicity studies on laboratory animals, the primary target organs of toxicity were the liver, kidneys, testes, and nervous system. Thiamethoxam was not genotoxic and there was no evidence of carcinogenicity in rats after longer-term dosing. An increase in liver tumours in mice following long-term dosing was associated with the mouse's greater ability, compared to rats and humans, to metabolize thiamethoxam to a hepatotoxic metabolite. A threshold approach was used for the cancer risk assessment as a result. Impaired fetal growth and effects on the fetal skeleton were observed in the presence of maternal toxicity in developmental toxicity studies. In the DNT study,

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11 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing* the *Toxic Substances Management Policy.*

12 SI/2005-114

13 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

14 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

thiamethoxam caused changes in brain morphometry and reductions in brain weight in young animals at a dose level which was slightly toxic to the maternal animal. In reproductive toxicity studies, thiamethoxam produced adverse effects in the testes and sperm of F_1 offspring at non-maternally toxic dose levels. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Mixers, loaders, applicators handling thiamethoxam and workers re-entering treated areas are not expected to be exposed to levels of thiamethoxam that will result in an unacceptable risk when Mainspring X Insecticide is used according to label directions and restricted to greenhouse potted ornamentals.

The personal protective equipment on the product labels and the additional mitigation measures are adequate to protect workers.

Residential and bystander exposure is not of concern.

7.2 Environmental Risk

For a summary of environmental risk to pollinators, refer to PRVD2017-24. For a summary of environmental risk to aquatic invertebrates, refer to PSRD2018-02.

For beneficial arthropods other than pollinators, thiamethoxam presents a potential risk from greenhouse use. Therefore, in order to inform users of the potential risk to these beneficial arthropods used in greenhouse production, statements are required on the label.

7.3 Value

Mainspring X Insecticide is a tool for use on greenhouse ornamentals to control or suppress aphids, dipteran leafminers mealybugs, soft scales, thrips and whiteflies which are prevalent pests in the greenhouse industry. It also is a new mode of action for use against dipteran leafminers, mealybugs and thrips on greenhouse ornamentals, and will aid in resistance management for these crop-pest combinations.

8.0 Proposed Regulatory Decision

With respect to greenhouse non-food crops uses of thiamethoxam, under the authority of section 8 of the *Pest Control Products Act*, the PMRA is proposing a three-year registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use product Mainspring X Insecticide. This consultation is carried out under 28(1)(a) of the *Pest Control Products Act*.

List of Abbreviations

AD	administered dose
ADI	acceptable daily intake
A/G ratio	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
ATPD	Area treated per day
BrdU	bromodeoxyuridine
BROD	7-benzyloxyresorufin-O-debenzylase
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CCl_4	carbon tetrachloride
cm^2/h	centimetres squared per hour
CNS	central nervous system
DA	Dermal absorption
DFR	Dislodgeable foliar residue
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
eNOS	endothelial nitric oxide synthase
EROD	7-ethoxyresorufin-O-deethylase
F_0	parental generation
F_1	first generation
F_2	second generation
fc	food consumption
fe	food efficiency
FOB	functional observational battery
g	gram(s)
GD	gestation day
GGT	gamma-glutamyl transferase
GST	glutathione S-transferase
ha	Hectare
HC	historical control
HDL	high density lipoprotein
HDT	highest dose level tested
HDW	hemoglobin distribution width
Hct	hematocrit
Hgb	hemoglobin
hr(s)	hour(s)
iNOS	inducible nitric oxide synthase
i.p.	intraperitoneal
kg	kilogram(s)
kg a.i./ha	Kilograms of active ingredient per hectare
kg ai/L	Kilograms of active ingredient per litre

kg bw	Kilograms of bodyweight
L	litre(s)
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDL	low density lipoprotein
LMA	locomotor activity
L-NAME	N-Nitroarginine methyl ester
LOAEL	lowest observed adverse effect level
MAS	maximum average score
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
M/L	Mixer/loader
M/L/A	Mixer/loader/applicator
mm	millimetre(s)
mM	millimole(s)
MMAD	mass median aerodynamic diameter
mg/kg ai/d	Milligrams per kilogram of active ingredient per day
mg/kg bw	Milligrams per kilogram of bodyweight
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
mg/kg/day	Milligrams per kilogram per day
MOE	margin of exposure
m.p.	Mechanically-pressurized
MRID	Master Record Identifier number
NO	nitrogen oxide
NOAEL	no observed adverse effect level
NOAEC	No observed adverse effect concentration
N/S	not stated
NT	Neurotoxicity
p.	Manually-pressurized
P	parental generation
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	post-natal day
PNS	peripheral nervous system
ppm	parts per million
PPE	Personal protective equipment
PROD	pentoxyresorufin-O-depentylase
REI	Restricted-Entry Interval
RBC	red blood cells
RfD	reference dose
SE	Suspo-emulsion
SER	smooth endoplasmic reticulum
SRBC	sheep red blood cell
SU	Suspension
TC	Transfer coefficient

THE	Thiamethoxam
TNFα	tumour necrosis factor alpha
TUNEL	terminal deoxynucleotidyl transferase mediated dUTP nick end labeling
UDP	uridine diphosphate
UTP	uridine triphosphate
µg/day	Micrograms per day
µg/cm^2	Micrograms per centimetres squared
µg/kg ai	Micrograms per kilogram of active ingredient
USC	Use-site category
WBC	white blood cells
WG	Wettable granule
wc	water consumption
wk(s)	week(s)
wt(s)	weight(s)
µg	microgram(s)
µL	microliter(s)
♂	males
♀	females
↑	increased
↓	decreased

Appendix I Tables and Figures

Table 1 Select Thiamethoxam Metabolites

Syngenta Code	Chemical Name (IUPAC)
CGA265307	*N*-(2-Chlorothiazol-5-ylmethyl)-*N'*-nitroguanidine
CGA322704	*N*-(2-Chlorothiazol-5-ylmethyl)-*N'*-methyl-*N"*-nitroguanidine
CGA330050	3-(2-Chlorothiazol-5-ylmethyl)-[1,3,5]-oxadiazinan-4-ylidene-N-nitroamine
CGA353968	1-(2-Chlorothiazol-5-ylmethyl)-3-methylurea
R6	2-Acetylamino-3-[5-(5-methyl-4-nitroimino[1,3,5]oxadiazinan-3-ylmethyl)-thiazol-2-ylsulfanyl]-propionic acid

Table 2 Toxicology Profile of Technical Thiamethoxam (CGA 293343)

