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EVALUATION REPORT

Thiamethoxam

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FOREWORD

Evaluation Report on Registration Decision for Thiamethoxam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and in accordance with the Pest Control Products Regulations, has granted conditional registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use products Actara 25 WG Insecticide and Actara 240SC Insecticide to control insects in pome fruit and potatoes.

Current scientific data from the registrant, scientific reports and information from other regulatory agencies were evaluated to determine if, under the proposed conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Evaluation Report summarizes the information that was evaluated, provides the results of the evaluation, describes the conditions that are required to ensure that the health and environmental risks and the value of these pest control products are acceptable for their intended use, and provides the reasons for the conditional registration decision (with an outline of the additional confirmatory scientific information being requested).

As these conditional registrations relate to a decision on which the public must be consulted[1], a public consultation document will be published when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The information in this Evaluation Report is presented in two parts. The "Overview" describes the key points of the evaluation, while the "Science Evaluation" provides detailed technical information on the human health, environmental and value assessment of thiamethoxam.

Also included is a List of References that indicates both the studies/information submitted by the registrant and the additional information considered by the Agency in support of the registration decision.

[1] As per subsection 28(1) of the *Pest Control Products Act*.

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OVERVIEW

Proposed Registration Decision for Thiamethoxam

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing conditional registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use products Actara 25WG Insecticide and Actara 240SC Insecticide for control of certain insects in pome fruit and potatoes.

Current scientific data from the registrant, scientific reports and information from other regulatory agencies were evaluated to determine if, under the proposed conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Evaluation Report summarizes the information that was evaluated, provides the results of the evaluation, describes the conditions that are required to ensure that the health and environmental risks as well as the value of the pest control products are acceptable for their intended use and provides the reasons for the conditional registration decision (with an outline of the additional confirmatory scientific information being requested).

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 conditions or proposed conditions of registration[2]. The Act also requires that products have value[3] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g., children) as well as organisms in the environment (e.g., those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present 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 PMRA's website at www.pmra-arla.gc.ca.

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

3 "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 ©) health, safety and environmental benefits and social and economic impact".

What is Thiamethoxam?

Thiamethoxam is a systemic insecticide belonging to the neonicotinoid class of chemistry. Actara 240SC is applied using in-furrow application equipment to control Colorado potato beetles, aphids and potato leafhoppers on potatoes. Actara 25WG is applied using foliar application equipment to control Colorado potato beetles, aphids and potato leafhoppers on potatoes as well as plum curculio, spotted tentiform leafminers, rosy apple aphids, pear psylla and mullein bugs on pome fruit. Thiamethoxam moves through the leaf surface and the translocation system of the plant, affecting the insects through contact and ingestion.

❖ Health Considerations

♦ Can Approved Uses of Thiamethoxam Affect Human Health?

Thiamethoxam is unlikely to affect your health when used according to proposed label directions.

Exposure to thiamethoxam may occur through diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels at which 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 (e.g., children and nursing mothers). Only those uses for which 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 thiamethoxam products according to label directions.

The technical grade active ingredient thiamethoxam was of moderate toxicity following oral ingestion. As a result, the label for this product contains the statement “Warning Poison”. Actara 25WG caused dermal and eye irritation in animals. Because of this, the statement “Caution Skin and Eye Irritant” is required on the label. Thiamethoxam was not found to be genotoxic. Thiamethoxam did not cause cancer in rats, but did produce tumours in mice. However, the process of tumour formation in the mouse is not expected to occur in humans under typical exposure conditions. Other health effects in animals included effects in the liver, kidneys and nervous system. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When thiamethoxam was given to pregnant animals, effects on the offspring were observed at doses that did not have health effects in the mother, indicating that the young were more sensitive to thiamethoxam than the adult animal. Consequently, extra protective measures were applied in the risk assessment to further reduce the allowable level of human exposure to thiamethoxam.

♦ Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Dietary intake estimates (food plus water) revealed that children, adults and seniors will typically consume less than 27% of the acceptable daily intake for thiamethoxam. Infants, the subpopulation which would ingest the most thiamethoxam relative to body weight, are expected to eat less than 20% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from thiamethoxam is not a concern for all population subgroups.

Animal studies revealed no acute health effects. Consequently, a single dose of thiamethoxam is not likely to cause acute health effects in the general population (including infants and children). An aggregate (food and water) dietary intake estimate for children (1 to 12 years old) was less than 10% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drug Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using end-use products containing thiamethoxam on pome fruit and potatoes were sufficient to propose MRLs for pome fruit, potatoes and their respective processed commodities. The proposed MRLs for thiamethoxam can be found in the Science Evaluation section of this Evaluation Report.

♦ Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern provided that directions specified on the label are observed.

♦ Occupational Risks From Handling Actara 240SC or 25WG

Occupational risks are not of concern when Actara 240SC or 25WG is used according to label directions and precautions, which include protective measures

Farmers and pesticide applicators mixing, loading or applying either Actara 240SC or Actara 25WG as well as field workers re-entering freshly treated fields can come in direct contact with thiamethoxam on the skin or through inhalation of spray mists. For this reason, the label specifies that anyone mixing or loading Actara 240SC or 25WG must wear a long-sleeved shirt, pants and chemical-resistant gloves, and that anyone applying the product must wear a long-sleeved shirt and pants. Taking into consideration that occupational exposure is expected to be moderate as this insecticide is applied up to twice per year, risk to farmers, applicators or workers is not a concern.

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

❖ Environmental Considerations

♦ What Happens When Thiamethoxam is Introduced Into the Environment?

Thiamethoxam is toxic to honeybees and other beneficial organisms such as predatory and parasitoid insects; therefore, label instructions are required to protect these organisms during application. This compound is also toxic to aquatic insects; therefore, buffer zones are required during broadcast spray application to minimize these risks.

Thiamethoxam presents a negligible risk to wild mammals, birds, earthworms, fish, crustaceans, amphibians, algae and aquatic plants.

Thiamethoxam enters the environment when used as an insecticide on potatoes and pome fruit trees. It is moderately persistent to persistent in soil and slightly to moderately persistent in water. Field data for broadcast spray application indicated that there was no leaching of thiamethoxam below 30 cm depth of soil. Field data for in-furrow application, however, indicated that there was a greater potential for leaching in the soil as residues were detected at depths up to 90 cm. Nonetheless, neither thiamethoxam nor its major breakdown products are expected to enter groundwater. Thiamethoxam is not expected to enter the atmosphere.

❖ Value Considerations

♦ What is the Value of Thiamethoxam?

Thiamethoxam is an insecticide that controls a variety of insects in pome fruit and potatoes.

A single application of thiamethoxam controls a variety of insects on or results in less insect damage to pome fruit and potatoes. It is also compatible with current management practices and conventional crop production systems. Growers are familiar with the monitoring techniques to determine if and when applications are needed.

Other insecticides from the same class of chemicals as thiamethoxam, the neonicotinoids, are currently registered for use on potatoes and pome fruit; therefore, prudent use of insecticides in this class should be observed to prevent the development of resistance. When applied according to label directions, thiamethoxam is effective at controlling Colorado potato beetles, apids and leafhoppers on potatoes as well as spotted tentiform leafminers, plum curculio, mullein bugs, rosy apple aphids and pear psylla on pome fruit.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions are required by law to be followed.

The key risk-reduction measures being proposed on the labels of products containing thiamethoxam to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures:

- **Human Health**

Technical grade thiamethoxam was of moderate toxicity following oral ingestion. As a result, the labels for the products contain the statement “Warning Poison”. Actara 25WG caused dermal and eye irritation in animals. Because of this, the label statement “Caution Skin and Eye Irritant” is required.

- **Environment**

Thiamethoxam cannot be when crops are in bloom and bees are visiting the treatment area. To protect honeybees, specific instructions are provided on the product label, such as a requirement for a minimum waiting period of five days before placing the beehives in the treated field. Spray drift should also be minimized to reduce harmful effects on bees and other beneficial insects. To reduce exposure of aquatic insects, a buffer zone of four metres is required to protect nearby bodies of water from the spray drift.

What Additional Scientific Information is Being Requested?

Although the risks and value have been determined to be acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional confirmatory scientific information is being requested from the registrant as a result of this evaluation (see Section 9.2) to refine the risk assessments. The registrant will be asked to submit this information along with the submission to convert this conditional registration to a full registration.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted[4], a public consultation document will be published when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e., the test data relevant in supporting the registration decision) will be made available for public inspection when, following public consultation, the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations. If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra_infoserv@hc-sc.gc.ca).

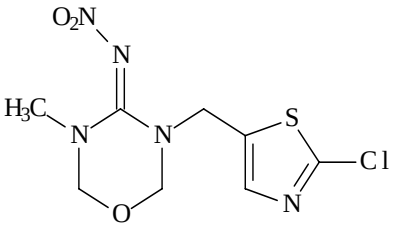
[4] As per subsection 28(1) of the *Pest Control Products Act*.

Science Evaluation

1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Identity of the active ingredient

Active substance	Thiamethoxam
Function	Insecticide
Chemical name	
International Union of Pure and Applied Chemistry	3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine
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	
Nominal purity of active	98 % (97 - 100 %)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade Thiamethoxam does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and chemical properties of active substance and end-use products

Property	Result
Colour and physical state	Off white powder
Odour	Odourless
Melting point or range	139.1°C
Boiling point or range	Not applicable
Density at 25°C	1.57×10^3 kg/m^3
Vapour pressure at 20°C	2.7×10^{-9} Pa
Henry's law constant at 20°C	1.9×10^{-10} Pa m^3/mol
Ultraviolet (UV) – visible spectrum	No absorption at wavelength > 300 nm.
Solubility in water at 25°C	4.1 g/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Acetone — 48 Dichloromethane — 110 Ethylacetate — 7 1-Octanol — 0.62 Methanol — 13 Toluene — 0.68
n-Octanol–water partition coefficient (K_{ow}) at 25°C	Log K_{ow} = -0.13
Dissociation constant (pK_a)	No dissociation constant within the range pH 2 to pH 12
Stability (temperature, metal)	The TGAI is not changed by contact with metals (stainless steel, cast steel, tin & aluminum) and with metal ions (Zn^{+2}, Al^{+3}, Cu^{+2} & Fe^{+2}).

End-use product: Actara 240 SC Insecticide

Property	Result
Colour	Dark beige
Odour	Aromatic
Physical state	Liquid
Formulation type	Suspension concentrate

Property	Result
Guarantee	240 g/L Nominal (Limits: 232.8 g/L - 247.2 g/L)
Formulants	The product does not contain any PMRA List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	High density polyethylene (HDPE) bottles.
Density	1.113 g/mL at 20°C
pH	5.6 (1% dispersion)
Oxidizing or reducing action	The product has no oxidizing or reducing properties.
Storage stability	The product was shown to be stable for at least one year under warehouse conditions.
Explodability	The product does not have any explosive properties.

End-use product: Actara 25 WG Insecticide

Property	Result
Colour	Light brown
Odour	Musty
Physical state	Solid
Formulation type	Wettable granules
Guarantee	25.0% N (Limits: 24.25% - 25.75%)
Formulants	The product does not contain any PMRA List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	High density polyethylene (HDPE) bottles.
Density	0.47 g/mL at 20°C
pH	7-11 (1% aqueous)
Oxidizing or reducing action	The product has no oxidizing or reducing properties.
Storage stability	The product was shown to be stable for at least one year under warehouse conditions.
Explodability	The product does not have any explosive properties

1.3 Details of uses

Syngenta Crop Protection Canada Inc., has applied for registration of two Commercial class end-use products, Actara 240 SC and Actara 25 WG Insecticides. Both products contain the active ingredient Thiamethoxam. Actara 240 SC is for use as an in-furrow treatment at potato planting to control Colorado potato beetle, aphids and potato leafhopper. Actara 25 WG is a foliar insecticide for use on potato to control Colorado potato beetle, aphids, and potato leafhopper and on pome fruit to control plum curculio, spotted tentiform leafminer, rosy apple aphid, pear psylla and mullein bug.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Thiamethoxam and the impurities present in the technical product were determined by high performance liquid chromatography (HPLC) with UV detection. The active ingredient and impurities were quantitated by external standard. The method was shown to be precise with a relative standard deviation (RSD) for the active ingredient of 0.21% and with a RSD of less than 5% for the impurities. Specificity was demonstrated by the absence of interferences at the retention times of the analytes of interest.

2.2 Method for formulation analysis

An HPLC method was used for the determination of Thiamethoxam in both formulations. Quantitation was by external standard. The method was shown to be linear, precise (RSD of < 0.5%) and accurate (mean recovery > 99 %). Specificity was demonstrated by the absence of interferences at the retention time of the analyte of interest. The method is acceptable for use as an enforcement analytical method.

2.3 Methods for residue analysis

2.3.1 Methods for environmental residue analysis

Methods for environmental residue analysis were not submitted, however this information has been requested from the applicant (Section 9.2).

2.3.2 Multiresidue methods for residue analysis

Existing multiresidue methods of analysis were not suitable for the determination of Thiamethoxam residues in canola and mustard, since in many cases, the recoveries were inconsistent. Residues of Thiamethoxam and CGA 322704 will be measured using specific methods outlined below.

2.3.3 Methods for residue analysis of plants and plant products

The residue definition (RD) was defined from the plant metabolism studies as the parent compound, Thiamethoxam and the major metabolite CGA 322704. The level of any possible metabolites are expected to be below the limit of detection for most GC/HPLC methods (<0.01 ppm for each analyte). Novartis HPLC-UV (or MS) Method AG-675 is adequate for collecting data on residues of Thiamethoxam and CGA 322704 in/on potatoes and pome fruit. Adequate method validation data were submitted for apples, pears and potatoes. The method has been adequately radiovalidated and has undergone a successful ILV trial. The validated limit of quantitation (LOQ) for residues of each analyte is 0.01 ppm in all plant matrices with the exceptions of fruit juices (0.005 ppm). Representative chromatograms of control and spiked samples of pome fruit and potato matrices showed no background interferences from matrix co-extractives, good peak shape, detectability and sensitivity at the LOQ.

2.3.4 Methods for residue analysis of food of animal origin

The RD was defined from the goat and poultry metabolism studies as the parent compound, Thiamethoxam and the major metabolite CGA 322704. Based on the evaluation of the submitted data, the level of any possible metabolites are expected to be below the LOQ for most GC/HPLC methods (<0.01 ppm for each analyte in meat and eggs and 0.005 ppm for each analyte in milk). Adequate method validation data using animal commodities have been submitted for Novartis HPLC-MS Method AG-675, and the method has undergone a successful ILV trial using milk, eggs and beef liver. The validated LOQ for residues of Thiamethoxam and CGA 322704 is 0.01 ppm each in meat, poultry and eggs, and 0.005 ppm each in milk. This method has also been adequately radiovalidated using samples of meat and milk from the goat metabolism study. Representative chromatograms of control and spiked samples of various tissues, milk and eggs showed no background interferences from matrix co-extractives, good peak shape, detectability and sensitivity at the LOQ.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

A detailed review of the toxicological database for the new insecticide, thiamethoxam (CGA 293343) was conducted. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies 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 define the majority of the toxic effects that may result from exposure to this chemical.