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted. Effects above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type Species/ PMRA No.	Study Results
Toxicokinetic Studies	
The absorption, distribution, metabolism, and excretion of thiamethoxam were investigated in rats and mice. Tif:RAIf rats (♂/♀) received gavage doses of thiamethoxam labelled with ^{14}C on either the oxadiazine or thiazole ring as a single low (0.5 mg/kg bw) dose, a single high (100 mg/kg bw) dose or as a single low dose following pre-treatment with unlabelled test material at the low dose for two wks. Additional animals received the low dose via a single intravenous administration. Biliary excretion was also assessed in animals that were bile duct-cannulated. Thiamethoxam was rapidly and extensively absorbed and widely distributed to tissues. Blood concentrations peaked within 4 hrs of dosing. Highest tissue concentrations were detected in skeletal muscle. Elimination was rapid; within 24 hrs of dosing, the majority of radioactivity (84–95% of the AD) was excreted in urine, with smaller amounts in the feces. Less than 0.2% of the AD was detected in expired air. Half-lives of elimination from tissues ranged from 2–6 hrs and residues in tissues 7 days post-dosing were low. Unchanged thiamethoxam accounted for most (69–83%) of the AD excreted in urine; only two metabolites, CGA322704 and CGA265307, accounted for 5–13% and up to 2% of the AD, respectively. There were fewer fecal metabolites isolated; however, the main constituents paralleled those found in urine. Biliary metabolites were fewer, but the main constituents were unchanged thiamethoxam and CGA322704. There were no significant differences in absorption, distribution, profile of metabolites, or excretion between sexes, or among the dosing regimens. (PMRA No. 1178128, 1178129, 1178149) MAG Tiflbm:MAG mice (♂) received gavage doses of thiamethoxam labelled with ^{14}C on the thiazole ring daily for 14 days by gavage at a dose level of 118 mg/kg bw/day. Thiamethoxam was rapidly excreted, predominantly in the urine. Approximately 72% of the AD was excreted in the urine, and 19% was excreted in the feces. A small but measurable amount was detected in expired air (approximately 0.2% of the AD). A large number of metabolites were isolated from the urine and feces; however, only three constituents in urine accounted for a significant amount of the AD. The predominant constituent was unchanged thiamethoxam, accounting for 33–41% of the AD. The two principal metabolites were CGA322704 (8–12% of the AD) and CGA265307 (9–18% of the AD). One additional significant metabolite (R6, approximately 2% of the AD) was isolated from feces. (PMRA No. 1178132)	

Study Type Species/ PMRA No.	Study Results
TIF:MAG mice (♂) received dietary administration of thiamethoxam radiolabelled with ^{14}C on the oxadiazine ring for 29 days at dose levels of 0, 17, 81, or 364 mg/kg bw/day. Animals received a gavage dose of 20 mg/kg bw radiolabelled test material one day after the end of this dosing period. A second radiolabelled dose was administered 72 hrs after this dose. Absorption (based on urinary excretion) was approximately 70% regardless of dose level. Approximately 70% of the AD was excreted via urine over a 72-hr period, with fecal excretion accounting for the remainder regardless of dose level. The majority of urinary and fecal excretion occurred within 24 hrs of dosing. Unchanged thiamethoxam accounted for the majority of urinary radioactivity, while both CGA322704 and CGA265307 (main urinary and fecal metabolites) and CGA353968, (minor urinary and fecal metabolite) were present. In plasma 6 hrs post-dosing, CGA265307 was the major metabolite (43–55% of radioactivity in plasma) and unchanged thiamethoxam and metabolite CGA322704 accounted for 17–26%, and 20–26% of plasma radioactivity, respectively. Bile contained low levels of unchanged thiamethoxam, CGA265307 and CGA322704, whereas a metabolite called R6 accounted for 15–22% of the AD. Metabolic profiles in bile and plasma samples were not impacted by dose level. Liver contained low levels of unchanged thiamethoxam, CGA265307 and CGA322704 at 6 hrs post-dosing. (PMRA No. 859906) ^{14}C-radiolabelled (oxadiazine ring) thiamethoxam was administered to ♂ TiF:MAG mice and ♂ Tif:RAI rats by gavage at a dose of 100 mg/kg bw and animals were sacrificed at several intervals up to 24 hrs post-dosing. Maximum blood concentrations were reached at 0.5 hrs (mice) and 6 hrs (rats) after administration. Half-lives of elimination from blood were 4 (mice) and 3 (rats) hrs. Unchanged thiamethoxam was the major component in blood extracts (78% mice, 82% rats). In mice, CGA322704, CGA265307 and CGA330050 were detected at comparable levels (10–15%). In rats, CGA322704 was detected in blood (16%) with only trace amounts of CGA265307 (0.3%). CGA330050 was not detected. (PMRA No. 859910, 859911) Tif:RAIf rats (♂) and Tif:MAG mice (♂) received ^{14}C-radiolabelled thiamethoxam (oxadiazine ring) via diet at dose levels of 2500 (mice) and 3000 (rats) ppm for 1 or 10 wks. Thiamethoxam and metabolites CGA322704, CGA265307 and CGA330050 were evenly distributed between red blood cells and plasma. A species difference in metabolism was observed. In mice, the plasma concentrations of thiamethoxam declined and those of CGA322704 and CGA265307 increased with increased duration of dosing, whereas in rats, thiamethoxam concentrations in plasma increased approximately 2.7-fold and those of the metabolites decreased with extended dosing. After 10 wks of dietary administration, CGA265307 was present in mouse plasma at 108-fold higher concentrations than in rat plasma. (PMRA No. 859909) Liver fractions extracted from rat, mouse and human tissue preparations were used to compare the in vitro liver metabolism of thiamethoxam across species. Depending on the metabolism pathway involved (either via oxidative loss of the oxadiazine ring to form CGA322704 or via oxidative N-demethylation to form CGA330050), metabolic rates in mouse liver were 54-fold (via CGA322704) and 87-fold (via CGA330050) higher than those in rat liver and 371-fold and 238-fold higher respectively than those in human liver. (PMRA No. 859909) ^{14}C-radiolabelled thiamethoxam (oxadiazine ring) was administered by gavage to Tif:MAG mice (♂/♀) as a single dose of 0.5, or 100 mg/kg bw with sacrifice 3 days later. Absorption was high (74–93% of the AD) and was similar between sexes and dose groups and did not appear to be saturated at the high dose. At the low dose, tissue residues 72 hrs following administration were low with highest amounts in liver. At the high-dose, residues in tissues 72 hrs post-dosing were about 200-times higher corresponding to the 200-fold increase in dose. Liver showed the highest residue levels. ♀ retained greater quantities of radioactivity than ♂. For all dose groups, total body radioactivity was ≤ 1% of AD at the 72-hr sacrifice. (PMRA No. 859907)

Study Type Species/ PMRA No.	Study Results
^{14}C-radiolabelled thiamethoxam (oxadiazine ring) was administered as a single gavage dose at 0.5 or 100 mg/kg bw to Tif:MAG mice (♂/♀) with sacrifice 3 days later. Metabolite patterns in urine and feces were independent of sex and dose. Unchanged thiamethoxam was the major component in excreta accounting for 28–44% of the AD. Major metabolites in excreta were CGA265307 and CGA322704 accounting for 16–22% and 12–18% of the AD, respectively. (PMRA No. 859908) In a special metabolism study, plasma and liver metabolites of thiamethoxam in rats and mice were compared after dietary administration for 1 wk up to 50 wks. Blood and liver samples from several dietary studies were used for this study. After 50 wks of thiamethoxam administration, concentrations of thiamethoxam in plasma were relatively similar in both species whereas the concentrations of metabolites were noticeably greater in mouse plasma than in rat plasma. The concentrations of CGA 265307 were approximately 22-fold greater in mouse plasma than in rat plasma after 1 wk of administration. After 10 wks administration, the concentration of CGA 265307 in mouse plasma had increased approximately 3.6-fold compared to after 1 wk of administration, whereas that in rat plasma had reduced. Plasma concentrations of CGA265307 and CGA330050 were up to 140-fold and 15-fold greater, respectively, in mice than rats. In Tif:MAG and CD-1 mice fed a diet containing 2000 ppm of the metabolite CGA322704 for up to 20 wks, only CGA322704 and CGA265307 were detected in plasma. The major difference between the metabolism of rats and mice is the production of metabolite CGA330050 in mice. (PMRA No. 859912)	
Acute Toxicity Studies	
Oral Mice, CD-1 PMRA No. 1178092	LD_{50} = 783/964 mg/kg bw ♂/♀ Combined LD_{50} = 871 mg/kg bw All deaths occurred within 1 day of dosing. Clinical signs noted on the day of dosing included clonic convulsions, ↓ spontaneous movement or prone position. Bwg was ↓ in surviving ♀ on the day following dosing. Moderately toxic.
Oral Rats, Sprague-Dawley PMRA No. 1178091	LD_{50} = 1563 mg/kg bw All deaths occurred within 6 hrs of dosing. Clinical signs noted on the day of dosing included ptosis, ↓ spontaneous movement and tonic convulsions. Bwg was ↓ for 2 days following dosing in all animals. Slightly toxic.
Oral (Metabolite CGA322704) Rats, Sprague-Dawley PMRA No. 1178093	LD_{50} > 2000 mg/kg bw No mortalities occurred. Clinical signs included tremors, piloerection, and hunched posture in all animals that recovered by day 1. Low toxicity.
Dermal Rats, Sprague-Dawley PMRA No. 1178094	LD_{50} > 2000 mg/kg bw No mortalities, clinical signs of toxicity or effects on bw. Low toxicity.
Inhalation (nose-only)	LC_{50} > 3.72 mg/L

Study Type Species/ PMRA No.	Study Results
Rats, Sprague-Dawley PMRA No. 1178095	No mortality or clinical signs of toxicity. Slightly ↓ bw in 2 high-dose ♀ on study day 7, recovery noted by day 14. Low toxicity.
Eye irritation Rabbits, Japanese White PMRA No. 1178096	MAS = 0 MIS = 10.0 (1 hr) Slight conjunctival redness and swelling observed at 1 hr with eye closure and more than normal discharge. All signs of irritation absent at 24 hrs. Minimally irritating.
Skin irritation Rabbits, Japanese White PMRA No. 1178097	MAS = 0 MIS = 0 No signs of irritation in any of the animals tested. Non-irritating.
Skin sensitization (Maximization) Guinea pigs, Pirbright White PMRA No. 1178099	Not a dermal sensitizer.
90-day oral (dietary) Mice, Tif:MAGf PMRA No. 1178100, 1178101	NOAEL = 14/19 mg/kg bw/day ♂/♀ LOAEL = 176/231 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ hepatocellular hypertrophy; ↓ kidney wt (♂).
28-day oral (gavage), range-finding Rats, Tif:RAlf, ♂ PMRA No. 1178137	NOAEL not established as this is a range-finding study. 100 mg/kg bw/day: hyaline change of renal tubular epithelium (not present in high-dose animals); ≥ 300 mg/kg bw/day: ↑ liver wt, dilatation of renal pelvis, hepatocellular hypertrophy, ↑ adrenocortical fatty change; 1000 mg/kg bw/day: ↓ bwg, ↓ plasma protein, ↑ AST, ALP and GGT, ↓ thymus wt.
28-day oral (dietary) Rats, Tif:RAlf PMRA No. 1178135, 859918	NOAEL = 8.0/211 mg/kg bw/day ♂/♀ LOAEL = 82/763 mg/kg bw/day ♂/♀ Effects at LOAEL: minimal to moderate hyaline change of renal tubular epithelium, basophilic proliferation of renal tubules, minimal to moderate dilatation of renal pelvis (♂);↓ bw and fc, ↑ cholesterol, urea and sodium, ↑ liver wt, minimal to marked hepatic cell hypertrophy, minimal to moderate fatty change of adrenal cortex, ↑ absolute kidney wt, ↑ relative adrenal wt, minimal and focal cholangiofibrosis of intrahepatic bile ducts, minimal hepatocellular hypertrophy, minimal dilatation of renal pelvis,

Study Type Species/ PMRA No.	Study Results
	hypertrophy of thyroid follicular epithelium (♀). Treatment of ♂ resulted in an ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
90-day oral (dietary) Rats, Tif:RAlf PMRA No. 1178103, 859915	NOAEL = 1.7/93 mg/kg bw/day ♂/♀ LOAEL = 18/182 mg/kg bw/day ♂/♀ Effects at LOAEL: minimal to marked hyaline change in renal tubular epithelium, ↑ incidence of chronic tubular lesions, slight to marked renal pelvic dilatation (♂); ↓chloride, ↓ sodium, minimal lymphohistiocytic infiltration of the liver parenchyma, ↑ incidence of chronic tubular lesions and ↑ severity of nephrocalcinosis, extramedullary hematopoiesis in spleen, minimal to moderate fatty change in the adrenal cortex (♀) Treatment of ♂ at 5000 ppm resulted in a slightly ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
28-day oral (dietary) Dogs, Beagle PMRA No. 1178154	NOAEL not established (2/sex/dose level) 48/43 mg/kg bw/day (HDT): ↓ bw and fc, ↑ urea, ↓ thymus wt, minimal accumulation of pigment within hepatic Kupffer cells, minimal to moderate atrophy of splenic white pulp-marginal zone, minimal to marked thymic atrophy; ↑ Hct, Hgb and RBC, leukopenia, ↑ ALT, ↑ thyroid wt (♂); ↓ WBC counts, ↑ creatinine, ↓ absolute brain wt (♀).
90-day oral (dietary) Dogs, Beagle PMRA No. 1178104	NOAEL = 8.2/9.3 mg/kg bw/day ♂/♀ LOAEL = 32/34 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ prothrombin time, ↓ calcium and A/G ratio, ↓ ALT; ↓ cholesterol and phospholipids (♂); ↓ albumin (♀)
12-month oral (dietary) Dogs, Beagle PMRA No. 1178105	NOAEL = 4.1/4.5 mg/kg bw/day ♂/♀ LOAEL = 21/25 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ creatinine and urea, ↓ ALT; atrophy of seminiferous tubules (♂); transient ↓ in fc (♀)
28-day dermal Rats, Tif:RAlf PMRA No. 1178136	NOAEL = 250/60 mg/kg bw/day ♂/♀ LOAEL = 1000/250 mg/kg bw/day ♂/♀ Effects at LOAEL: slightly ↓ bw, minimal tubular hyaline change in kidneys (♂); ↑ glucose and ALP, minimal inflammatory cell infiltration in the liver, minimal hepatocellular degeneration (♀)
78-wk oral (dietary) Mice, Tif:MAGf PMRA No. 1178113, 1178114	NOAEL = 2.6/3.7 mg/kg bw/day ♂/♀ LOAEL = 64/88 mg/kg bw/day ♂/♀ Effects at LOAEL: hepatocellular hypertrophy, foci of cellular alteration, necrosis of single hepatocytes, ↑ mitotic activity, inflammatory cell infiltration, pigment deposition; Kupffer cell hyperplasia (♂); ↑ liver wt, ↑ incidence of hepatocellular adenomas (♀);