The toxicokinetics and metabolism of Thiamethoxam was evaluated in rats and mice. In rats, approximately 84–95% was excreted in the urine and 2.5–6% was excreted in the faeces within 24 h. The parent compound accounted for the majority of the excreted radioactivity, while only two other metabolites accounted for up to 2% or more of the administered dose. Metabolism in the mouse was more extensive than in the rat and the rate of metabolism increased with duration of dosing, suggesting the activation of phase 2 metabolic pathways. The major difference

between the metabolism of rats and mice, which may lead to a difference in long term toxicity, is the production of metabolite CGA330050 in mice. With increased duration of dosing, mice metabolized Thiamethoxam to a greater extent, while in rats, the proportion of Thiamethoxam which was metabolized decreased with repeated dosing.

In acute toxicity studies, technical thiamethoxam was slightly toxic to rats and moderately toxic to mice via the oral route, of low toxicity to rats via the dermal and inhalation routes of exposure, minimally irritating to rabbit eyes and nonirritating to rabbit skin. Technical thiamethoxam was nonsensitizing in a dermal sensitization study in guinea pigs. The formulated product, Actara 240 SC was considered to be of low toxicity via the oral and dermal routes of exposure, of slight acute toxicity via the inhalation route, non-irritating to the eyes, slightly irritating to the skin and was not considered to be a dermal sensitizer. Actara 25WG was considered to be of low toxicity via the oral, dermal and inhalation routes of exposure, mildly irritating to the eyes and skin, and was not considered to be a dermal sensitizer.

In short-term toxicity studies in rats, the primary target organs were identified as kidney and liver. Males were more sensitive to effects on the kidneys than females. Liver toxicity was observed at higher doses, manifested as hepatocellular hypertrophy, increased liver weights and associated changes in clinical biochemical parameters (including increased cholesterol levels and activity of certain liver enzymes). It was postulated that the observed hyaline change in the proximal convoluted tubules of the male rat kidneys was due to the accumulation of α-2-μ globulin, a protein that is unique to male rats. A series of special studies and literature papers were provided to further characterize the relevance of this lesion. The occurrence of α-2-μ globulin toxicity in male rats was considered to be of no toxicological significance for human health risk assessment since this lesion only occurs in rats. It should also be noted that the same hyaline change, consisting of eosinophilic droplets within the cytoplasm of the proximal convoluted tubules, was observed in one female of the F_1 generation in the two-generation rat reproduction study. In addition, other kidney toxicity was observed in female rats, consisting of chronic tubular lesions and nephrocalcinosis.

Several sub-chronic feeding studies were conducted in mice and rats to determine the similarities and differences in toxicity in these species. A temporal and dose relationship was demonstrated for the liver toxicity noted in mice fed thiamethoxam-treated diets, which was not noted in rats. Reduced cholesterol and serum protein (week 1 onward), and increased ALT (week 10 onward) were effects noted early on in treatment. Hepatocellular hypertrophy, necrosis and apoptosis were noted later, from week 10 onwards while inflammatory cell infiltration and increased AST were noted at week 20. Increased hepatocellular mitotic index was observed at doses of 500 ppm and greater after 40 weeks of treatment. Following treatment at 2500 and 5000 ppm, a dose-dependent increase of the mean hepatic concentration of reduced and oxidized glutathione was observed in mice but not in rats. Treatment 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 metabolising enzymes in the mouse. Liver effects were noted in 2 strains of mice (Tif:MAGf and CD-1), suggesting that the toxicity noted was not specific to a single strain. These differences in liver toxicity between rats and mice confirmed the differential metabolism of thiamethoxam in these species.

Mice fed the metabolites CGA322704 or CGA265307 had no evidence of liver toxicity. CGA33050 at 1000 ppm demonstrated similar toxicity to thiamethoxam with evidence of decreased cholesterol and serum protein, increased hepatocellular hypertrophy, necrosis, apoptosis and inflammatory cell infiltration. CGA33050 at 500 and 1000 ppm increased the liver enzymes ALT and AST in female rats after one week of dosing, while liver weights were unaffected, suggesting a lack of liver toxicity in rats. When the toxicity of thiamethoxam was compared between weanling and adult mice, weanling mice demonsterated higher serum levels of thiamethoxam in the absence of increased toxicity. The increase in serum levels of test material, in the absence of an increased liver toxicity demonstrates that weanling animals are not more sensitive than adult animals to the liver effects of the compound.

The 28-day dermal toxicity study in rats revealed systemic effects that were consistent with those observed in dietary studies; however, females were more sensitive than males. Hyaline changes in renal tubules were observed only in high-dose males, whereas liver and kidney toxicity were observed in mid and high dose females.

Thiamethoxam was tested in a battery of five in vitro and in vivo genotoxicity studies. There was no evidence of genotoxicity in any of the studies.

There was no evidence of oncogenicity after chronic administration of thiamethoxam in rats. Systemic toxicity was observed in males and females, manifested as chronic nephropathy and lymphocytic infiltration in the kidneys of males and decreased body weight gain, chronic tubular lesions in the kidneys and foci of cellular alteration in the liver of females. Body weight was unaffected in males, leading to questions on the adequacy of the high dose. The dose selection, however, was based on the observed reduction in body weight gain (approximately 20% at 1250 ppm) in the subchronic toxicity study. As well, higher doses would not have been well tolerated by male rats due to the previously mentioned α-2-u-globulin toxicity noted at higher doses.

In mice, the primary target organ was the liver, and males were more sensitive to the liver pathology than females. Subchronic administration of high doses resulted in decreased ovarian weights and ovarian atrophy. In subchronic and chronic studies, liver pathology included hepatocellular hypertrophy, necrosis of single hepatocytes, lymphocytic infiltration and Kupffer cell pigmentation (subchronic) or Kupffer cell hyperplasia (chronic). Chronic dosing resulted in the development of benign and malignant liver tumours in both sexes. There was an increase in the number of animals with multiple tumours; however, treatment did not affect the latency to tumour formation or lethality from the observed tumours. The incidence of non-neoplastic and neoplastic pathology was increased at the same dose level, i.e., there was no clear departure point between doses that induced tumours and other systemic toxic effects. On the basis of the observed tumour response, it was concluded that thiamethoxam demonstrated oncogenic potential in mice.

Several studies were conducted to elucidate the etiology of the mouse liver tumours. Based on the weight of evidence, mice appear to be much more susceptible than rats or humans to metabolizing thiamethoxam to a toxic metabolite, (purported to be CGA 33050). The tumours are considered to be the result of chronic liver toxicity. The development of the liver toxicity

over time was demonstrated to follow a clear sequence of events starting with enzyme and cholesterol disruption, leading to cellular damage, (necrosis and apoptosis) repair and turn over. The increased cellular turn over predisposed the mice to the development of liver tumours, over the course of a lifetime of exposure to Thiamethoxam. The special studies provided by the registrant demonstrated a clear dose and temporal relationship for the development of liver toxicity, leading to tumour formation following chronic administration. Since tumours were only noted at doses which produced overt indications of liver toxicity, a threshold approach to the cancer risk assessment was taken.

In the dog, the main target organ appeared to be the testis. In the 90-day study, the high dose initially caused severely decreased food consumption and concomitant body weight loss, necessitating cessation of treatment for seven days and resumption at a lower dose. Animals in 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. In addition, decreased ovary weights associated with delayed maturation of the ovaries was observed at this dose. Atrophy of the seminiferous tubules and decreased testis weight were observed after 12 months of treatment with thiamethoxam. In both the 90-day and the one-year study, significant decreases were observed in alanine aminotransferase (ALT) activity. Hematological parameters (primarily prolonged prothrombin times) were affected at higher doses.

There was no evidence of teratogenicity in developmental toxicity studies in rats and rabbits, and thiamethoxam did not affect the standard reproductive indices (mating, gestation, fertility, viability) in two multi-generation reproductive toxicity studies, or in a developmental neurotoxicity study. However, atrophy of the seminiferous tubules was observed in the F_1 generation (in the first multi-generation reproductive toxicity study) in the absence of parental systemic toxicity, indicating the potential for increased qualitative and quantitative sensitivity of the young. This lesion was not observed in the F_0 generation, nor was it observed in the developmental neurotoxicity study or any of the subchronic or chronic toxicity studies conducted in rodents. However, atrophy of the seminiferous tubules and reduced testes weight were observed in adult dogs in both the 90-day and the one-year studies. In the second multi-generation reproductive toxicity study, decreased sperm counts were observed in F_1 males in the absence of parental systemic toxicity. The NOAEL for atrophy of the seminiferous tubules (among F_1 males) is the lowest NOAEL from the entire toxicity database for thiamethoxam (1.2 mg/kg bw/d; combined results from the reproductive toxicity studies).

Acute high doses of thiamethoxam resulted in effects on functional observational battery (FOB) and locomotor activity (LMA) parameters, most likely attributed to general toxicity. There was no neurotoxicity observed in a subchronic neurotoxicity study and there was no neurohistopathology after acute or subchronic dosing. Reduced brain weights, and alterations in brain morphometric parameters in both males and females, without associated behavioural changes, were noted at the high dose in the developmental neurotoxicity study.

A number of parameters were affected in various species following treatment with thiamethoxam for varying durations that suggest possible interaction with endocrine systems. The specific findings in rats included increased plasma cholesterol, hepatocellular hypertrophy, increased adrenal weights, fatty change of the adrenal cortex and hypertrophy of thyroid follicular epithelium. In the multi-generation reproductive toxicity studies, decreased testis weights, sperm per testes, and increased incidence and severity of atrophy of seminiferous tubules were observed in the F_1 generation males. Sperm motility was altered in high dose males as well. Delayed sexual maturation in males was noted in the developmental neurotoxicity study. However, histopathology and sperm motility analysis was not conducted in this study. In mice, high doses caused decreased ovary weight and ovarian atrophy in the 90-day study and a slight, transient increase in adrenal weight in females at interim sacrifice in the oncogenicity study. In dogs, decreased testis and ovary weight were observed in the 90-day study at a dose that resulted in significant body weight loss, necessitating cessation of treatment for seven days and resumption at a lower dose. These organ weight changes were accompanied by histopathological evidence of delayed maturation in the ovaries and reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in the testes. Atrophy of the seminiferous tubules was the key observation in the establishment of the NOAEL in the one-year dog study.

There is evidence of increased susceptibility of the young in the rat reproduction study as evidenced by effects on male reproductive tissues. Therefore, an additional factor of 3x will be applied to the occupational and dietary risk assessments for thiamethoxam to protect susceptible sub-populations including children and fetuses of pregnant workers.

3.2 Determination of acceptable daily intake (ADI)

The recommended acceptable daily intake (ADI) for thiamethoxam is 0.004 mg/kg bw/d. The most appropriate studies for the selection of a toxicity end point for chronic dietary exposure were the two-generation reproduction studies in rats. When the results of both studies were combined, the NOAEL of 1.2 mg/kg bw/day was considered appropriate to protect against adverse effects noted at the LOAELS from both studies (based on testicular and sperm toxicity of the F_1 generation at the LOAEL of 1.8 and 3.0 mg/kg bw/day from both studies). The standard uncertainty factor of 100 is applied to account for intraspecies variability and interspecies extrapolation. An additional factor of 3 was applied due to the evidence of increased susceptibility of the young. The NOAEL from these studies provides margins of 10500 to endocrine effects noted elsewhere in the database.

The liver tumours noted in mice at doses of $\geq$64 mg/kg bw/day were late in onset, developed following chronic exposure and were preceded by a consistent pattern of liver toxicity including enzyme changes, hypertrophy, apoptosis, necrosis and cell turn-over. While this pattern of tumour formation is biologically plausible in humans, a prolonged exposure to high concentrations of thiamethoxam would be required to elicit this effect. The ADI provides a margin of 16,000 to the LOAEL for this endpoint (64 mg/kg bw/day). These margins were considered protective, given the differences in toxicokinetics between species.

The ADI proposed is calculated according to the following formula:

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

3.3 Acute reference dose (ArfD)

The recommended acute reference dose (ARfD) for thiamethoxam is 0.12 mg/kg bw. The most appropriate study for the selection of a toxicity end point for acute dietary exposure was the developmental neurotoxicity study in the rat, which had a NOAEL of 34.5 mg/kg bw/day based on brain effects in the presence of minor maternal toxicity. The changes in brain measures noted in this study may occur as a result of a single exposure to a toxic chemical. The standard uncertainty factor of 100 is applied to account for intraspecies variability and interspecies extrapolation. An additional factor of 3 was applied due to the evidence of increased susceptibility of the young.

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{34.5 \text{ mg/kg bw/day}}{300} = 0.12 \text{ mg/kg bw/day of Thiamethoxam}$$

3.4 Toxicological endpoint selection: occupational and bystander risk assessment

Exposure to the end use product, Actara, is expected to be intermittent over a short term for mixer/loader and applicators. There is potential for short to intermediate-term exposure to workers scouting, pruning, hand line irrigating, hand harvesting and thinning pome fruits and potatoes. Dermal and inhalation exposure are the predominant routes of exposure.

For the risk assessment, it was considered appropriate to use the NOAEL of 1.2 mg/kg bw/d from the combined reproductive toxicity studies in the occupational risk assessment from short to intermediate duration. Due to the evidence of increased susceptibility of the young an additional factor of 3 is applied resulting in a target margin of exposure (MOE) of 300.

It was considered appropriate to ensure that the occupational risk assessment also address workers who may have occasional elevated exposures. The relevant end point for these exposures is the NOAEL used in establishing the dietary acute reference dose (34.5 mg/kg bw from the developmental neurotoxicity study in rats). The target MOE was 300 for the reasons noted above.

Based on in vivo rodent dermal absorption studies conducted with various formulations containing this active ingredient, dermal absorption was calculated to be 2.5%.

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

3.5.1 Operator Exposure Assessment

3.5.1.1 Handler Exposure and Risk

Farmers have potential for exposure to thiamethoxam during mixing, loading, and application either in-furrow to potatoes (Actara 240SC) or through foliar application to potatoes and pome fruits (Actara 25WG). Only ground application is proposed (groundboom, in furrow, and airblast). Actara 240SC Insecticide is applied at a rate of 3.4 - 4.4 ml/100 m in-furrow (378-489 ml product/ha or 91 - 117 g ai/ha assuming 90 cm row spacing) depending on the length of control required and the furrow width. Actara 25WG is applied at application rate of 105 g product/ha for potatoes (26 g ai/ha) and 315 - 385 g product/ha for apples, pears and crabapples (79 - 96.25 g ai/ha). The typical area treated per day ranges from 16 - 80 ha/day for farmers and up to 300 ha for custom applicators, depending on the type of application equipment. Farmers and custom applicators may be exposed intermittently over a short-term duration and intermediate term duration, respectively.

Exposure estimates for mixers, loaders and applicators (M/L/A) are based on data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. Appropriate subsets of A and B grade data (high confidence) were created from the database files of PHED for either dry flowable mixing/loading or liquid mixing/loading and for groundboom (including in-furrow application) and airblast application. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part.

The exposure estimates are based on mixer/loaders wearing a single layer of clothing (long pants and long sleeved shirt) plus gloves and applicators wearing a single layer and no gloves.

For the short to intermediate-term risk assessments, route-specific estimates were generated based on the a NOAEL of 1.2 mg/kg bw/day from the rat reproduction study. All MOEs exceed the target of 300 and are considered acceptable.