Study Type Species/ PMRA No.	Study Results
	≥ 162/215 mg/kg bw/day: ↑ incidence of hepatocellular adenocarcinomas; ↑ liver wt, ↑ incidence of hepatocellular adenomas (♂); 354/479 mg/kg bw/day: ↑ incidence of hepatocellular hypertrophy, necrosis of single hepatocytes, inflammatory cell infiltration and Kupffer cell pigmentation (9-month interim sacrifice), ↓ bw and bwg, extramedullary hematopoiesis in spleen, epithelial hyperplasia in glandular stomach. At dose levels of 0/0, 0.7/0.9, 2.6/3.7, 64/88, 162/215 or 354/479 mg/kg bw/day, respectively in ♂/♀: Hepatocellular adenoma ♂: 11/50[a], 5/50, 10/49, 17/50, 27/50**, 40/50** ♀: 0/50[a], 0/50, 0/50, 5/50*, 8/50**, 31/50** (HC range: ♂ 10-46%; ♀ 0-8%) Hepatocellular carcinoma ♂: 1/50[a], 4/50, 2/50, 5/50, 7/50*, 20/50** ♀: 0/50[a], 0/50, 0/50, 0/50, 2/50, 11/50** (HC range: ♂ 0-24%; ♀ 0-2%) Combined (adenoma or carcinoma) ♂: 12/50[a], 7/50, 12/50, 19/50, 27/50**, 45/50** ♀: 0/50[a], 0/50, 0/50, 5/50*, 9/50**, 32/50** * $p < 0.05$ compared to control ** $p < 0.01$ compared to control [a] denotes a linear trend, $p < 0.01$ Evidence of oncogenicity**.**
2-yr oral (dietary) Rats, Tif:RAlf PMRA No. 1178121, 1178122, 1178123, 859916, 859917	NOAEL = 21/50 mg/kg bw/day ♂/♀ LOAEL = 63/155 mg/kg bw/day ♂/♀ Effects at LOAEL: slightly ↑ wc, ↑ incidence of lymphocytic infiltration in kidneys and chronic nephropathy (♂);↓ bwg, ↑ incidence of foci of cellular alteration in liver, ↑ incidence of chronic tubular lesions in kidneys (♀); No evidence of oncogenicity. Treatment of ♂ at 1500 ppm for 52 weeks or 2 years resulted in a slightly ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
Bacterial reverse mutation PMRA No. 1178144	Negative in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537, and in E. Coli WP2uvrA with and without metabolic activation.
Bacterial reverse mutation PMRA No. 1188411	Negative in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 with and without metabolic activation.
In vitro chromosome aberrations PMRA No. 1178145	Negative in Chinese hamster V79 cells with and without metabolic activation.

Study Type Species/ PMRA No.	Study Results
In vitro unscheduled DNA synthesis PMRA No. 1178148	Negative in primary hepatocytes from Tif:RAlf rats with and without metabolic activation.
In vitro chromosome aberrations PMRA No. 1178146	Negative in Chinese hamster ovary cells (CCL 61) with and without metabolic activation.
In vivo bone marrow micronucleus PMRA No. 1178147	Negative in Tif:MAGf Mice with and without metabolic activation.
Range-finding oral (dietary) reproduction Rats, Tif:RAlf PMRA No. 1178127	NOAEL not established as this is a range-finding study. ≥ 75 mg/kg bw/day: ↓ bwg during pre-mating period (♀); ≥ 126/136 mg/kg bw/day : ↓ fc during pre-mating period; 241/275 mg/kg bw/day (highest dose level tested): ↓ bwg during pre-mating period (♂); ↓ bwg during lactation (♀).
Oral (dietary) two-generation reproduction Rats, Tif:RAlf PMRA No. 1178124,1178125, 1178126, 1178143, 1063161, 1996080, 1997353	Parental Toxicity NOAEL = 1.8/202 mg/kg bw/day ♂/♀ LOAEL = 61/not determined (HDT) ♂/♀ Effects at LOAEL: ↑ incidence of hyaline change in renal tubules (F_0 and F_1) and renal tubular casts (F_0) (♂); 158/202 mg/kg bw/day: slightly ↓ bwg (F_0 and F_1), ↑ incidence of renal tubular casts (F_1) (♂); hyaline change in renal tubules (1 F_1 ♀) (♀). Offspring Toxicity NOAEL = 2.4 mg/kg bw/day LOAEL = 79 mg/kg bw/day Effects at LOAEL: ↓ bw and bwg (F_{2a} and F_{2b}, PNDs 7, 14 and/or 21) (♀); 202 mg/kg bw/day: ↓ bw and bwg (F_{1a}, F_{1b}, F_{2a} and F_{2b} PNDs 7, 14 and/or 21). Reproductive Toxicity NOAEL = 0.6/79 mg/kg bw/day ♂/♀ LOAEL = 1.8/202 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ incidence and severity of atrophy of the seminiferous tubules in the testes (F_1: 6/30, 8/30, 15/30, 24/30 and 14/30 at 0, 10, 30, 1000 and 2500 ppm) (♂); slightly ↓ mean litter sizes at birth (F1a and F1b) (♀); 158 mg/kg bw/day: ↓ absolute testicular wts (F_1) (♂).

Study Type Species/ PMRA No.	Study Results
	Evidence of sensitivity of the young (testis effects observed only after in utero and postnatal exposure). Equivocal results in sperm motility (↓ at all dose levels tested with no apparent dose-relationship), evaluated further in a separate, complementary study that revealed no effect of treatment on sperm motility; however, the study was conducted only on F_0 animals whereas seminiferous tubule atrophy was observed in F_1 animals.
Complementary study: Investigation on sperm cells (10-wk dietary) Rats, Tif:RAlf PMRA No. 1178125	Supplemental 165 mg/kg bw/day (HDT): ↓ bw, ↓ bwg, ↓ fc. No treatment-related effects on total number of testicular sperm cells or sperm cell concentration in cauda epididymis luminal fluid, epididymal sperm motility, or sperm morphology.
Oral (dietary) two-generation reproduction Rats, Tif:RAlf PMRA No. 859896 to 859905	Parental Toxicity NOAEL = 3.0/3.1 mg/kg bw/day ♂/♀ LOAEL = 62/62 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ incidence of renal tubular casts and hyaline droplets (F_0 and F_1) (♂); ↓ absolute pituitary wt (15%) (F_0) (♀); 156/159 mg/kg bw/day: ↑ relative liver wts (F_1); ↓ bw, bwg and fc (F_0), ↑ relative adrenal and kidney wts (F_0), ↑ adrenal cortex hyperplasia (F_0) (♂). Offspring Toxicity NOAEL = 62/62 mg/kg bw/day ♀ LOAEL = 156/159 mg/kg bw/day ♀ Effects at LOAEL: pup deaths (wks 3 to 4), ↓ litter wt (F_1 and F_2, during lactation); delayed preputial separation (F_2 ♂). Reproductive Toxicity NOAEL = 1.2/159 mg/kg bw/day ♂/♀ LOAEL = 3.0/not determined (HDT) ♂/♀ Effects at LOAEL: ↓ total sperm and number of sperm/gram of testes wt (F_1) (♂); ≥ 62 mg/kg bw/day: ↑ relative epididymides and testes wts (F_1) (♂); 156 mg/kg bw/day: slightly delayed preputial separation (F_1), ↑ absolute epididymides wt (F_1), ↑ seminal vesicle wt (F_0), ↑ sperm with reduced straight line, curvilinear, and average path velocities (F_1), ↑ incidence of abnormal sperm (F_0), minimal germ cell loss/disorganization and Sertoli cell vacuolation in testes (F_1) (♂). Evidence of sensitivity of the young (sperm effects observed only after in utero and post-natal exposure).
Range-finding oral (gavage) developmental toxicity	NOAEL not established as this is a range-finding study. Maternal Toxicity:

Study Type Species/ PMRA No.	Study Results
Rats, Tif:RAlf PMRA No. 1178116 and 1178117	≥ 500 mg/kg bw/day: ↓ bwg (during first half of dosing), ↓ fc (during dosing); 1000 mg/kg bw/day: ↓ bw (during first half of dosing), piloerection, hypoactivity and hunched posture (during dosing). Developmental Toxicity: 1000 mg/kg bw/day: ↓ fetal bw.
Oral (gavage) developmental toxicity Rats, Tif:RAlf PMRA No. 1178115	Maternal Toxicity: NOAEL: 30 mg/kg bw/day LOAEL: 200 mg/kg bw/day Effects at LOAEL: ↓ bwg (during first half of dosing), ↓ fc (during dosing); Developmental Toxicity: NOAEL: 200 mg/kg bw/day LOAEL: 750 mg/kg bw/day Effects at LOAEL: ↓ fetal bw, ↑ incidence of skeletal findings (asymmetrically shaped sternebrae 6 and irregular ossification of the occipital bone). Developmental toxicity in the presence of maternal toxicity.
Range-finding oral (gavage) developmental toxicity Rabbits, Russian Chbb:HM PMRA No. 1178119, 1178120	NOAEL not established as this is a range-finding study. Maternal Toxicity: ≥ 50 mg/kg bw/day: ↓ bwg and fc (during dosing); ≥ 150 mg/kg bw/day: ↓ bw (during dosing), ↓ mean gravid uterus wt; 500 mg/kg bw/day: all dams died between GDs 10 and 16. Developmental Toxicity: ≥ 150 mg/kg bw/day: ↓ fetal bw.
Oral (gavage) developmental toxicity Rabbits, Russian Chbb:HM PMRA No. 1178118	Maternal Toxicity: NOAEL = 50 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at LOAEL: 3 unscheduled deaths, hemorrhagic uterine contents, hemorrhagic discharge in the perineal area, ↓ bw (during dosing), ↓ fc (during dosing), ↑ post-implantation loss. Developmental Toxicity: NOAEL = 50 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at LOAEL: ↓ fetal bw, slightly ↑ incidence of skeletal findings (fused or asymmetrically shaped sternebrae) - not statistically significant, ↑ on fetal basis only, and slightly outside of the upper end of the HC

Study Type Species/ PMRA No.	Study Results
	range). Developmental toxicity in the presence of maternal toxicity.
Acute oral (gavage) neurotoxicity Rats, Sprague-Dawley PMRA No. 1178165	NOAEL = 100 mg/kg bw LOAEL = 500 mg/kg bw Effects at LOAEL: drooped palpebral closure, ↓ rectal temperature, ↑ forelimb grip strength and ↓ locomotor activity; No evidence of neuropathology.
13-wk oral (dietary) neurotoxicity Rats, Sprague-Dawley PMRA No. 1178133	NOAEL = 95/216 mg/kg bw/day ♂/♀ (HDT) There were no treatment-related systemic or neurological effects observed in this study.
Range-finding Oral (dietary) Developmental Neurotoxicity Rats, Alpk:APfSD PMRA No. 1036615	NOAEL not established as this is a range-finding study. Maternal: <u>213 mg/kg bw/day</u>: ↓ bw (slight at this dose level; during gestation) and fc (GD11-18, PND 8-11); <u>362 mg/kg bw/day</u>: ↓ bw and fc (during gestation and lactation). Offspring: <u>213 mg/kg bw/day:</u> ↓ pup bw (at birth); ↓ bwg (PND 15 and 22) (♂). <u>362 mg/kg bw/day</u>: ↓ pup bw and bwg (at birth and throughout the postnatal period).
Oral (dietary) developmental neurotoxicity Rats, Alpk:APfSD PMRA No. 1036606 to 1036611, 1036617 to 1036621	Maternal Toxicity NOAEL = 35 mg/kg bw/day LOAEL = 298 mg/kg bw/day Effects at LOAEL: ↓ bw, bwg and fc (during gestation and lactation). Offspring Toxicity NOAEL = 35 mg/kg bw/day LOAEL = 298 mg/kg bw/day Effects at LOAEL: ↓ pup bw, ↓ absolute brain wt (PND 12), significantly ↓ dorsal cortex thickness, thalamus width, thalamus/cortex overall width and hippocampus width (PND 63); ↓ absolute brain wt (PND 63), significantly ↓ molecular layer of the cerebellum and the cerebellum length (PND 12), delayed sexual maturation, significantly ↓ piriform cortex thickness, corpus callosum thickness and thalamus height (PND 63) (♂); significantly ↓ thalamus width (PND 12) (♀). Serious effects in the young in the presence of maternal toxicity.
Effects on biochemical	20 mg/kg bw/day: slightly ↑ PROD and BROD activity (♀);

Study Type Species/ PMRA No.	Study Results
parameters in the liver, 14-day dietary study Mice, Tif:MAGf PMRA No. 1178140	≥ 74/92 mg/kg bw/day: ↑ PROD and BROD activity; slightly ↑ PROD and BROD activity (♂); slightly ↑ EROD activity (♀); 367/486 mg/kg bw/day: slightly ↑ liver wts, moderate ↑ in cytochrome P450 content, slight to moderate ↑ in activity of several microsomal enzymes, slightly ↑ cytosolic glutathione-S-transferase; ↑ PROD and BROD activity (♂); slightly ↑ microsomal protein content in liver (♀).
Assessment of hepatic cell proliferation, dietary study (3, 7, 13, 27 or 59 days) Mice, Tif:MAGf PMRA No. 1178141	20 mg/kg bw/day: ↑ BrdU labelling index (day 7) (♀); 72/87 mg/kg bw/day: ↑ BrdU labelling index (♂: days 13, 27 and 59; ♀: days 7 and 13); 386/463 mg/kg bw/day: ↑ liver wts, speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation at 59 days, ↑ BrdU labelling index (days 3, 7, 13 and 59).
Determination of induction of liver enzymes, dietary study (7, 14, 28 or 60 days) Mice Tif:MAG ♂ PMRA No. 859919	≥ 448 mg/kg bw/day: slightly ↓ cytosolic protein content (28 days), slightly ↓ glutathione reductase activity (60 days), ↑ glutathione S-transferase activity and γ-glutamylcysteine synthetase activity (all timepoints); 976 mg/kg bw/day: slightly ↓ cytosolic protein content (60 days).
Determination of parameters indicative for oxidative stress, dietary study (7, 14, 28 or 60 days) Mice, Tif:MAG ♂ PMRA No. 859920	No treatment-related mortalities or clinical signs of toxicity were noted. ≥ 448 mg/kg bw/day: slightly ↑ mean free 8-isoprostane F2α in plasma (day 14 onwards), ↑ mean hepatic concentration of reduced glutathione (all timepoints); 976 mg/kg bw/day: ↓ final bw, ↓ bwg (throughout study), slightly ↓ mean 8-isoprostane F2α concentration in the liver (7 days), slightly ↓ mean hepatic concentration of oxidized glutathione (at 28 days). There was no indication of oxidative stress in the livers of treated mice, as indicated by little change in antioxidants (α-tocopherol) or indicators of peroxidation (oxidized glutathione and malondialdehyde).
Comparative hepatotoxicity of thiamethoxam in weanling (21-day old) and adult mice, 7-day dietary study Mice, Tif:MAG ♂ PMRA No. 859925	There were no mortalities, clinical signs of toxicity, and effects on body weight or alterations in plasma levels of liver enzymes in adult or weanling mice noted in this study. Adults: ≥ 62 mg/kg bw/day: ↓ cholesterol levels; 314 mg/kg bw/day: centrilobular vacuolation and ↓ eosinophilia of the liver. Weanlings: ≥ 151 mg/kg bw/day: ↓ cholesterol levels; 314 mg/kg bw/day: centrilobular vacuolation and ↓ eosinophilia of the

Study Type Species/ PMRA No.	Study Results
	liver (same frequency but less severe than that noted in adults). Concentrations of thiamethoxam and CGA265307, CGA322704 and CGA330050 were higher in all weanling animals compared to adults but without increased liver toxicity.
Histochemical assessment of hepatic apoptosis, dietary study (3, 7, 13, 27, 59 days, 9 months) Mice, Tif:MAG ♂ PMRA No. 859914	In this retrospective examination, the following was noted from dietary studies in mice of various durations: ≥ 25 mg/kg bw/day: significantly ↑ numbers of apoptotic figures, mostly localized centrilobularly often adjacent to central veins (after 59 days); 314 mg/kg bw/day: significantly ↑ numbers of apoptotic figures, mostly localized centrilobularly, often adjacent to central veins (after 9 months).
Comparative hepatotoxicity of metabolites in 2 different strains of mice, dietary study (1, 10, 20 wks) Mice, Tif:MAGf and CD-1 ♂ PMRA No. 859927, 859928, 859933, 859934, 859935	Animals received 0 or 2500 ppm thiamethoxam (~ 0 or 314 mg/kg bw/day), 2000 ppm CGA322704, or 500 ppm CGA265307 for up to 20 wks. There were no treatment-related clinical signs of toxicity, effects on hematology, macroscopic findings or mortalities noted in this study. No ↑ in BrdU labelling index in CGA322704-treated mice at any time point. Tif:MAGf mice: CGA322704: slightly ↓ bw, ↓ fe (wks 1–4, lesser during wks 5–8), ↓ kidney wts (1 and 20 wks), ↑ liver wts (10 and 20 wks); CGA265307: slightly ↑ bw, ↑ liver wts (10 wks), ↓ median BrdU labelling index (10 wks); thiamethoxam: ↓ total protein and plasma cholesterol (all timepoints), ↓ albumin and ↑ inflammatory cell infiltration and median BrdU labelling index (20 wks), ↑ hepatocellular apoptosis (10 wks), ↓ kidney and ↑ liver wts (1, 10 and 20 wks), ↑ ALT, hepatocellular necrosis and hepatocellular hypertrophy characterized by enlarged centrilobular/ midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (10 and 20 wks). CD-1 mice: CGA322704: ↓ bw (10 animals sacrificed prematurely in wks 10 and 11), ↓ fe (wks 1–4, lesser during wks 5–8), ↓ kidney wts (1, 10 and 20 wks), ↓ liver wts (1 wk); CGA265307: ↓ kidney wts (10 wks); thiamethoxam: slightly ↓ bw, slightly ↓ plasma albumin, total protein and plasma cholesterol (all timepoints), ↑ ALT, ↓ kidney wts, ↑ hepatocellular necrosis, ↑ hepatocellular apoptosis and pigmentation, ↑ median BrdU labelling index and ↑ hepatocellular hypertrophy characterized by enlarged centrilobular/midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (10 and 20 wks), ↑ inflammatory cell infiltration (20 wks). Similar liver toxicity was noted in 2 strains of mice; mainly attributed to thiamethoxam and not the main metabolites.
Assessment of hepatic cell proliferation, 40-wk dietary study Mice, Tif:MAG ♂ PMRA No. 859932	≥ 62 mg/kg bw/day: ↑ hepatocellular mitotic index (BrdU labelling index).

Study Type Species/ PMRA No.	Study Results
(Satellite study of PMRA No. 859923)	
Role of nitric oxide in the development of hepatotoxicity, in vitro study Mice, Tif:MAG PMRA No. 859924	The metabolite CGA265307 inhibited nitric oxide synthase to a similar extent as the selective iNOS inhibitor L-NAME. Thiamethoxam and metabolites CGA322704, CGA330050, NOA421276, NOA412275, and NOA404617 were not as effective at inhibiting iNOS over a range of substrate concentrations from 0–0.5 mM.
Role of nitric oxide in the development of hepatotoxicity, dietary study Mice, Tif:MAG ♂ PMRA No. 859924	Animals received 0 or 2000 ppm CGA652307 in diet for 7 days and were then injected i.p. with 10 uL/kg CCl_4, or 0, 10 or 20 uL/kg CCl_4 alone, by injection, In vivo experiment: CGA652307: no evidence of liver toxicity. CGA652307 plus i.p. CCl_4: ↑ ALT (greater than animals given i.p. CCl_4 alone), inhibition of nitric oxide synthase (similar extent as the selective iNOS inhibitor L-NAME), microscopic examination of the liver revealed evidence of liver toxicity (further details not available). ≥10 µL/kg CCl_4 i.p. alone: slightly ↑ ALT (maximal 16 hrs post-dosing), ↑ TNFα (16 hrs post-dosing); 20 µL/kg CCl_4 i.p. alone: ↑ ALT, ↑ serum levels of nitrite (20 hrs post-dosing). A reduction of iNOS or NO in vivo was not demonstrated in this study.
Determination of oxidative stress in the liver, dietary study (10, 20, 30, 40 or 50 wks) Mice, Tif:MAG ♂ PMRA No. 859921	There were no treatment-related mortalities or clinical signs of toxicity noted. ≥ 314 mg/kg bw/day: ↓ final bw, ↑ incidence of accentuated lobular pattern of the liver correlated with hepatic fatty change (after 10, 30 and 40 wks), ↑ hepatic oxidized glutathione (after 10 and 50 wks), ↑ mean hepatic γ-glutamylcysteine synthetase activity, mean hepatic glutathione S-transferase activity, mean hepatic concentration of reduced glutathione and hepatocellular hypertrophy and necrosis characterized by enlarged centrilobular/ midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (all time points); 684 mg/kg bw/day: ↑ incidence of hepatocellular apoptosis with mainly centrilobular location, slightly ↓ mean concentration of 8-isoprostane F2α in the liver (20 wks onward), ↑ hepatic oxidized glutathione (all time points).
Assessment of hepatic cell proliferation and apoptosis, dietary study (10, 20, 30, 40 or 50 wks) Mice, Tif:MAG ♂	There were no treatment-related clinical signs or deaths during the study. ≥ 62 mg/kg bw/day: hepatocellular necrosis affecting single cells or small groups of cells with mainly centrilobular localization and often accompanied by inflammatory cells (wk 40 onwards), accentuated lobular pattern of the liver, inflammatory cell infiltration of the liver correlated