Table 3.5.1.1.1 Summary of Daily Exposure Estimates and Margins of Exposure for Thiamethoxam

Scenario	Equipment	Dermal Exposure [a] mg/kg bw/day	Inhalation Exposure [b] mg/kg bw/day	Total Exposure mg/kg bw/day	MOE [c]
Farmer Mixer/Loader/Applicator	Groundboom	0.00014	0.00006	0.0002	5983
Custom Mixer/Loader	Groundboom	0.00046	0.00011	0.00057	2107
Custom Applicator	Groundboom	0.00009	0.00011	0.0002	6050
Farmer & Custom Mixer/Loader/Applicator	Airblast	0.00055	0.00015	0.0007	1723
Farmer Mixer/Loader/Applicator	In-furrow Groundboom	0.00028	0.00034	0.00062	1942
Custom Mixer/Loader	In-furrow Groundboom	0.00064	0.0008	0.00144	831
Custom Applicator	In-furrow Groundboom	0.00041	0.00048	0.00089	1344

a Where exposure mg/kg/day = maximum rate * area treated per day * unit exposure * dermal absorption * conversion factor (1/1000 mg/µg)/70 kg bw.

b Where exposure mg/kg/day = maximum rate * area treated per day * unit exposure * conversion factor (1/1000 mg/µg) / 70 kg bw.

c Where MOE = NOAEL/Exposure; the MOE is based on a NOAEL of 1.2 mg/kg bw/day from a Rat multi-generation reproduction study (short and intermediate term exposure). The target MOE is 300.

3.5.1.2 Postapplication Exposure and Risk

There is potential for postapplication exposure to workers re-entering areas treated with Actara 25WG to perform activities such as pruning, scouting, handline irrigating, hand harvesting and thinning. Post-application exposure to Actara 240SG is expected to be minimal since it is applied in-furrow and residues potato foliage is not expected to occur. The primary route of exposure for re-entry workers is dermal through contact with treated foliage. Dermal exposure to workers re-entering treated areas is calculated by coupling crop-specific dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity-specific transfer coefficients are based on Agricultural Re-entry Task Force (ARTF) data, of which Syngenta is a member. An 8 hour work day and have a 70 kg body weight is assumed.

DFR data for thiamethoxam were derived from a study conducted on apples in Oregon, Washington and New York. All three study sites have climates and conditions that are representative of Canadian growing regions and the study was deemed acceptable. The application regime during the study was 2 applications (96 g thiamethoxam/ha), 10 days apart which is identical to the proposed regime for apples but not for foliar use on potatoes. Based on the proposed application regime and the application equipment used it was determined that the study could be used to predict DFR residues on apples in Canada, but not on potatoes. A peak DFR value of 0.83 µg/cm^2 from the New York site was used to estimate exposure associated

with post-application activities. The exposure estimates generated represent re-entry on the day of the last application. Exposure estimates were coupled with the NOAEL of 1.2 mg/kg bw/day from the rat reproduction study. MOEs for all post-application activities for pome fruit production exceed the target of 300 and are considered acceptable. Reentry activities associated with potato cultivation are generally less intensive pome fruit cultivation and are therefore also considered acceptable. For good hygiene practices, a 12 hour REI is required.

Table 3.5.1.2-1 Occupational Post-Application Exposure Estimates and Margins of Exposure for Thiamethoxam.

Scenario	Transfer Coefficient (cm^2/hr) [A]	DFR Value ($\mu g/cm^2$)	Dermal Deposition (mg/kg bw/day) [B]	Systemic Exposure (mg/kg bw/day) [C]	MOE [D]
Apple Pruning, scouting	500	0.283	0.0162	0.00040	**2968**
Apple Hand line irrigation	1100	0.283	0.0356	0.00089	**1349**
Apple Hand harvesting	1500	0.283	0.0485	0.00121	**989**
Apple Thinning	3000	0.283	0.0970	0.00243	**495**

a Transfer Coefficients, based on ARTF data. The applicant, Syngenta Crop Protection Canada, is a member of ARTF.

b Exposure estimates were calculated using the following formula:

$$\frac{\text{DFR Value } (\mu g/cm^2) \times \text{Transfer Coefficient } (cm^2/hr) \times \text{Hours Worked per Day (hr)} \times \text{Conversion Factor } (1mg/1000\mu g)}{\text{Body Weight (70 kg)}}$$

c Based on a dermal absorption value of 2.5 % from the in vivo rat study: 10 hour exposure duration.

d Based on a NOAEL of 1.2 mg/kg bw/day from a Rat multi-generation reproduction study and compared to the target MOE of 300.

Thiamethoxam can break down to clothianidin in the environment and that there is a possibility of exposure to clothianidin by workers entering treated fields and orchards. This scenario was evaluated and it was determined, based on environmental fate considerations and the toxicology profiles of these active ingredients, that the current risk assessment is protective.

3.5.2 Bystanders

3.5.2.1 Handler Exposure and Risk

There are no domestic products; therefore, a residential handler assessment was not required.

3.5.2.2 Post-Application Exposure and Risk

There is no residential post-application exposure associated with the use of this product; therefore, a residential post-application assessment was not required.

4.0 Residues

4.1 Residue summary

The metabolism of Thiamethoxam was investigated in plants following a number of different application methods (i.e., seed treatment, foliar, stem injection, etc.) of [thiazol-2-^{14}C] or [oxadiazin-4-^{14}C]-Thiamethoxam to corn, cucumber, pear, potato and lettuce. Although multiple application scenarios and very different harvest times were used in the different metabolism studies, the results obtained are similar in all experiments. Irrespective of the mode of application (i.e., foliar or seed treatment), the major residues found were Thiamethoxam and CGA 322704. The metabolic profiles for the target crop were also similar to the profiles found in the rotational crops. The metabolic pathway for Thiamethoxam was evaluated in livestock following three consecutive daily oral doses of [thiazol-2-^{14}C] or [oxadiazin-4-^{14}C]-Thiamethoxam to lactating goats and laying hens. Some qualitative and quantitative differences between goats and laying hens were observed but were not considered to impact the overall metabolic profile assessment. In the majority of animal tissues the major residues were the same as in plant, Thiamethoxam and CGA 322704. In both plants and animals, Thiamethoxam is primarily metabolized either by cleavage of the oxadiazine ring to form CGA 322704, loss of the nitro group from the parent molecule or cleavage at the N-C bridge.

Crop field trial data reflected the proposed use pattern for Actara 240 SC and Actara 25 WG Insecticide formulation on pome fruit and potatoes. Processing data indicated that total Thiamethoxam-derived residues concentrated 1.9-fold in potato chips, 1.2-fold in potato granules and 0.75-fold in apple juice. Expected total Thiamethoxam-derived residues in the processed fractions will be covered by the respective agricultural commodities MRLs for potato granules and apple juice. A separate MRL 0.04 ppm is recommended for potato chips. The magnitude of residues (MORs) in the rotational crops from the confined crop rotation studies triggered the need for field accumulation studies. The predominant residues identified in the soil and rotational crops from the field accumulation study were Thiamethoxam and CGA 322704. A plant back interval of 120 days will be required on the label for crops not registered for Thiamethoxam use. MRLs on rotational crops will not be required. The available storage stability data are adequate to support the storage intervals and conditions of samples from all associated field trials. MRLs are currently established for animal commodities. The addition of the proposed uses do not increase the anticipated residues in animal commodities, therefore no new MRLs are required. The available storage stability data for animal commodities are adequate to support the proposed uses.

The proposed agricultural use of Thiamethoxam on pome fruit and potato does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

4.2 Residues relevant to consumer safety

Aggregate Exposure and Risk Assessment
While there is potential exposure resulting from pick-your-own operations in pome fruits, an aggregate (dietary and residential) exposure is not required since the pre harvest interval (PHI) for pome fruits is 60 days and no appreciable residues are expected to occur on plant surfaces during u-pick activities.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

Thiamethoxam was determined to be very soluble (4.10 g/L) in water, which is one of the indicators of high potential for the compound to leach in soil or to runoff in surface water. The vapour pressure of Thiamethoxam at 20°C was calculated to be 2.7×10^{-9} Pa, which indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's law constant was calculated to be 1.9×10^{-10} Pa m^3/mol, which indicates that the chemical will be non-volatile from water and moist soil surfaces. Therefore, based on both the vapour pressure and Henry's law constant, Thiamethoxam has a very low potential for mobility in the air.

The magnitude of the n-octanol/water partition coefficient for Thiamethoxam (log K_{ow} = - 0.13) indicates a low potential for bioaccumulation. The compound does not dissociate within the range of pH 2 to 12.

The UV/visible absorption spectrum of Thiamethoxam showed that there was no significant absorption at wavelengths over 300 nm in neutral, acidic and basic solutions. This result indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

The transformation of Thiamethoxam was addressed in the studies submitted. Although there are a number of major transformation products formed in laboratory studies, some at pHs not relevant to the environment, only two major transformation products were found under field conditions: CGA 322704 and CGA 355190. Of these, CGA 322704 is the chemical code for the active ingredient clothianidin which has been reviewed previously and is a registered active ingredient. It is, however, very persistent in soil. CGA 355190 was a minor transformation product in one Canadian field study, but a major one in another, and is expected to be persistent in soil and in water.

5.2 Abiotic transformation

Thiamethoxam was stable to hydrolysis at acidic to neutral pH, but hydrolyzed with half-life values of 4.2 - 8.4 days at pH 9, with the formation of two major transformation products, CGA 355190 and NOA 404617 (for guanidine and thiazolyl labels); and an additional major transformation product, CGA 309335 (for thiazolyl label) formed from further hydrolysis of NOA 404617. These results indicated that Thiamethoxam was susceptible to hydrolysis at alkaline pH values, but was not hydrolysed at acidic to neutral pH. The results of phototransformation studies on soil and in aqueous solution yielded half lives of 79 - 97 days and 2.3 - 3 days, respectively. There were no major transformation products formed on soil, but two major transformation products (CGA 353042 for guanidine label and the volatile carbonyl sulfide for thiazolyl label) were formed in water.

5.3 Biotransformation

Results of biotransformation studies in soil under aerobic conditions at 20 - 30°C yielded half-life values of 101 - 353 days, with the formation of one major transformation product, CGA 355190. This major transformation product further transformed into CGA 353968, with a half-life of 459 days. Under aerobic conditions at 25°C, the half-life in water was determined to be 9.5 - 22 days, with the formation of two major transformation products, CGA 355190 and NOA 404617. These major transformation products were formed by hydrolysis. Results of biotransformation studies in aerobic water/sediment from a pond system at 25°C yielded half-life value of 16 days, with the formation of one major transformation product, NOA 407475. Under anaerobic conditions at 25°C, the half life in the water/sediment system was determined to be 25 - 50 days, with the formation of one major transformation product NOA 407475. Results of biotransformation studies in anaerobic water/sediment from a pond system at 5°C yielded half-life values of 12 - 44 days, with the formation of one major transformation product, NOA 407475.

5.4 Mobility

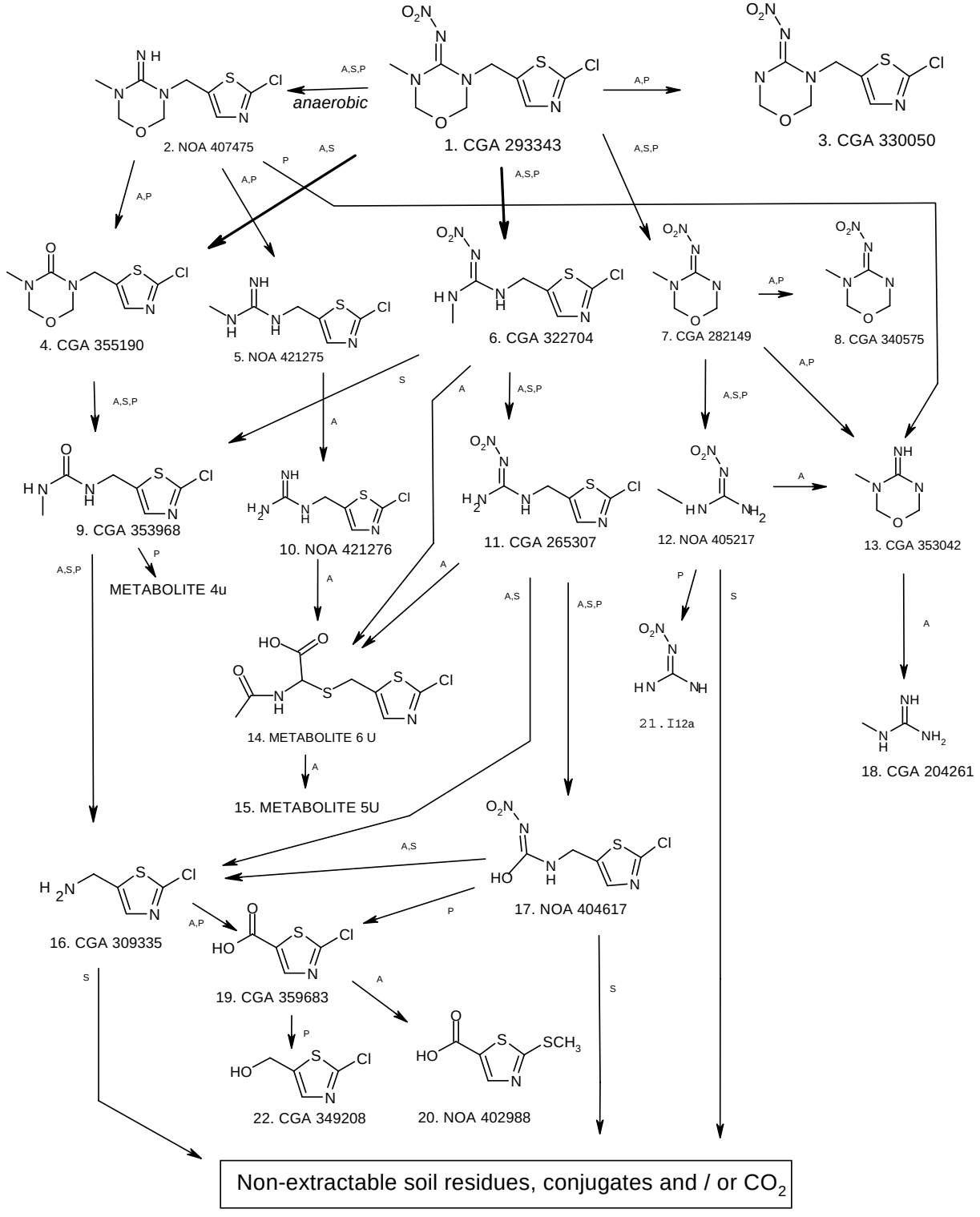
The adsorption K_{oc} of ^{14}C-Guanidine-Thiamethoxam in six agricultural soils ranged from 33.1-176.7 mL/g carbon, indicating that Thiamethoxam has a medium to very high potential for mobility in soil according to the classification scheme of McCall et al. (1981). There was no correlation apparent in the data between the adsorption K_d value and % organic carbon or % clay content of the soils. Results of an aged soil column leaching study indicated that Thiamethoxam will be less mobile in soil after ageing, than indicated by the adsorption data. The mobility of the major transformation product CGA 355190 or that of its subsequent transformation product CGA 353968 was not investigated. Based on the values for vapour pressure and Henry's law constant, volatilization of Thiamethoxam is not expected to be a route of dissipation.

5.5 Dissipation and accumulation under field conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that Thiamethoxam was moderately persistent to persistent in soil, with DT_{50} values ranging from 48 to 239 days. Thiamethoxam was found to be more persistent at Manitoba than Ontario or PEI sites. Significant carryover of residues to the next field season is expected in Manitoba, as compared to the other two sites based on these results. There were no major transformation products detected at all three sites. Several minor transformation products, however, were detected during the course of the study. There was no evidence of leaching of Thiamethoxam or its transformation products though the soil profile. These results indicate that Thiamethoxam will dissipate slowly in soil under field conditions in Canada with little or no leaching.

Field dissipation studies (broadcast and in-furrow treatments) conducted in Michigan yielded DT_{50} values ranging from 34 to 35 days. CGA 322704 was the only major transformation product detected. Thiamethoxam and its transformation products were not detected below the 30 cm depth of soil for broadcast application, but was detected at depths up to 90 cm for in-furrow application. These results indicate that Thiamethoxam will be slightly persistent in soil under field conditions in the United States with slight potential for leaching if applied as an in-furrow treatment.

Figure 1. Proposed biotransformation pathways for Thiamethoxam in soil (S), plants (P) and animals (A).



5.6 Bioaccumulation

No study was submitted, but based on the octanol/water partition coefficient (log K_{ow}) of -0.13 at 25°C, bioconcentration/bioaccumulation is not expected to occur.

5.7 Summary of fate and behaviour in the terrestrial environment

Thiamethoxam was stable to hydrolysis at acidic to neutral pH, but hydrolyzed with half-life values of 4.2 - 8.4 days at pH 9, with the formation of two major transformation products, CGA 355190 and NOA 404617 (for guanidine and thiazolyl labels); and an additional major transformation product, CGA 309335 (for thiazolyl label) formed from further hydrolysis of CGA (NOA) 404617. These results indicated that Thiamethoxam was susceptible to hydrolysis at alkaline pH values, but was not hydrolysed at acidic to neutral pH. The results of phototransformation studies on soil yielded half lives of 79 -97 days. There were no major phototransformation products formed on soil.

Results of biotransformation studies in soil under aerobic conditions at 20 - 30°C yielded half life values of 101 - 353 days, with the formation of one major transformation product, CGA 355190. This major transformation product further transformed into CGA 353968, with a half-life of 459 days.

The adsorption K_{oc} of ^{14}C-Guanidine-Thiamethoxam in six agricultural soils ranged from 33.1 - 176.7 mL/g carbon, indicating that Thiamethoxam has a medium to very high potential for mobility in soil according to the classification scheme of McCall et al. (1981). Results of an aged soil column leaching study indicated that Thiamethoxam will be less mobile in soil after ageing. The mobility of the major transformation product CGA 355190 or that of its subsequent transformation product CGA 353968 was not investigated. Based on the values for vapour pressure and Henry's law constant, volatilization of Thiamethoxam is not expected to be a route of dissipation.

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that Thiamethoxam was moderately persistent to persistent in soil, with DT_{50} values ranging from 48 to 239 days. Thiamethoxam was found to be more persistent in Manitoba than Ontario or PEI sites. Significant carryover of residues to the next field season is expected in Manitoba, as compared to the other two sites based on these results. There were no major transformation products detected in all three sites. Several minor transformation products, however, were detected during the course of the study. There was no evidence of leaching of Thiamethoxam or its transformation products though the soil profile. These results indicate that Thiamethoxam will dissipate slowly in soil under field conditions in Canada with little or no leaching.

Field dissipation studies (broadcast and in-furrow treatments) conducted in Michigan yielded DT_{50} values ranging from 34 to 35 days. The only major transformation product detected at this site was CGA 322704. Thiamethoxam and its transformation products were not detected below the 30 cm depth of soil for broadcast application, but were detected at depths up to 90 cm for in-furrow application. These results indicate that Thiamethoxam will be slightly persistent in soil under certain field conditions with a slight potential for leaching if applied as an in-furrow treatment.

The fate and behaviour of Thiamethoxam in the terrestrial environment is summarized in Table 5.7-1, and the transformation products of Thiamethoxam are summarized in Table 5.7-2 (Appendix III).

5.8 Summary of fate and behaviour in the aquatic environment

Thiamethoxam was stable to hydrolysis at acidic to neutral pH, but hydrolyzed with half-life values of 4.2 - 8.4 days at pH 9, with the formation of two major transformation products, CGA 355190 and NOA 404617 (for guanidine and thiazolyl labels); and an additional major transformation product, CGA 309335 (for thiazolyl label) formed from further hydrolysis of CGA (NOA) 404617. These results indicated that Thiamethoxam was susceptible to hydrolysis at alkaline pH values, but was not hydrolysed at acidic to neutral pH. The results of phototransformation studies in aqueous solution yielded half lives of 2.3 - 3 days, with the formation of two major transformation products (CGA 353042 for guanidine label and volatile carbonyl sulfide for the thiazolyl label). Phototransformation, therefore, may be a route of transformation in the photic zone of clear natural water.

Under aerobic conditions at 25°C, the half life in water was determined to be 9.5 - 22 days, with the formation of two major transformation products, CGA 355190 and NOA 404617. These major transformation products were formed by hydrolysis. Results of biotransformation studies in aerobic water/sediment from a pond system at 25°C yielded half-life value of 16 days, with the formation of one major transformation product, NOA 407475. Under anaerobic conditions at 25°C, the half life in the water/sediment system was determined to be 25 - 50 days, with the formation of one major transformation product NOA 407475. Results of biotransformation studies in anaerobic water/sediment from a pond system at 5°C yielded half-life values of 12 - 44 days, with the formation of one major transformation product, NOA 407475.

A study of bioconcentration of Thiamethoxam in bluegill sunfish was not submitted. Given the magnitude of the n-octanol/water partitioning coefficient, however, Thiamethoxam is not expected to bioconcentrate/ bioaccumulate in organisms.

The fate and behaviour of Thiamethoxam in the aquatic environment is summarized in Table 5.8-1, and the transformation products of Thiamethoxam are summarized in Table 5.8-2 (Appendix III).

5.9 Expected environmental concentrations

The concentrations of Thiamethoxam in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was assumed that, per the proposed Canadian label for Actara 25 WG, a maximum of two applications per growing season, at 10 day interval, was made at the maximum label rate of 96 g a.i./ha. The label rate for Actara 240 SC, to be applied as a single in-furrow treatment, was 117 g a.i./ha. The latter rate, however, was not considered in these calculations as it does not represent a maximum exposure scenario.

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, and a scenario in which the "maximum cumulative rate" is applied to bare soil, the EEC of residues in soil would be 0.084 mg a.i./kg soil.

5.9.2 Water

5.9.2.1 Direct over spray in surface water

Assuming a water density of 1.0 g/mL, a water depth of 80 cm, and a screening-level scenario in which a body of water is over-sprayed with the "maximum label rate", the EEC in water would be 0.02 mg a.i./L water. For a water depth of 15 cm for amphibian habitat, the EEC in water would be 0.11 mg a.i./L.

5.9.2.2 Aquatic Ecoscenario Assessment: Runoff Simulation Level 1:

Estimated environmental concentrations of Thiamethoxam for a Level 1 receiving water body runoff scenario for aquatic risk assessment were simulated using the PRZM/EXAMS models. This water body consists of a 1 ha wetland with an average depth of 0.8 m and a 10 ha drainage area.

Information on application rates and timing was gathered for the major uses of Thiamethoxam (apples and potatoes). Information for use on pears was also available, but pears are a smaller crop and use is nearly identical to that on apples, therefore, pear use was not considered separately. Up to two applications at ten day intervals are allowed on apples: one pre-bloom application at a rate of 79 g a.i./ha and one post-bloom applications at a rate of 96 g a.i./ha, or two post-bloom applications at 96 g a.i./ha. Based on typical dates of first application, the PRZM/EXAMS ecoscenario models were run with initial application dates from mid-April to late June (depending on the region). As the bloom date was not available, blooming was assumed to occur during the first two dates of the modelled range. The first two dates for all apple runs were modelled using the lower rate for the first application and the higher rate for the second application. Subsequent dates for apple runs were modelled with two applications at the higher rate.

Potato use of Thiamethoxam can be either a foliar spray (two applications of 26 g a.i./ha at seven day intervals) or an in-furrow spray (single application of 117 g a.i./ha). Modelling for the aquatic ecoscenario was performed only for the foliar spray, using initial application dates ranging from early June to the end of July, depending on the region.

The following geographic scenarios were simulated, for apples and potatoes: wetlands adjacent to an apple orchard or a potato field in the Pacific Region, Ontario, Quebec and the Atlantic Region, and wetlands adjacent to a potato field in the Prairies. Apples were not modelled in the Prairies. The model was run for 20 to 81 years, depending on the scenario.

Table 5.9.2-1 lists the application information and main environmental fate characteristics used in the models.

For each year of the simulation, PRZM/EXAMS calculates both peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day, and 1 year). The highest 90^{th} percentiles of the peak and the time-averaged concentrations (µg/L) are reported in Table 5.9.2-2.

5.9.2.3 Level 2 Estimated Environmental Concentrations in Drinking Water Sources

EECs of Thiamethoxam in potential drinking water were previously modelled as a seed treatment by the PMRA in 2004. At that time, Level 2 modelling was requested. For that reason, for the foliar and in-furrow uses, Level 1 was skipped and a Level 2 modelling considering regional scenarios and application dates was conducted for Thiamethoxam and its transformation product, CGA 322704.

EECs for Thiamethoxam and CGA 322704 in potential drinking water sources (groundwater and surface water) were calculated using computer simulation models. EECs in groundwater were calculated using the LEACHM model, which simulates leaching through a layered soil profile over a multi-year period (20 years). The concentrations calculated using LEACHM are estimates of the flux, or movement, of pesticide into shallow groundwater (2 or 5 m depth) with time. Surface water EECs were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body.

Application rates of Thiamethoxam for apples and potatoes (foliar and in-furrow application) were the same as those used for the aquatic ecoscenario assessment. Regional scenarios and dates of application were used. For the apple use, the models were run with initial application dates ranging from mid-April to early June. Similar to ecoscenario modelling, the first two dates for all apple runs were modelled using the lower rate for the first application, and the higher rate for the second application. Subsequent dates for apple runs were modelled with two applications at the higher rate. Modelling for potatoes was performed using dates ranging from mid-June to mid-July for the foliar application, and from April or May for in-furrow use (depending on the region).

CGA 322704 was assumed to take one year to form, and thus the application dates used were the same as for the parent, and it was assumed that 25% of Thiamethoxam transforms into CGA 322704 (highest projected result from one of four field studies for the two end-use products). After adjusting for the lower molecular weight of CGA 322704, application rates used in the modelling of CGA 322704 were 21% of those for Thiamethoxam.

The application information and main environmental fate characteristics used in the models are presented in Table 5.9.2-1.

The Level 2 estimated concentrations of Thiamethoxam and CGA 322704 in potential surface water and groundwater sources of drinking water are presented in Tables 5.9.2-3 and 5.9.2-4, respectively. Several EECs were provided, as it was uncertain how the values would be used in the dietary risk assessment. If the EECs for the two compounds are considered separately, the maximum EECs for Thiamethoxam and CGA 322704 can be used (bolded values in Tables 5.9.2-3 and 5.9.2-4). These values are scattered on different application dates. If the EECs for both compounds are considered together, the highest combined EEC (same date) can be used. While transformation of Thiamethoxam to CGA 322704 does not reach its peak levels for one year, and CGA 322704 in groundwater does not reach its peak concentrations for a few years, the levels reported below indicate that CGA 322704 will likely be present along with Thiamethoxam in potential sources of drinking water.

5.9.3 Vegetation and other food sources

The applicant did not submit data on the concentrations of Thiamethoxam on crops immediately after application. Therefore, residue concentrations on vegetation were estimated using a nomogram developed by the U.S. EPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), and modified according to Fletcher et al (1994), for use in ecological risk assessment (Table 5.9.3). A wet weight to dry weight conversion was also calculated. A conservative half-life in plants of 35 days was used as a default value since no foliar dissipation studies were submitted.

5.9.4 Monitoring data

Not applicable.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The 14-day LC_{50} and NOEC to the earthworm, *Eisenia foetida*, were > 1000 mg a.i./kg soil and 1000 mg a.i./kg soil, respectively. The acute contact LD_{50} of Thiamethoxam to the honeybee, *Apis mellifera*, was 0.024 µg a.i./bee and the acute oral LD_{50} to the same species was 0.005 µg a.i./bee. In a 24-h acute foliar residue contact toxicity study using formulated Thiamethoxam, the NOEL was 0.004 µg a.i./bee (~5 g a.i./ha). Results from a field toxicity study in an apple orchard showed that formulated Thiamethoxam had no impact on honeybees, but the study was determined to be deficient.

Results of acute contact toxicity studies with formulated Thiamethoxam showed that the LR_{50} value for the predatory ladybird beetles *Coccinella septempunctata*, the predatory mite *Typhlodromus pyri* and the parasitic wasp *Aphidius rhopalosiphi* were 12.4 g a.i./ha, 41 g a.i./ha and 0.131 g a.i./ha, respectively.

The acute (21-d) oral LD_{50} and NOEC, for mortality and clinical signs, of Thiamethoxam to the bobwhite quail (*Colinus virginianus*) was 1552 and 125 mg a.i./kg body weight, respectively. The acute (14-d) oral LD_{50} of Thiamethoxam to the mallard duck (*Anas platyrhynchos*) was 576 mg a.i./kg body weight. The acute (5-d) dietary LC_{50} of Thiamethoxam to the bobwhite quail and the mallard duck was > 5200 mg a.i./kg diet, for both species. The dietary NOEC for the two species was 1300 and 163 mg a.i./kg diet, respectively. The NOEC of Thiamethoxam on the reproduction of the bobwhite and the mallard was 900 and 300 mg a.i./kg diet, respectively.

Thiamethoxam was determined to be slightly toxic to rats and moderately toxic to mice when administered as a single dose via the oral route (LD_{50}: 1563 and 871 mg a.i./kg bw, respectively). Thiamethoxam was reported to be of low toxicity to rats when administered via the dermal route (LD_{50}: > 2000 mg/kg bw). Thiamethoxam was also of low toxicity to rats when administered by the inhalation route (LC_{50}: > 3.72 mg a.i./L). Thiamethoxam was found to be non-irritating to the skin and minimally irritating to the eye of rabbits, and non-sensitizing to the skin of guinea pig.

Repeated short-term oral dosing of Thiamethoxam to Beagle dogs resulted in decreased body weights and food consumption, increased hematocrit, hemoglobin and erythrocytes, increased urea, creatinine, accompanied by increased thyroid, decreased brain weight and histopathology in liver, thymus and spleen (NOAEL: 32.6 mg a.i./kg bw/d for females and 31.6 mg a.i./kg bw/d for males). Oncogenicity studies with mice and rats indicated a trend for increase in liver weights in females, hepatocellular adenoma, hepatocellular hypertrophy, hepatocellular carcinoma, kidney lesions and necrosis of single hepatocytes (NOAEL: 2.6 and 21 mg a.i./kg bw/d, respectively). Thiamethoxam was not genotoxic and was non-mutagenic in a standard battery of genotoxicity and mutagenicity tests such as bacterial gene mutation, mammalian cell gene mutation, unscheduled DNA synthesis and mammalian cytogenetics (micronucleus assay). Thiamethoxam was not neurotoxic to rats on a subchronic basis but showed neurotoxicity on an acute basis (NOAEL: 100 mg a.i./kg bw) and was non-teratogenic to rats and rabbits.