Study Type Species/ PMRA No.	Study Results
PMRA No. 859923	with hepatic fatty change (wk 30 onwards), ↑ incidence and/or severity of pigmentation characterized by yellow/brown pigment granules in the cytoplasm of centrilobular hepatocytes (wk 50), ↑ median TUNEL area densities; ≥ 151 mg/kg bw/day: ↓ fc (wk 40 onward), ↑ AST (all timepoints) and ALT (all timepoints), ↑ incidence and/or severity of hepatocellular apoptosis affecting single cells or small groups of cells with mainly centrilobular localization (wks 20 and 30), ↑ median BrdU labelling index (wk 40 onwards); ≥ 314 mg/kg bw/day: ↓ bw (wk 50), ↓ fc (wk 9 onward), ↑ relative liver wt (wks 20 and 40), ↓ absolute kidney wt (wk 30 onward), ↓ relative kidney wt (wk 30 and 40), ↑ incidence of hepatocellular hypertrophy characterized by enlarged centrilobular/midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (wk 30 onward); 684 mg/kg bw/day: ↑ relative liver wt (wk 10 onward), ↓ absolute kidney wt (wk 10 onward), ↓ absolute spleen wt (wk 40), ↑ relative testis wt (wks 20 and 40).
Comparative hepatotoxicity of metabolites in two species of animals, dietary study Mice, Tif:MAG ♂; Rats, Tif:RA1f ♀ PMRA No. 859926	Study 1 (PMRA No. 859927, 859928, 859933, 859934, 859935): 2500 ppm thiamethoxam (~ 314 mg/kg bw/day), 2000 ppm CGA322704 or 500 ppm CGA265307 in ♂ mice for 1, 10 or 20 wks. 314 mg/kg bw/day thiamethoxam: ↓ plasma cholesterol and serum protein (wk 1 onward), ↑ ALT and hepatocellular hypertrophy, necrosis and apoptosis (wk 10 onwards), ↑ AST, inflammatory cell infiltration and pigmentation in the liver and hepatic cell replication rates (wk 20). CGA322704 and CGA265307: no evidence of liver toxicity. Study 2 - CGA330050: 0, 500 or 1000 ppm CGA330050 in ♂ mice for 1 or 10 wks ≥ 500 ppm: similar toxicity to mice dosed with thiamethoxam in Study 1 (↓ plasma cholesterol (4 and 10 wks); 1000 ppm: similar toxicity to mice dosed with thiamethoxam in Study 1 (↓ total protein (4 and 10 wks), ↑ hepatocyte hypertrophy characterized by enlarged, pale-staining centrilobular hepatocytes with a floccular or microvesicular cytoplasm, apoptotic hepatocytes showing single cell necrosis and ↑ cell replication rates (S-phase) in the liver (10 wks)). Study 3 - CGA330050: 0, 500 or 1000 ppm CGA330050 in ♀ rats for 1 wk ≥ 500 ppm: ↓ plasma cholesterol, ↑ ALT and AST. No effect on liver wt.
Assessment of replicative DNA synthesis, 28-day dietary study Rats, Tif:RAIf ♂ PMRA No. 1178139	Immunohistochemical staining of liver sections from control and high-dose (~ 711 mg/kg bw/day) ♂ for proliferating cell nuclear antigen gave no indication of a treatment-related ↑ in the fraction of DNA-synthesizing hepatocytes in S-phase.

Study Type Species/ PMRA No.	Study Results
Investigation of induction of liver enzymes, 10-wk dietary study Rats, Tif:RAIf ♀ PMRA No. 859922	No treatment-related effects noted on the liver protein content or levels of cytochrome P450, 7-ethoxy, 7-pentoxy and 7-benzyloxyresorufin-O-dealkylase, coumarin 7-hydroxylase, testosterone hydroxylation, lauric acid 11 and 12-hydroxylation, UDP-glucuronosyltransferase, reduced and oxidized glutathione or cytosolic γ-glutamylcysteine synthetase following exposure to thiamethoxam. ≥ 59 mg/kg bw/day: slightly ↓ activity of liver microsomal methoxyresorufin O-demethylase (1 wk); 180 mg/kg bw/day: slightly ↑ activity of liver cytosolic glutathione S-transferase, microsomal epoxide hydrolase and peroxisomal β-oxidation (10 wks).
Assessment of hepatic cell proliferation and apoptosis, up to 50 wks dietary study Rats, Tif:RAIf ♀ PMRA No. 859929, 859930, 859931	No treatment-related effects in clinical chemistry, urinalysis, organ weights, histopathology, hepatocyte proliferation, cell turn over or apoptosis noted in this study. ≥ 59 mg/kg bw/day: ↑ urinary volume (first 11 wks), significant ↑ in urinary pH (wk 11), ↓ mononuclear hepatocyte S-phase (up to 31 wks); 180 mg/kg bw/day: ↑ hunched posture or clinical signs of morbidity prior to sacrifice, ↑ mortality rate (up to 30 wks), ↓ bw, bwg and fc (first 3 wks), ↓ fe (first 13 wks), significant ↓ in urinary pH (21 to 42 wks), ↑ incidence of kidney lesions (dilated pelvis, enlarged, pale, roughened surface or discoloured), spleen (reduced size, pale), urinary bladder (distended, bloody urine) and thymus (small), ↓ mononuclear hepatocyte S-phase (11, 31, 41 and 51 wks), ↓ total number of apoptotic bodies (2 wks). Thiamethoxam treatment for up to 50 wks did not demonstrate specific toxicological effects in the livers of rats.
Summary of cholesterol data from various studies to identify patterns of effect which could be correlated with occurrence of tumours in long-term studies, dietary studies Mice, Tif:MAG and CD-1; Rats, Tif:RAIf PMRA No. 859895	50 wk dietary study in mice (PMRA No. 859923): A dose-dependent ↓ in plasma cholesterol levels starting at 500 ppm from 10 wks onward. 7-day dietary study in mice: ↓ plasma cholesterol levels after 1, 4 and 7 daily doses and ↓ HDL and LDL after 4 and 7 daily doses of 350 mg/kg bw/day. 20-wk dietary study of thiamethoxam and its metabolites in 2 strains of mice (PMRA No. 859927, 859928, 859933, 859934, 859935): ↓ cholesterol in both strains of mice at 2500 ppm for 1, 10 and 20 wks. Neither CGA322704 nor CGA265307 altered plasma cholesterol levels. 50-wk dietary study in rats (PMRA No. 859929, 859930, 859931): No treatment-related alterations in cholesterol levels in rats fed diets containing 0, 1000 or 3000 ppm for 1, 10, 20, 30, 40 or 50 wks. 10-wk CGA330050 dietary study in mice (PMRA No. 859926): Mice fed diets containing CGA330050 had ↓ plasma cholesterol following exposure to 500 and 1000 ppm for 1, 4 and 10 wks.

Study Type Species/ PMRA No.	Study Results
	4-wk dietary study with 2 wk recovery in mice: ↓ plasma cholesterol levels after 2500 ppm for 4 wks, recovery noted after 2 wks of control diet. HMG-CoA reductase activity in mice - in vitro: Neither thiamethoxam nor its metabolites inhibited the HMG-CoA reductase mediated-metabolism of HMG-CoA to mevalonate. HMG-CoA reductase activity in mice - in vivo: Administration of 2500 ppm in the diet for 20 wks did not affect HMG-CoA reductase activity. 3H-Mevalonate incorporation in mice - in vivo: No treatment-related alterations in cholesterol after 5000 ppm for 7 days whereas the level of squalene was ~4-fold ↑ in the livers from mice fed thiamethoxam compared to control animals.