In a multi-generation reproduction study with rats (effects on pregnancy and fetuses), Thiamethoxam caused no treatment-related adverse effects on the outcome of pregnancy nor the development of the fetuses (NOAEL: 202 mg a.i./kg bw/d, for reproductive effects in females).

Data/information on the toxicity of Thiamethoxam to non-target terrestrial vascular plants were not submitted.

The effects of Thiamethoxam on terrestrial organisms are summarized in Table 6.1.1.

6.2 Effects on aquatic organisms

The 48-hr EC_{50} of Thiamethoxam to *Daphnia magna* STRAUS was > 105.8 mg a.i./L (measured concentration). The NOEC based on immobilization effects was 36.5 mg a.i./L. The 48-hr EC_{50} of Thiamethoxam to the midge *Chironomus riparius* was 35 µg a.i./L. The NOEC based on immobilization and sublethal adverse effects, i.e. lethargic behaviour, was 13 µg a.i./L. The 21-day-chronic EC_{50} of Thiamethoxam to *Daphnia magna* STRAUS was > 100.5 mg a.i./L (measured concentration). The NOEC based on mortality and sublethal effects was 100.5 mg a.i./L (measured concentration).

The 30-day-chronic EC_{50} of Thiamethoxam to sediment dwelling *Chironomid riparius* was 0.011 mg a.i./L for exposure scenario A and 0.099 mg a.i./L for exposure scenario B. The 30-day NOEC based on emergence rate and mean development rate was 0.005 mg a.i./L and 0.043 mg a.i./L for exposure scenario A and B, respectively. The most sensitive end point was emergence rate.

The 96-h LC_{50} of Thiamethoxam to the rainbow trout (*Oncorhynchus mykiss*) was > 100 mg a.i./L. The NOEC, based on mortality/sublethal effects, was 100 mg a.i./L. The 96-h LC_{50} of Thiamethoxam to the bluegill sunfish (*Lepomis macrochirus*) was > 114 mg a.i./L. The NOEC value, based on mortality/sublethal effects, was 114 mg a.i./L. The 88-day chronic NOEC, for effects on time to hatch, hatching success, time to reach swim-up, larvae survival, fry survival, or growth, of Thiamethoxam to early life stage of rainbow trout (*Oncorhynchus mykiss*) was 20 mg a.i./L. The LOEC and MATC for each of the above endpoints were considered to be > 20 mg a.i./L.

The 96-hour acute NOEC and EC_{50} of Thiamethoxam to the green algae *Selenastrum capricornutum*, based on cell density, were 100 mg a.i./L and > 100 mg a.i./L, respectively. The NOEC and EC_{50} values based on growth rate were 100 mg a.i./L and > 100 mg a.i./L, respectively. There were no compound related phytotoxic effects. The 7-day acute NOEC and EC_{50}, based on frond number and frond dry weight, of Thiamethoxam to the freshwater floating aquatic vascular plant duckweed (*Lemna gibba*) were 90.2 and > 90.2 mg a.i./L, respectively. There were no compound related phytotoxic effects.

The 96-hr-acute LC_{50} of Thiamethoxam to saltwater mysid (*Mysidopsis bahia*) was 6.8 mg a.i./L. The 96-hour EC_{50}, based on sublethal effects, was 4.5 mg a.i./L. The 96-hr- NOEC based on mortality and sublethal adverse effects was < 2.0 mg a.i./L. The 96-hr-acute EC_{50} of Thiamethoxam to the Eastern oyster (*Crassostrea virginica*) was >119 mg a.i./L. The 96-hr-NOEC based on shell growth inhibition was 119 mg a.i./L.

The 96-h acute LC_{50} of Thiamethoxam to the sheepshead minnow (*Cyprinodon variegatus*) was > 111 mg a.i./L. The NOEC and EC_{50} values, based on mortality/sublethal effects, were 111 and > 111 mg a.i./L, respectively.

No data/information on the toxicity of Thiamethoxam to marine/estuarine algae were submitted.

The effects of Thiamethoxam on aquatic organisms are summarized in Table 6.2.1.

6.3 Effects on biological methods of sewage treatment

Not applicable.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. Environmental risk is characterized using the quotient method which is the ratio of the EEC ÷ toxicity endpoint. The endpoint used for both acute and chronic toxicity is the NOEC from the appropriate laboratory study. Those cases for which a NOEC was not reported, the value was estimated as $0.1 \times LD_{50}$ or $0.1 \times LC_{50}$. Risks were then classified based on the scheme presented in Table 6.4-1 (Appendix III).

The risk to non-target organisms was calculated using EEC values of 0.084 mg a.i./kg in a 15-cm depth of soil and 0.02 mg a.i./L in a 80-cm depth of water. For amphibians, the EEC in water in a 15 cm depth was 0.11 mg a.i./L The EEC in wildlife food sources, expressed in mg a.i./kg dw, are shown in Table 5.9.3. If, using a screening-level exposure scenario, risk was indicated, then further refinement of exposure estimates was done where possible.

6.4.1 Environmental behaviour

Thiamethoxam was determined to be very soluble in water, with low adsorption to soil, which indicates high potential for mobility in soil. Field data for broadcast application, however, indicated that there was no leaching of Thiamethoxam below 30 cm depth of soil. Field data for in-furrow application indicated that there was a greater potential for leaching in the soil owing to the detection of residues at depths up to 90 cm. It is not expected to volatilize from water and moist soil surfaces. Thiamethoxam is moderately persistent to persistent in soil and slightly to moderately persistent in water. It has a high potential for carryover to the following growing season. The principal route of transformation is biotransformation in soil and in aquatic environments. The major transformation products CGA 322704 and CGA 355190 are expected to be persistent and have a potential for mobility in soil. It should be noted that the other identified major transformation products of Thiamethoxam were not detected in the field studies of dissipation and are not likely to be formed in the environment in significant quantities. CGA 322704, is also the active ingredient clothianidin, which is registered for use as a seed treatment insecticide. The aquatic toxicity of the major transformation products CGA 355190, CGA 353042, NOA 404617 and NOA 407475 is unknown.

6.4.2 Terrestrial organisms

Non-target terrestrial invertebrates
The acute NOEC of Thiamethoxam to the earthworm (*Eisenia foetida*), is 1000 mg a.i./kg soil. Given that the maximum residue of Thiamethoxam in soil (estimated environmental concentration (EEC) in soil) would be 0.084 mg a.i./kg soil, Thiamethoxam will pose a negligible risk (Risk quotient (RQ) = 8.4×10^{-5}) to earthworms.

The acute contact NOEL of foliar residues of Thiamethoxam to the honeybee (*Apis mellifera*) is 0.004 µg a.i./bee. Based on Atkins *et al.* (1981), this value is equivalent to 4.48 g a.i./ha. Given that the maximum label rate for a single application of ACTARA 25 WG will be 96 g a.i./ha, Thiamethoxam will pose a high risk (RQ = 21.42) to the honeybee. The chronic risk to honeybees from residues of Thiamethoxam in pollen and nectar are unknown owing to the lack of data.

Terrestrial plants
Given that data on the toxicity of Thiamethoxam to non-target terrestrial plants were not submitted, it is not possible to assess the environmental risk that this product may pose to non-target vegetation if exposure occurs by over spray or spray drift.

Wild birds
Thiamethoxam will pose a negligible acute risk to bobwhite quail and mallard duck, based on a RQs of 0.02 and 0.004, respectively.

The most sensitive endpoint is adverse effects on reproduction of the bobwhite quail (*Colinus virginianus*) and the mallard duck (*Anas platyrhynchos*), with a NOEC of 900 mg a.i./kg diet and 300 mg a.i./kg diet, respectively.

Wild birds, such as bobwhite quail and mallard duck, could be exposed to Thiamethoxam residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey.

The bobwhite diet may consist of approximately 27 % small insects and 73 % seeds (EPA 1993). Since the EECs of Thiamethoxam on small insects and pods with seeds are 34.5 and 7.3 mg a.i./kg dry weight, respectively (Table 5.10.4), the estimated ingestion of Thiamethoxam via contaminated food sources by the bobwhite can be calculated as follows:

$$(0.27 \times 34.5) + (0.73 \times 7.3) = 14.64 \text{ mg a.i./kg dry weight}$$

The bobwhite quail (live weight 170 grams) daily consumes food equivalent to 8.94 % of its body weight (Urban and Cook, 1986). Therefore, the bird would acquire a dose of:

$$(0.089 \times 170) \times 14.64 \div 1000 = 0.22 \text{ mg a.i./day}$$
equivalent to: $(1000 \div 170) \times 0.22 =$ **1.3** mg a.i./kg body weight/day

The mallard duck diet may consist of approximately 10 % large insects or snails, 10 % leafy plants and 80 % grain (EPA 1993). Since the EECs of Thiamethoxam on large insects, leaves/leafy plants and grain are 5.91, 215.3 and 5.91 mg a.i./kg dry weight, respectively (Table 5.10.4), the estimated ingestion of Thiamethoxam through contaminated food sources by the mallard can be calculated as follows:

$$(0.10 \times 5.91) + (0.10 \times 215.3) + (0.80 \times 5.91) = 26.85 \text{ mg a.i./kg dry weight}$$

The mallard duck (live weight 1.2 kg) daily consumes food equivalent to 4.17 % of its body weight (Urban and Cook, 1986). Therefore, the bird would acquire a dose of:

$$(0.041 \times 1200) \times 26.85 \div 1000 = 1.32 \text{ mg a.i./day}$$
$$\text{equivalent to: } (1000 \div 1200) \times 1.32 = \mathbf{1.1} \text{ mg a.i./kg body weight/day}$$

These values are lower than the NOECs for the bobwhite quail and the mallard duck (converted to mg a.i./kg body weight/day) at which there were no adverse reproductive effects on the test birds. It is, therefore, expected that Thiamethoxam will pose a negligible risk to the bobwhite quail (RQ = 0.016) or the mallard duck (RQ = 0.08) on a reproductive effects basis.

Wild mammals

The most likely route for exposure of wild mammals to Actara 25 WG would be through consumption of food contaminated with Thiamethoxam insecticide.

For purposes of this assessment, the acute oral LD_{50} of Thiamethoxam to mouse (871 mg a.i./kg body weight) is used. The clinical symptoms in dosed mice included clonic convulsion, decrease in spontaneous movement or prone position, and decrease in body weight gain in surviving females on the day following dosing. Since data on the toxicity of Thiamethoxam to wild mammals were unavailable, the mouse acute oral LD_{50} was used as a surrogate endpoint for small, medium and large wild mammals.

Assuming that a small mammal (body weight 0.015 kg), medium mammal (body weight 0.035 kg) and a large mammal (body weight 1 kg), each consume food at 14.6%, 12.5 % and 6.9 %, respectively, of their body weight per day (Nagy, 1987), the estimated food consumption by each mammal would be:

$$\text{small mammal: } 0.015 \text{ kg} \times 14.6\ \% = 0.0022 \text{ kg/day } (= 146.6 \text{ g/kg body weight/d})$$
$$\text{medium mammal: } 0.035 \text{ kg} \times 12.5\ \% = 0.0044 \text{ kg/day } (= 125.7 \text{ g/kg body weight/d})$$
$$\text{large mammal: } 1.0 \text{ kg} \times 6.9\ \% = 0.069 \text{ kg/day } (= 69.0 \text{ g/kg body weight/d})$$

The mouse diet consists of approximately 25 % short grass, 50 % grain/seeds and 25 % leaves/leafy crops (EPA 1993). Since the EECs of Thiamethoxam on short grass, grain/seeds and leaves/leafy crops are 123.4, 5.91 and 215.3 mg a.i./kg dry weight, respectively (Table 5.10), the estimated ingestion of Thiamethoxam via contaminated food sources by the mouse can be calculated as follows:

$$(0.25 \times 123.4) + (0.50 \times 5.91) + (0.25 \times 215.3) = 87.63 \text{ mg a.i./kg dry weight}$$

Therefore, the estimated dose acquired by the wild mammal would be:

small mammal:
$(146.6 \times 87.63) \div 1000 = 12.84$ mg a.i./kg bw/day

medium mammal:
$(125.7 \times 87.63) \div 1000 = 11.01$ mg a.i./kg bw/day

large mammal:
(69.0 × 87.63) ÷ 1000 = 6.04 mg a.i./kg bw/day

The calculated RQs for small, medium and large wild mammals are 0.014, 0.012 and 0.007, respectively. Thiamethoxam, therefore, will pose a negligible risk to wild mammals on an acute basis when used as a foliar spray.

The risk of Thiamethoxam to terrestrial organisms is summarized in Table 6.4.2.

6.4.3 Aquatic organisms

Non-target aquatic invertebrates
The most sensitive endpoint is chronic effects on the chironomid midge (*Chironomus riparius*) with a NOEC of 5 µg a.i./L. An assessment using the direct over spray (screening level) scenario indicated a moderate risk to *C. riparius* (RQ = 4). Therefore, a refined aquatic ecoscenario (Level 1 runoff simulation) was used to model EEC in water. Given that the refined EEC in water will be 4.2 µg a.i./L, Thiamethoxam will pose a negligible risk (RQ = 0.84) to aquatic invertebrates, such as the chironomid midge.

Non-target marine/estuarine invertebrates
The most sensitive endpoint is acute effects on the saltwater mysid (*Mysidopsis bahia*) with a NOEC of 2 mg a.i./L. Given that the EEC of Thiamethoxam in water will be 0.020 mg a.i./L, Thiamethoxam will pose a negligible risk (RQ = 0.01) to marine/estuarine invertebrates, such as the saltwater mysid.

Fish
Thiamethoxam will pose a negligible acute risk to fish, based on a RQ of 0.002 to rainbow trout.

The most sensitive endpoint is adverse effects on early life-stages of the rainbow trout (*Oncorhynchus mykiss*) with a NOEC of 20 mg a.i./L. Given that the EEC of Thiamethoxam in water will be 0.020 mg a.i./L, Thiamethoxam will pose a negligible risk (RQ = 0.001) to fish.

Amphibians
The most sensitive surrogate endpoint for amphibians is adverse effects on early life-stages of the rainbow trout (*Oncorhynchus mykiss*) with a NOEC of 20 mg a.i./L. Given that the EEC of Thiamethoxam in water body 15 cm deep will be 0.11 mg a.i./L, Thiamethoxam will pose a negligible risk (RQ = 0.005) to amphibians.

Aquatic plants and algae
The most sensitive endpoint is adverse effects on the duckweed (*Lemna gibba*) with an acute NOEC of 90.2 mg a.i./L. Given that the EEC of Thiamethoxam in water will be 0.020 mg a.i./L, Thiamethoxam will pose a negligible risk (RQ = 0.0002) to aquatic organisms, such as the freshwater alga.

The risk of Thiamethoxam to aquatic organisms is summarized in Table 6.4.3-a and 6.4.3-b.

6.4.4 Incident reports and additional considerations

Not applicable.

6.5 Risk mitigation

Thiamethoxam will be moderately persistent to persistent in soil under field conditions in Canada. Thiamethoxam was determined to be very soluble in water, with low adsorption to soil, which indicates high potential mobility in soil. Field data for broadcast application, however, indicated that there was no leaching of Thiamethoxam below 30 cm depth of soil. Field data for in-furrow application indicated that there was a greater potential for leaching in the soil owing to the detection of residues at depths up to 90 cm.

The major transformation products CGA 322704 and CGA 355190 are expected to be persistent and have a potential to be mobile in soil. It should be noted that CGA 322704 is also the active ingredient clothianidin, which is registered for use as a seed treatment insecticide.

Thiamethoxam will pose a high risk to honeybees and other beneficial arthropods such as predatory and parasitoid insects.

There are no data on the toxicity of Thiamethoxam to terrestrial and marine/estuarine plants, as well as systemic residues to honeybees under field conditions.

The aquatic toxicity of the major transformation products CGA 355190, CGA 353042, NOA 404617 and NOA 407475 is unknown.

The risk posed by Thiamethoxam to beneficial arthropods can be mitigated by precautionary label statements contraindicating application in a manner that will result in exposure of these organisms to the active ingredient.

Calculation of Buffer Zones
For a summary of the calculation, and the size requirement of buffer zones, see table 6.5.1 and Table 6.5.2 (Appendix III).

Mitigative Labelling
LABEL REVISIONS FOR ACTARA 240 SC (IN-FURROW USE)

In both, label and the booklet for Actara 240 SC, the following revisions are required:

In the section entitled "**Environmental Precautions**", the proposed statements therein should be **replaced** by the following:

DO NOT apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands), estuaries or marine habitats.

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

This product is toxic to bees exposed to direct treatment or to residues on blooming crops and weeds. DO NOT apply this product to flowering crops or weeds if bees are visiting the treatment area. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site.

This product is toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

Thiamethoxam is persistent and will carryover. It is recommended that any products containing Thiamethoxam not be used in areas treated with this product during the previous season.

The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow.

To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted or fine textured such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

LABEL REVISIONS FOR ACTARA 25 WG (FOLIAR USE)

In both, label and the booklet for Actara 25 WG, the following revisions are required:

In the section entitled "**Environmental Precautions**", the proposed statements therein should be **replaced** by the following:

DO NOT apply this product directly to freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands), estuaries or marine habitats.

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

This product is toxic to bees exposed to direct treatment or to residues on blooming crops and weeds. DO NOT apply this product to flowering crops or weeds if bees are visiting the treatment area. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site.

This product is toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

Thiamethoxam is persistent and will carryover. It is recommended that any products containing Thiamethoxam not be used in areas treated with this product during the previous season.

The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable (e.g. sandy soil) and/or the depth to the water table is shallow.

To reduce runoff from treated areas into aquatic habitats, consider the characteristics and conditions of the site before treatment. Site characteristics and conditions that may lead to runoff include, but are not limited to: heavy rainfall, moderate to steep slope, bare soil, poorly draining soil (e.g. soils that are compacted or fine textured such as clay).

Avoid application of this product when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

In the booklet for Actara 25 WG, the following additional revisions are required:

1) A section entitled **Environmental Hazards** should be inserted in the booklet for Actara 25 WG.

2) In the section entitled **Environmental Hazards**, the following statement should be inserted:

TOXIC to aquatic organisms. Observe buffer zones specified under **Application Procedures**.

3) In the section entitled **Application Procedures**, the following statements should be inserted:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) fine classification.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

DO NOT apply by air.

Buffer zones:

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands).

Method of application	Crop	Buffer Zones (metres) Required for the Protection of: Freshwater Habitat of Depths:		
		Less than 1 m	1 - 3 m	Greater than 3 m
Airblast (early growth stage)	Apple, pear, crabapple	4	3	1

4) In the section entitled **Pollinator Precautions** under **Use Directions** for potato, the waiting period should be revised to 5 days from 3 days.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Syngenta Crop Protection Canada Inc., has applied for registration of two Commercial class end-use products, Actara 240 SC and Actara 25 WG Insecticides. Both products contain the active ingredient Thiamethoxam. Actara 240 SC is for use as an in-furrow treatment at potato planting to control Colorado potato beetle, aphids and potato leafhopper. Actara 25 WG is a foliar insecticide for use on potato to control Colorado potato beetle, aphids and potato leafhopper and on pome fruit to control plum curculio, spotted tentiform leafminer, rosy apple aphid, pear psylla and mullein bug.

7.1.2 Mode of action

Thiamethoxam is a second generation neonicotinoid and an agonist of the nicotinic acetylcholine receptor. It affects synapses in the insect central nervous system, and has contact, stomach and systemic activity. When applied as a seed treatment, or as an in-furrow treatment to potato pieces, it has systemic activity, and is transported acropetally in the xylem of the plant. When applied as a foliar spray, Thiamethoxam has translaminar activity.

7.1.3 Crops

Actara 240 SC Insecticide is for use on potatoes and Actara 25 WG is for use on potatoes and pome fruit (apples, crabapples, pear and Oriental pear).

7.1.4 Effectiveness against pests

Effectiveness of Actara 240 SC and Actara 25 WG on potato

Application rates of Actara 240 SC tested in efficacy trials ranged from 0.60 to 1.15 g a.i./100 m row, and two or three application rates of Thiamethoxam were tested in each trial. Application rates of Actara 25 WG tested were 13 and 26 g a.i./ha, and both application rates were tested side-by-side in 13 trials. All trials included an untreated control and imidacloprid as a commercial standard, although pymetrozine was included as a commercial standard for aphid control in two trials.

Colorado potato beetle on potato

Data from thirteen trials conducted in Canada were evaluated and assessed parameters including larval counts and percent defoliation. Efficacy data supported control of Colorado potato beetle, aphids (including green peach aphid, foxglove aphid, etc.) and potato leafhopper at application rates of 3.4 - 4.4 mL product/100 m row (0.82 - 1.06 g a.i./100 m) for Actara 240 SC and 105 g product/ha (26 g a.i./ha) for Actara 25 WG (see table 7.6-1). For in-furrow treatment with Thiamethoxam (Actara 240 SC), a rate effect for control of Colorado potato beetle was consistently demonstrated in efficacy trials, with the higher application rate (1.06 g a.i./100 m) providing extended control. Performance of Actara 240 SC and Actara 25 WG at the supported application rate(s) was comparable to that of the commercial standard. No phytotoxic effects were observed in any of the trials. Two applications at a 7 - 10 day interval may be needed for control.

Potato leafhopper and aphids on potato

Data from seven trials on leafhopper and five trials on aphids were evaluated. Assessment of aphids included counts for green peach aphid and potato aphid in three trials; in the other trials, counts for all aphid species were pooled. Assessment for potato leafhopper were counts of the nymph and/or adult stages, and percent foliar damage. At supported application rates, performance of Thiamethoxam for control of potato leaf hopper as an in-furrow treatment and for control of aphids as an in-furrow and foliar treatment was comparable to that of imidacloprid, the registered commercial standard. Three studies demonstrated that foliar application of Actara 25 WG provided significant reduction (76-100%) in the numbers of leafhopper nymphs. There was no evidence for control of leafhopper adults, but evidence for this extremely mobile life stage would be difficult to obtain.

Effectiveness of Actara 25 WG on pome fruit

Spotted tentiform leafminer on pome fruit

Data from four trials conducted in Ontario on apple and conclusions from three previously reviewed trials conducted in New York were used to assess efficacy. Under sufficient pest pressure, Thiamethoxam provided adequate control of spotted tentiform leafminer on apple across a wide range of application rates (20-96 g a.i./ha), including the proposed rates of 79 g a.i./ha applied pre-bloom and 79-96 g a.i./ha applied post-bloom. A rate response was not observed; therefore, the lowest proposed rate, 79 g a.i./ha, is sufficient for control of spotted tentiform leafminer when applied both pre- and post-bloom.

Rosy apple aphid on pome fruit

Data from two trials conducted in Ontario and Nova Scotia were submitted; however, one of the trials had insufficient pest pressure and was not considered reliable. As well, conclusions from five trials on rosy apple aphid and six trials on green apple aphid conducted in New York and Washington were considered in the efficacy assessment. Rates from 12.5-96 g a.i./ha were assessed, and it was concluded that 40 g a.i./ha was the lowest effective rate for rosy apple aphid on pome fruit when applications are made both pre- and post-bloom.

Mullein bug on pome fruit

Data from three trials conducted in Ontario were assessed for efficacy to control mullein bug. The assessed rates include 48-79 g a.i./ha applied pre-bloom at the pink stage and 79-96 g a.i./ha applied post-bloom. A rate response indicated that 79 g a.i./ha is the lowest effective rate for control of mullein bug; therefore, the proposed rates of 79 g a.i./ha applied prebloom and 79-96 g a.i./ha applied post-bloom are acceptable.

Plum curculio on pome fruit

Data from two trials on apple and three trials on pear, all conducted in Ontario, as well as the conclusions from three previously reviewed trials on apple that were conducted in Michigan and New York and two on pear that were conducted in Ontario, were assessed for efficacy. Rates from 40-96 g a.i./ha were assessed. The proposed application rates, 79 g a.i./ha applied pre-bloom to apples and 79-96 g a.i./ha applied post-bloom to apples and pears, are considered to be acceptable.

Pear psylla on pome fruit

Data from five trials on pear that were conducted in Ontario were assessed, as were the conclusions from four previously reviewed trials that were conducted in New York, Washington, and Ontario. Rates from 50-96 g a.i./ha were assessed. The proposed application rates, 79-96 g a.i./ha applied post-bloom, are considered to be adequate and represent the lowest effective rate for pear psylla.

7.1.5 Total spray volume

Actara 240 SC is to be applied as an in-furrow spray during planting and should be sprayed directly on the seed pieces or seed potatoes in the furrow. Water volume should be sufficient to ensure good coverage of seed pieces or potatoes.

Actara 25 WG is to be applied as a foliar treatment to potatoes by conventional ground application equipment. Sufficient water volume should be used to ensure thorough coverage of foliage, and should not be less than 100 L/ha. For pome fruit, Actara 25 WG is to be applied as a foliar treatment by conventional ground application equipment. A minimum spray volume of 1000 L/ha is recommended; however, if adequate spray coverage of the plant canopy requires less water per hectare, the spray volume should be adjusted accordingly while using the same spray concentration (ratio of litres of product to litres of water).

7.2 Phytotoxicity to target plants or target plant products (OECD 2.7.6)

Based on the submitted trials, phytotoxicity is not likely on potato or pome fruit provided that the label directions are followed.

7.3 Observations on undesirable or unintended side effects

7.3.1 Impact on succeeding crops

Not applicable.

7.3.2 Impact on adjacent crops

Not applicable.

7.3.3 Impact on seed viability

Not applicable.

7.3.4 Tank mixing recommendations

Tank mixes were not proposed.

7.4 Economics

The economics were not assessed.

7.5 Sustainability

7.5.1 Survey of alternatives

The major alternative insecticide active ingredients currently registered for control of listed pests on potato include, but are not necessarily limited to, the following:

Pest	Available Alternative Active Ingredients
Colorado potato beetle	carbamates (carbaryl, carbofuran, oxamyl), organophosphates (azinphos-methyl, chlorpyrifos, diazinon, malathion, methamidophos, naled, phosmet), cyclodiene organochlorine (endosulfan), methoxychlor, pyrethrin, pyrethroids (cypermethrin, deltamethrin, lambda-cyhalothrin, permethrin), neonicotinoids (acetamiprid, imidacloprid), spinosyns (spinosad), insect growth regulators (cyromazine), biologicals (*Bacillus thuringiensis* ssp. *tenebrionis*), diatomaceous earth (silicon dioxide), rotenone, and potassium salts of fatty acids.

Pest	Available Alternative Active Ingredients
Aphids (including green peach aphid, potato aphid, floxglove aphid, and buckthorn aphid)	carbamates (methomyl, pirimicarb), organophosphates (acephate, chlorpyrifos, diazinon, dimethoate, malathion, methamidophos), cyclodiene organochlorine (endosulfan), pyrethroids (deltamethrin, permethrin), neonicotinoids (imidacloprid), pymetrozine
Potato leafhopper	carbamates (carbaryl, carbofuran, methomyl, oxamyl, pirimicarb), organophosphates (azinphos-methyl, acephate, diazinon, dimethoate, malathion, methamidophos, naled), cyclodiene organochlorine (endosulfan), methoxychlor, pyrethrin, pyrethroids (cypermethrin, deltamethrin, lambda-cyhalothrin, permethrin), neonicotinoids (imidacloprid)

The major alternative insecticide active ingredients currently registered for control of listed pests on pome fruit include, but are not necessarily limited to, the following:

Pest	Available Alternative Active Ingredients
Plum curculio on apple	carbamates (carbaryl), organophosphates (azinphos-methyl, malathion, phosalone, phosmet), pyrethroids (cypermethrin, lambda-cyhalothrin, permethrin), kaolin clay
plum curculio on pear	carbamates (carbaryl), organophosphates (azinphos-methyl, malathion, phosmet), pyrethroids (cypermethrin), kaolin clay
Pear psylla on pear	carbamates (carbaryl), organophosphates (azinphos-methyl, diazinon, dimethoate, malathion, phosalone, phosmet), cyclodiene organochlorine (endosulfan), pyrethroids (deltamethrin, lambda-cyhalothrin, permethrin), pyrethrin, neonicotinoids (acetamiprid), avermectins (abamectin), amitraz, pyridaben, potassium salts of fatty acids, kaolin clay, mancozeb, mineral oil
Rosy apple aphid on apples	carbamates (methomyl, oxamyl on non-bearing trees, phosalone, pirimicarb), organophosphates (diazinon, malathion, phosmet), cyclodiene organochlorines (endosulfan), pyrethroids (deltamethrin, lambda-cyhalothrin), pyrethrin, neonicotinoids (acetamiprid, imidacloprid), potassium salts of fatty acids
Mullein bug on apples	carbamates (methomyl), organophosphates (azinphos-methyl, diazinon), pyrethroids (cypermethrin, deltamethrin, permethrin) neonicotinoids (imidacloprid)
Spotted tentiform leafminer on apples	carbamates (carbaryl, methomyl, oxamyl), organophosphates (diazinon, phosmet), pyrethroids (cypermethrin, lambda-cyhalothrin, permethrin), neonicotinoids (acetamiprid, imidacloprid), avermectins (abamectin), diacylhydrazines (methoxyfenozide, tebufenozide)

Non-chemical practices

A number of non-chemical control practices have been developed for Colorado potato beetle that usually focus on reducing the overwintering population. Crop rotation is one of the few non-chemical control practices currently available to potato growers, and can significantly reduce numbers of Colorado potato beetle in a potato field. This practice may also concentrate beetles on the periphery of a field, where insecticides can be applied as a spot treatment. However, not all growers can use this strategy because they may not have the land needed for rotation or they

cannot grow economically valuable alternative crops. Another example of a non-chemical control practice for the Colorado potato beetle is the use of early plantings of potatoes around the border of fields. Border plantings, planted one to two weeks prior to the rest of the field, may act to concentrate spring adults. However, alternative host crops used in rotation or near the potato crop can adversely affect this control practice. Removal of volunteer plants and cull piles in the spring, propane flaming, and use of trench traps are other methods that may help reduce overwintering populations. Another option available to growers is the use of the biological control agent, *Beauveria bassiana*, an entomopathogenic fungus, which attacks larvae and adults of the Colorado potato beetle. The bacterium *Bacillus thuringiensis* has also shown to be an effective biological control agent under the appropriate conditions.