Table 3 Toxicity Profile of End-Use Products (Mainspring X Insecticide)

Study Type/Animal/ PMRA No.	Study Results
Acute oral (Up-and-Down) Rat (Wistar) PMRA No. 2071414	LD50 (♂/♀) > 5000 mg/kg bw Low toxicity
Acute dermal Rat (Wistar) PMRA No. 2071415	LD_{50} (♂/♀) > 5000 mg/kg bw Low toxicity
Acute inhalation (nose-only exposure) Rat (Wistar) PMRA No. 2071416	LC_{50} (♂/♀) > 5.04 mg/L Low toxicity
Skin irritation Rabbit (New Zealand White) PMRA No. 2071417	MAS = 0 MIS = 0.33 (1 hr) Non-irritating

Study Type/Animal/ PMRA No.	Study Results
Eye irritation Rabbit (New Zealand White) PMRA No. 2071418	MAS = 1.56 MIS = 8.67 (1 hr) Minimally irritating
Skin sensitization (Buehler) Guinea Pig (LAL/HA/BR) PMRA No. 2071419	Not a dermal sensitizer

Table 4 Toxicology Reference Values for Use in Human Health Risk Assessment for Thiamethoxam

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary - general population	Developmental neurotoxicity study in rats	NOAEL = 35 mg/kg bw/day Brain wt reductions and morphometric changes	300
	ARfD = 0.1 mg/kg bw		
Repeated dietary - general population	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
	ADI = 0.004 mg/kg bw/day		
Short-, intermediate- and long-term dermal[2]	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
Short-, intermediate- and long-term inhalation[3]	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
Cancer	Not genotoxic and not oncogenic in rats. Liver tumours in mice linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite; threshold approach to cancer risk assessment taken.		

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

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

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 5 Mixer/Loader/Applicator Risk Assessment

Crop	Application Equipment	Application Rates [a] (kg ai/ha)	Area treated per day [b] (ha)	Dermal Exposure [c] (ug/kg bw/day)	Inhalation Exposure [d] (ug/kg bw/day)	Dermal MOE [e]	Inhalation MOE [f]	Combined MOE [g]
Foliar								
outdoor ornamentals	backpack	1.50E-04 kg a.i./L	150 L	0.05	0.02	26621	59147	18358
greenhouse ornamentals	m.p. handheld sprayer		3800 L	1.17	1.24	1025	969	498
	p. handheld sprayer		150 L	0.16	0.46	7563	2624	1948
Soil								
greenhouse ornamentals	backpack	1.50E-04 kg a.i./L	150 L	0.05	0.02	26621	59147	18358
	m.p. handheld sprayer		3800 L	1.17	1.24	1025	969	498
	p. handheld sprayer		150 L	0.16	0.46	7563	2624	1948

MOE = Margin of Exposure
[a] Maximum label rate.
[c] Maximum Area Treated Per Day based on PMRA HED ATPD Table, July 2010.
[d] Where dermal exposure µg/kg/day = (unit exposure × area treated per day × application rate × DA)/70 kg bw. A 2.5% Dermal Absorption (DA) factor was applied in the risk assessment.
[e] Where inhalation exposure µg/kg/day = (unit exposure x area treated per day × application rate)/70 kg bw.
[f] Based on a dermal NOAEL of 1.2 mg/kg/day and a target MOE of 300.
[g] Based on an inhalation NOAEL of 1.2 mg/kg/day and a target MOE of 300.
[h] Combined MOE = 1 /(1/MOE_D + 1/MOE_I).

Table 6 Postapplication Risk Assessment - Ornamentals

Crop	Application Rates [a] (kg ai/ha)	Activities	Transfer Coefficient (cm^2/hr)	DFR On Day 0 of final application	Dermal Exposure [b] (ug/kg bw/day)	Dermal MOE [c]
greenhouse ornamentals	0.15	disbudding, hand pruning and hand harvesting cut flowers	4000	0.75	8.57	140
		irrigation	1750	0.75	3.75	320
		all other activities	230	0.75	0.49	2435
outdoor ornamentals	0.15	irrigation	1750	0.46	0.30	3963
		all other activities	230	0.46	2.30	521

MOE = Margin of Exposure
[a] Maximum label rate assuming 1000L/ha; 15g a.i./100 L = 0.15 kg a.i./ha. Two applications 14 days apart were assumed.
[b] Where dermal exposure (µg/kg/day) = DFR × TC × 8 hr / 70 kg. A 2.5% dermal absorption factor was applied.
[c] Based on a dermal NOAEL of 1.2 mg/kg bw/day and a target MOE of 300.

Table 6 Fate and Behaviour in the Environment

Up to date information on the fate and behaviour of thiamethoxam and its transformation products can be found in PRVD2017-24 and PSRD2018-02.

Table 7 Predator and parasite toxicity information and risk assessment for Thiamethoxam, relevant for Mainspring X Insecticide risk assessment.

Species	Study [reference]	Toxicity endpoint	EEC	RQ (EEC/toxicity endpoint)	LOC exceeded
Thiamethoxam related toxicity information and risk assessment					
Predatory arthropod (*Coccinella septempunctata*)	Contact (thiamethoxam) [ERC2007-01]	LR_{50} = 12.4 g a.i./ha (reproduction capacity)	150 g ai/ha	12	YES
Predatory arthropod (*Typhlodromus pyri*)	Contact (thiamethoxam) [ERC2007-01]	LR_{50} = 41 g a.i./ha (fecundity)	150 g ai/ha	3.7	YES
Parasitic arthropod (*Aphidius rhopalosiphi*)	Contact (thiamethoxam) [ERC2007-01]	LR_{50} – 0.131 g a.i./ha (reproduction capacity)	150 g ai/ha	1145	YES
Note: The LOC is set to 2 for screening level risk assessment with *Typhlodromus pyri* and *Aphidius rhopalosiphi*. Higher tiered assessments use an LOC of 1.					

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
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1992074	2004, Batch Data, DACO: 2.13.3 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
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3.0 Environment

Refer to PRVD2017-24, PSRD2018-02, and ERC2007-01. In addition, the following information was used.

PMRA Document Number	**Reference**
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1552173 and 1529720	Validation of REM 179.03: Summary of Results of Fortified Specimens of Representative Plant Materials and Soil Analyzed According to REM 179.03. DACO: 8.2.2.3
1552176 and 1529724	Determination of CGA 293343 and CGA 322704 by HPLC - Potable Water and Surface Water. DACO: 8.2.2.3
1552177 and 1529725	Validation of Method REM 179.05 for Use With Surface Water - Validation by Analysis of Fortified Fortified Specimens and Determination of Recoveries
1552178 and 1529726	Validation of Method REM 179.05 - Validation By Analysis of Fortified Fortified Specimens and Determination of Recoveries (Potable Water). DACO: 8.2.2.3
1552179 and 1529727	Residue Analytical Method for the Determination of the Thiamethoxam Metabolites NOA-459602 and SYN-501406 in Water. DACO: 8.2.2.3

4.0 Value

PMRA Document Number	Reference
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B. ADDITIONAL INFORMATION CONSIDERED

i) Published Information

Environment

Refer to PRVD2017-24 and PSRD2018-02.

ii) Unpublished Information

Environment

Refer to PRVD2017-24 and PSRD2018-02.