Cultural controls for aphids include planting field borders with non-host crops to attract aphids and cleanse their mouthparts of non-persistent viruses before they entr into the potato crop. To limit the spread of viruses, only certified seed should be used, and top-killing of potato plants should be done soon after aphid flight begins. Cultural control for potato leafhoppers include the avoidance of forages, such as alfalfa, near potato fields. When forage crops are harvested, leafhoppers may migrate into any nearby potato fields.

General management practices in an orchard can help reduce the infestation level of some insect pests. Alternate hosts should be removed from the area surrounding the orchard. Wild hosts and abandoned fruit trees can become a reservoir for pests and lead to unnecessary insecticide sprays (Solymar, 1999). Some pest specific cultural controls are available. For plum curculio, fruit that has dropped should be removed from the orchard and destroyed in June or July prior to emergence of the larvae for pupation in the soil (Cornell Cooperative Extension, 2001). To control spotted tentiform leafminer, mulching and application of urea to fallen leaves may enhance their decomposition and reduce the number of overwintering leafminers. As well, biological controls, such as the parasitoid *Pholetesor ornigis*, a Braconid wasp, and several species of chalcid wasps, are important for the control of populations in eastern Canada. In B.C., *Pnigalio flavipes* is the primary natural enemy of leafminers (AAFC, 2004). Terminal growth on pome fruit can become extensive when too much nitrogen fertilizer is applied, which may attract aphids and pear psylla (AAFC, 2004; British Columbia Ministry of Agriculture and Lands, 2004). To better manage nitrogen levels in the orchard and prevent over-fertilization, a leaf analyses should be completed annually. As well, summer pruning should be avoided until terminal buds have set to prevent shoot regrowth. There are many natural predators of aphids that may make insecticides unnecessary (AAFC, 2004). *Syrphids*, lacewings and ladybird beetles are good aphid predators and often keep populations below economically damaging levels. The presence of these predators around aphid colonies should be noted (Schooley, 2005).

7.5.2 Compatibility with current management practices including integrated pest management

Use of Actara 240 SC on potato and Actara 25 WG on potato and pome fruit is compatible with current management practices and can be applied with conventional ground application equipment used in potato and pome fruit production for insect pest management. Growers are familiar with the monitoring techniques to determine if and when applications are needed.

7.5.3 Contribution to risk reduction

The contribution to risk reduction was not assessed.

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

Development of resistance to Thiamethoxam has been noted in Colorado potato beetle on potato in the eastern United States. Research indicates that Colorado potato beetles highly resistant to imidacloprid may also demonstrate resistance to Thiamethoxam (Byrne et al., 2003; Graffius, 2005). Plum curculio, pear psylla, mullein bug, aphids, or spotted tentiform leafminer have no documented resistance to Thiamethoxam or any other neonicotinoid; however, prudence in the use of insecticides in the neonicotinoid class should be observed to prevent the development of resistance.

7.6 Conclusions

The following conclusions are based on a complete review of the submitted efficacy data for Actara 240 SC and Actara 25 WG on potato and pome fruit:

1. Adequate efficacy data have been submitted for Actara 240 SC to support the control of Colorado potato beetle, aphids (including green peach aphid, buckthorn aphid, foxglove aphid, and potato aphid), and potato leafhopper on potato when applied at an application rate at 3.4 - 4.4 mL product/100 m (0.82 - 1.06 g a.i./ha/100 m). Actara 240 SC can be applied once per year as an in-furrow spray during planting. The higher applicant rate is used for extended control.

2. Adequate efficacy data have been submitted for Actara 25 WG to support the control of Colorado potato beetle, aphids (including green peach aphid, buckthorn aphid, foxglove aphid, and potato aphid), and potato leafhopper on potato when applied at an application rate of 105 g product/ha (26 g a.i./ha). Actara 25 WG can be applied as a foliar spray using conventional ground application equipment, and should be applied before pests reach damaging levels. Control may require the use of two applications at 7 - 10 day intervals.

3. Adequate efficacy data have been submitted to support the control of the following pests on apples and crabapples: plum curculio and mullein bug at a rate(s) of 315 g Actara 25 WG/ha when applied pre-bloom and 315 - 378 g Actara 25 WG/ha when applied post bloom, spotted tentiform leafminer at a rate of 315 g Actara 25 WG/ha when applied pre and post-bloom, and rosy apple aphid at a rate of 160 g Actara 25 WG/ha when applied pre and post-bloom.

4. Adequate efficacy data have been submitted to support the control of the following pests on pear and Oriental pear: plum curculio and pear psylla at rates of 315 - 385 g Actara 25 WG/ha when applied post-bloom.

5. The maximum amount of Actara 25 WG to be applied to pome fruit per year is 770 g/ha with no more than two applications. There should be a minimum of 10 days between applications. Higher application rates tended to perform more consistently and for longer periods of time than lower rates. Application timing and good plant coverage are critical for effective performance. Application timing is summarized in Table 7.6-1.

6. Phytotoxicity is not likely on potatoes and pome fruit if the label directions are followed.

7.6.1 Summary

Actara 240 SC and Actara 25 WG are for use on potato to control Colorado potato beetle, aphids (including green peach aphid, buckthorn aphid, foxglove aphid, and potato aphid), and potato leafhopper. Actara 25 WG is also for use on pome fruit to control spotted tentiform leafminer, mullein bug, rosy apple aphid, and plum curculio on apple and crabapple, and plum curculio and pear psylla on pear and Oriental pear. The technical active ingredient, Thiamethoxam is classified as a Group 4 insecticide, a neonicotinoid. Acceptable application rates and a summary of application timings are provided in Table 7.6-1. Phytotoxicity is not likely on potatoes and pome fruit if the label directions are followed.

Table 7.6-1. Acceptable pests and application rates for use of Actara 240 SC and Actara 25 WG for control of Colorado potato beetle, aphids (including green peach aphid, buckthorn aphid, foxglove aphid, and potato aphid), and potato leafhopper on potatoes.

Pest Crop	Product	Application Rate	Remarks
Colorado potato beetle, aphids (including green peach aphid, buckthorn aphid, foxglove aphid, and potato aphid), and potato leafhopper on potatoes	Actara 240 SC	3.4 - 4.4 mL product/100 m (0.82 - 1.06 g a.i./ha/100 m). Use the higher rate for extended control.	One application per year. Apply as an in-furrow spray during planting. Do not follow a soil application of ACTARA 240 SC Insecticide with a foliar application of ACTARA 25 WG Insecticide
	Actara 25 WG	105 g product/ha (26 g a.i./ha)	Apply as a foliar spray before pests reach damaging levels. Scout fields and treat again in 7-10 days if populations rebuild to potentially damaging levels. Use sufficient water volume to ensure thorough coverage of foliage. Do not use less than 100 L/ha.

Pest Crop	Product	Application Rate	Remarks
Plum curculio and mullein bug on apples and crabapples	Actara 25 WG	315 g product/ha (79 g a.i./ha)	PRE-BLOOM: one application only. Apply before pests reach damaging levels. Mullein bug: Apply only when thresholds have been reached. Plum Curculio: Consult local extension personnel for recommendations relevant to your area
		315-385 g product/ha (79-96 g a.i./ha)	POSTBLOOM: up to 2 applications. Apply before pests reach damaging levels. Allow a minimum of 10 days between applications. Mullein bug: Make first application immediately after petal fall, when thresholds have been reached. A second application may be necessary if pest pressure continues. Plum curculio: Make first application immediately following petal fall. A second application may be necessary if pest pressure continues.
Spotted tentiform leafminer on apples and crabapples	Actara 25 WG	315 g product/ha (79 g a.i./ha)	Apply before pests reach damaging levels. Allow a minimum of 10 days between applications. PRE-BLOOM: one application only. Apply when eggs are being deposited POSTBLOOM: up to 2 applications To control first generation populations make application immediately following petal fall. For control of second and third generations make applications to coincide with egg deposition.
Rosy apple aphid on apples and crabapples	Actara 25 WG	160 g product/ha (40 g a.i./ha)	Apply before pests reach damaging levels. Allow a minimum of 10 days between applications. PREBLOOM: one application only Apply when aphid colonies are first observed at the green tip through pink growth stage before leaf curling occurs. POSTBLOOM: up to 2 applications Apply before leaf curling occurs.

Pest Crop	Product	Application Rate	Remarks
Plum curculio and pear psylla on pear and Oriental pear	Actara 25 WG	315-385 g product/ha (79-96 g a.i./ha)	POST-BLOOM ONLY: up to 2 applications. Apply before pests reach damaging levels. Allow a minimum of 10 days between applications. Pear psylla: Apply immediately following petal fall. A second application may be necessary if pest pressure continues. Plum curculio: Apply immediately following petal fall. A second application may be necessary if pest pressure continues.

8.0 Toxic Substances Management Policy considerations

During the review of Thiamethoxam and its end-use products Actara 25 WG and Actara 240 SC, the PMRA has taken into account the federal Toxic Substances Management Policy[5] and has followed its Regulatory Directive DIR99-03[6]. It has been determined that this product does not meet TSMP Track-1 criteria because of the following:

1. The value for half-life of Thiamethoxam technical in soil (353 days) is above the TSMP Track-1 cut-off criteria for soil (≥ 182 days). The half-life of Thiamethoxam in water and sediment (50 days), however, is below the TSMP Track-1 cut-off criteria for water and sediment (≥ 182 days). Persistence in air was not determined as Thiamethoxam is unlikely to volatilize, based on its low vapour pressure.

2. Thiamethoxam is not bioaccumulative. Studies have shown that the n-octanol/water partitioning coefficient (log K_{ow}) is −0.13, which is below the TSMP Track-1 cut-off criterion of ≥ 5.0.

3. Thiamethoxam does not contain any by-products or microcontaminants known to be Track-1 substances. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

4. The formulated products do not contain any formulants that are known to contain TSMP Track-1 substances.

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5 The federal Toxic Substances Management Policy is available through Environment Canada's web site at www.ec.gc.ca/toxics.

6 The PMRA's *Strategy for Implementing the Toxic Substances Management Policy*, DIR99-03, is available through the Pest Management Information Service: phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); fax 613-736-3798; e-mail pminfoserv@hc-sc.gc.ca or through our web site at www.pmra-arla.gc.ca.

5. The persistence, bioaccumulation and toxicity of the major transformation product CGA 355190 is unknown. Therefore, the potential for the entry of a TSMP Track-1 substances into the environment, resulting from the use of Actara 25 WG and Actara 240 SC cannot be determined.

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

9.0 Regulatory decision

9.1 Regulatory decision

The active ingredient Thiamethoxam and the end-use products Actara 25 WG Insecticide and Actara 240 SC Insecticide have been granted conditional registrations for the control of various insects on pome fruit and potatoes. Actara 240 SC is applied to potato using in-furrow application equipment to control Colorado potato beetle, aphids and potato leafhopper. Actara 25 WG is applied to potatoes and pome fruit using foliar application equipment to control Colorado potato beetle, aphids and potato leafhopper on potato and plum curculio, spotted tentiform leafminer, rosy apple aphid, pear psylla and mullein bug on pome fruit. Conditional registration is granted pursuant to the Pest Control Products Regulations subject to the fulfilment of the data requirements listed in section 9.2.

9.2 Data requirements

Thiamethoxam technical

DACO 8.2.1	N-octanol-water partitioning coefficient for the major transformation product CGA-355190.
DACO 8.2.2.1	Analytical methodology for soil.
DACO 8.2.2.3	Analytical methodology for water.
DACO 8.2.2.4	Analytical methodology for biota.
DACO 9.3.4	Toxicity of the major transformation products CGA-355190, CGA-353042, NOA-404617 and NOA-407475 to an aquatic invertebrate (*Chironomus* sp.)

ACTARA 25 WG (in-furrow use)

No data gaps identified.

ACTARA 240 SC (foliar spray)

DACO 9.2.9	Toxicity of Thiamethoxam to honey bees, including from systemic residues, under field conditions (monitoring study).
DACO 9.8.4	Toxicity of Thiamethoxam to terrestrial plants (plant screening data).

List of Abbreviations

°C	degree Celsius
µg	microgram
µL	microlitre
a.i.	active ingredient
ADI	acceptable daily intake
AlkP	alkaline phosphatase
ALT	alaminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
BrdU	Bromodeoxyuridine
BROD	benzyloxyresorufin-*O*-debenzylase
bw	body weight
bwg	body-weight gain
CAS	Chemical Abstracts Service
cm	centimetre
DFR	dislodgeable foliar residue
DT_{50}	dissipation time 50%
dw	dry weight
EC_{50}	effect concentration 50%
EEC	expected environmental concentration
EROD	ethoxyresorufin-*O*-deethylase
EXAMS	Exposure Analysis Modeling System
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
fw	fresh weight
g	gram
GGT	gamma glutamyl transferase
GLC	gas liquid chromatography
ha	hectare
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit
HDW	red blood cell distribution width
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography with mass spectrometry
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPLC-UV	high performance liquid chromatography with ultraviolet detection
Ht	hematocrit
ILV	independent laboratory validation
iNOS	inductible nitric oxide synthase
kg	kilogram
K_d	adsorption coefficient
K_{oc}	organic carbon partition coeffient
K_{ow}	*n*-octanol–water partition coefficient

L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LR_{50}	lethal rate 50%
LOAEL	lowest observed adverse effect level
LOEC	no observed effect concentration
LOQ	limit of quantitation
m	metre
MAS	maximum average score
MATC	maximum acceptable toxicant concentration
MCV	mean cell volume
MCH	mean cell hemoglobin
mg	milligram
MIS	maximum irritation score
mL	millilitre
MMAD	mass median aerodynamic medium
MOE	margin of exposure
mol	molar
MRL	maximum residue limit
N/A	not applicable
NQ	not quantifiable
nm	nanometre
NO	nitric oxide
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NOEC	no observed effect concentration
Pa	Pascal
PBI	plantback interval
PHI	plantharvest interval
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
ppm	parts per million
PMRA	Pest Management Regulatory Agency
PROD	pentoxyresorufin-*O*-depentylase
PRZM	Pesticide Root Zone Model
RBC	red blood cell
RQ	risk quotient
SDEV	standard deviation
$t_{1/2}$	half-life
TSMP	Toxic Substances Management Policy
TRR	total radioactive residue
UF	uncertainty factor
UV	ultraviolet

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Appendix I Toxicology

METABOLISM

Rate and extent of absorption and excretion: Rapidly absorbed and eliminated in rats and mice. Absorption, distribution metabolism and excretion were independent of sex, dose, pretreatment and position of the radiolabel. **Rats:** Blood concentrations peaked at 4-6 hours, followed by rapid elimination. The half-life of elimination of the radioactivity in blood was 3 hours. Thiamethoxam was the major component detected in blood extracts (82%) followed by CGA 322704 (16%). Only trace amounts of CGA 265307 (0.3%) were found andCGA 330050 was not detected. Approximately 84-95% of the dose is excreted in the urine and 2.5-6% is excreted in the faeces within 24 hours. Less than 0.2% of the dose was detected in expired air. Approximately 20-30% of the dose is biotransformed. **Mice:** The maximum serum concentration was reached at 0.5 hours after administration while the half-life of elimination of the radioactivity in blood was 4 hours. Approximately 72% of the dose is excreted in the urine and 19% is excreted in the faeces. The majority of excretion was complete by 24 hours post-dosing. A small amount was detected in expired air (0.2%). Approximately 30-60% of the dose is biotransformed.

Distribution / target organ(s): **Rats:** Widely distributed to the tissues, with the highest concentrations detected in skeletal muscle, within 8 hours of dosing and accounting for 10-15% of the administered dose. Tissue half-times of elimination ranged from 2-6 hours. After 7 days, tissue residues were all very low, with the highest amounts detected in liver (0.01-0.04% of the dose). **Mice:** Thiamethoxam was the major component detected in blood extracts (78%) within the first 4 hours post-dosing, while CGA265307 was noted to be the major plasma metabolite at 6 hours following dosing (43.3 - 54.5% of radioactivity), indicating rapid metabolism of the parent. CGA322704 was also noted in plasma at a similar concentration (19.5 - 25.6%) as the parent.

Toxicologically significant compound(s): Only three urinary metabolites accounted for greater than 1-2% of the administered dose in rats. Unchanged parent CGA 293343 accounted for 69-83% in rats (31-44% in mice); CGA 322704 was the major urinary metabolite in rats (5-13% of the dose) and mice (8-12% of the dose). CGA 265307 accounted for 1-2% of the dose in rats and 9-18% of the dose in mice. The concentrations of CGA265307 were approximately 22-fold greater in mouse plasma than in rat plasma after 1 week of feeding. After 10 weeks feeding, the concentration of CGA265307 in mouse plasma had increased approximately 3.6-fold (suggesting induction of metabolic pathways) whereas that in rat plasma had reduced, the difference between the two approximately 140-fold. The 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. The difference between the two species for CGA330050 was up to 15-fold over the duration of the study. The major difference between the metabolism in rats and mice, which may lead to a difference in long term toxicity, is the production of metabolite CGA330050 in mice.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES - TECHNICAL			
Oral	Rat, Crj:CD(SD) SPF 0, 900, 1500, 2300, 2800 or 6000 mg/kg	LD_{50} = 1563 mg/kg	**Sightly toxic**, All deaths occurred within 6 hours of dosing. Clinical signs noted on the day of dosing included ptosis, decrease in spontaneous movement and tonic convulsions. Body weight gain was retarded for two days following dosing (all treated animals)
Oral	Mouse, Crj:CD-1 (ICR) SPF 0, 500, 700, 1000, 1400 or 2000 mg/kg	LD_{50} = 871 mg/kg	**Moderately toxic**, All deaths occurred within 1 day of dosing. Clinical signs noted on the day of dosing included clonic convulsion, decrease in spontaneous movement or prone position. Body weight gain was retarded in surviving females on the day following dosing
Dermal	Rat, Crj:CD(SD) SPF 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, No mortality, no adverse clinical signs and no effect on body weight

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Inhalation	Rat, Crj:CD(SD) SPF 1.02 or 3.72 mg/L	LC_{50} > 3.72 mg/L	**Low toxicity**, No mortality, no treatment-related clinical signs. Slight body weight decreases noted in 2 high-dose females on day 7, recovered by day 14.
Eye Irritation	Rabbit, Japanese White 0.1 g	Max Average Score = 0 Max Irritation Score = 10.0 (1 hour)	**Minimally irritating**, Slight conjunctival redness and swelling observed at 1 hour, with eye closure and more than normal discharge. All signs of irritation absent at 24 hours.
Skin Irritation	Rabbit, Japanese White 0.5 g	Max Average Score = 0 Max Irritation Score = 0	**Non-irritating**, No signs of irritation in any of the animals tested
Skin Sensitization (Maximization Test)	Guinea pig, Pirbright White, Tif:DHP	Non-sensitizing	**Non-sensitizing**, No evidence of sensitization
ACUTE STUDIES - Actara 240 SC			
Acute Oral LD_{50} Standard Test (401)	5 rats/sex/dose Dosed at 5000 mg/kg	LD_{50} ♂♀ > 5000 mg/kg	**Low toxicity-**
Acute Dermal LD_{50}	5 rats/sex/dose Dosed at 2000 mg/kg	LD_{50} ♂♀ > 2000 mg/kg	**Low toxicity**, No mortality, no adverse clinical signs and no effect on body weight
Acute Inhalation LC_{50}	5 rats/sex/dose Dosed at 0.641 and 2.67 mg/L	LC_{50} ♂♀ > 0.641 mg/L	The MMAD for the 2.67 mg/l dose was too high (>4mm), indicating that the test substance did not reach the aveolar tissue, therefore only the low dose (0.641 mg/L) could be considered.
Primary Eye Irritation	3 rabbits/sex (eyes unwashed) 3 rabbits (♀ only) (eyes washed at 30 secs post-instillation for 1 min) Dosed with 0.1 mL	MAS[a] = 0 MIS[b] = 4(unwashed), 4.67(washed)	**Minimally irritating**,- Mild to moderate redness was noted in all animals, which had receded by 24 hours
Primary Skin Irritation	3 rabbits/sex Dosed with 0.5 mL for 4 hours	MAS= 0.17/8 MIS= 0.67/8 at 4 hr	**Slightly irritating** -slight erythema with desquamation remained present in one female until day 7. Edema was not evident in any of the test animals.
Skin Sensitization Buehler	20 guinea pigs (♂) 10 for control Dosed with 0.4 mL for 6 hours; 3 inductions, 1 challenge	Non-sensitizing	**Non-sensitizing**, No evidence of sensitization
ACUTE STUDIES - Actara 25 WG			
Acute Oral LD_{50} Standard Test (401)	5 rats/sex Dosed at 5000 mg/kg	LD_{50} ♂♀> 5000 mg/kg	**Low toxicity-** Clinical signs of toxicity, including hypoactivity, staggered gait, tremors, mydriasis, hunched posture and squinting of the eyes were recorded in all test animals on the day of treatment
Acute Dermal LD_{50}	5 rabbits/sex/dose Dosed at 2000 mg/kg	LD_{50} ♂♀ > 2000 mg/kg	**Low toxicity**, No mortality, no adverse clinical signs and no effect on body weight

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Acute Inhalation LC_{50}	5 rats/sex Dosed at 2.79 mg/L	LC_{50} ♂♀ > 2.79 mg/L	**Low toxicity**, No mortality, no treatment-related clinical signs.
Primary Eye Irritation	6 rabbits (♂) Dosed with 0.1 mL, eyes left unwashed post-instillation	MAS[a] = 5.6 MIS[b] = 24.8 (1hr) Eye irritation unresolved at 72 hrs	**Mildly irritating**- redness and chemosis of the conjunctivae, combined with clear discharge, cornea opacity and iridal irritation. Corneal epithelial peeling was observed in some test animals at 24 and 48 hours post-instillation. Ocular irritation was no longer evident by day 7
Primary Skin Irritation	3 rabbits/sex Dosed with 0.5 g for 4 hours	MAS= 1.3 MIS= 1.7 Dermal irritation unresolved irritation at 72 hrs	**Mildly irritating**- Well-defined to slight erythema with desquamation was evident. Resolved by day 7
Skin Sensitization Buehler	20 guinea pigs (♂) 10 for control Dosed with 0.4 g moistened with 0.25 mL for 6 hours; 3 inductions, 1 challenge	Non-sensitizing	**Non-sensitizing**, No evidence of sensitization
SHORT TERM TOXICITY			
28-day gavage	Male Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 100, 300, 1000 mg/kg bw/day	NOAEL/LOAEL not established since the study was conducted for range-finding purposes only.	**≥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, AlkP and GGT, ↓ thymus wt.
28-day dietary	Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 100, 1000, 2500 or 10000 ppm (♂ = 0, 8.0, 82, 199 or 711 mg/kg bw/day, ♀ = 0, 8.7, 89, 211 or 763 mg/kg bw/day)	NOAEL = 100 ppm (8.0/8.7 mg/kg bw/day, ♂/♀) LOAEL = 1000 ppm (81.7/89.3 mg/kg bw/day, ♂/♀)	**≥1000 ppm (81.7/89.3 mg/kg bw/day, ♂/♀)-** hyaline change of renal tubular epithelium (♂, not present in high-dose animals), basophilic proliferation of renal tubules (incidence dropped at high dose) **≥2500 ppm (199/211 mg/kg bw/day, ♂/♀)-** hepatocellular hypertrophy, hypertrophy of thyroid follicular epithelium (♂) **10000 ppm (711/763 mg/kg bw/day, ♂/♀)-** ↓bw gain and food consumption (♂), ↑cholesterol, AST (♂), abs and rel liver wt, dilatation of renal pelvis, fatty change of adrenal cortex, hypertrophy of thyroid follicular epithelium (♀)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
28-day dietary	Beagle Dogs, 2/sex/dose at 0, 300, 1000 or 3000 ppm (♂ = 0, 10.0, 31.6 or 47.7 mg/kg bw/day, ♀ = 0, 10.7, 32.6 or 43.0 mg/kg bw/day)	NOAEL = 1000 ppm (31.6/32.6 mg/kg bw/day, ♂/♀) LOAEL = 3000 ppm (47.7/43.0 mg/kg bw/day, ♂/♀)	**3000 ppm (47.7/43.0 mg/kg bw/day, ♂/♀)-** ↓fc, ↓bw, leukopenia, ↑Hct, Hb and RCB (♂), ↑urea, ↑creatinine, ↓thymus wt (♂/♀), ↑thyroid wt (♂), ↓brain wt (♀), histopathology in liver, thymus and spleen Note - 1 high-dose male died on day 15 due to blockage of small intestine (unrelated to treatment)
28-day dermal	Rat, Tif:RAIf (SPF), 5/sex/dose at 0, 20, 60, 250 or 1000 mg/kg bw/day	NOAEL = 60 mg/kg bw/day (♀) NOAEL = 250 mg/kg bw/day (♂) LOAEL = 250 mg/kg bw/day (♀) LOAEL = 1000 mg/kg bw/day (♂)	**≥250 mg/kg bw/day -** ↑glucose, alkaline phosphatase and triglyceride (♀) Inflammatory cell infiltration in the liver, hepatocellular degeneration, chronic tubular lesions in the kidneys, and inflammatory cell infiltration in the adrenal cortex **1000 mg/kg bw/day** - slight ↓bw (♂), hyaline change in renal tubules (♂)
90-day dietary	Rat, Tif:RAIf (SPF), 10/sex/dose at 0, 25, 250, 1250, 2500 or 5000 ppm (♂ = 0, 1.7, 17.6, 84.9, 168 or 329 mg/kg bw/day, ♀ = 0, 1.9, 19.2, 92.5, 182 or 359 mg/kg bw/day)	NOAEL = 25 ppm (1.7 mg/kg bw/day, ♂) NOAEL = 1250 ppm (92.5 mg/kg bw/day, ♀) LOAEL = 250 ppm (17.6 mg/kg bw/day, ♂) LOAEL = 2500 ppm (182 mg/kg bw/day, ♀)	**≥250 ppm (17.6/19.2 mg/kg bw/day, ♂/♀)-** ↑ hyaline change in renal tubular epithelium (♂), ↑ chronic tubular lesions (♂) **≥1250 ppm (84.9/92.5mg/kg bw/day, ♂/♀)-** ↓ bw, bwg and fc (♂), ↑ creatinine, urea, cholesterol and platelets (♂), ↑ acute renal tubular lesions and basophilic proliferation (♂) **≥2500 ppm (168/182 mg/kg bw/day, ♂/♀)-** ↑hepatocellular hypertrophy (♂), ↑ chronic renal tubular lesions and ↑ severity of nephrocalcinosis (♀), ↑ adrenal fatty change (♀) **5000 ppm - (329/359 mg/kg bw/day, ♂/♀)** slight ↑ platelets (♂), ↑ abs adrenal wt (♂), ↑rel liver, kidney, adrenal, heart and spleen wt (♂), ↓abs heart and thymus wt (♀), ↑ hepatocellular hypertrophy (♀), ↑ Kupffer cell pigmentation (♀), ↑ renal cast formation and extramedullary hematopoiesis in spleen (♂)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
90-day dietary	Mouse, Tif:MAGf (SPF), 10/sex/dose at 0, 10, 100, 1250, 3500 or 7000 ppm (♂ = 0, 1.4, 14.3, 176, 543 or 1335 mg/kg bw/day, ♀ = 0, 2.0, 19.2, 231, 626 or 1163 mg/kg bw/day)	NOAEL = 10 ppm (1.4 mg/kg bw/day, ♂) NOAEL = 100 ppm (19.2 mg/kg bw/day, ♀) LOAEL = 100 ppm (14.3 mg/kg bw/day, ♂) LOAEL = 1250 ppm (231 mg/kg bw/day, ♀)	**≥100 ppm (14.3/19.2 mg/kg bw/day, ♂/♀)**- hepatocellular hypertrophy (♂) **≥1250 ppm (176/231 mg/kg bw/day, ♂/♀)**- ↓ abs/rel kidney wt (♂), ↑ abs/rel liver wt (♀), hepatocellular hypertrophy (♀) **≥3500 ppm (543/626 mg/kg bw/day, ♂/♀)**- ↓ abs/rel ovary and abs spleen wt (♀), ovarian atrophy, necrosis of single hepatocytes (♀), lymphocytic infiltration in liver and Kupffer cell pigmentation (♂/♀) **7000 ppm (1335/1163 mg/kg bw/day, ♂/♀)**- ↓ RCB, Ht, Hb,↑ MCV and MCH (♂), ↓ bw (♂) and bwg (♂/♀), necrosis of single hepatocytes (♂),
90-day dietary	Beagle Dogs, 4/sex/dose at 0, 50, 250, 1000 or 2500/2000 ppm (♂ = 0, 1.6, 8.2, 32 or 55 mg/kg bw/day, ♀ = 0, 1.8, 9.3, 34 or 51 mg/kg bw/day) 2500 ppm dose reduced to 2000 ppm, animals fed control diets day 19-25, treatment resumed at 2000 ppm for remainder of study,	NOAEL = 250 ppm (8.2/9.3 mg/kg bw/day, ♂/♀) LOAEL = 1000 ppm (32/34 mg/kg bw/day, ♂/♀)	**≥1000 ppm (32/34 mg/kg bw/day, ♂/♀)**- ↑ prothrombin times, ↓ albumin, A/G ratio, ↓ ALT (♂/♀), ↓ calcium (♀), ↓ cholesterol and phospholipid (♂) **2500/2000 ppm (55/51 mg/kg bw/day, ♂/♀)** - ↓ fc, bw, ↓ bwg and fc (♂/♀), microcytic anemia, leukopenia (♀), ↓ monocytes, MCH and ↑ HDW, ↓ testis and ovary wt, delayed maturation in ovaries and ↓ spermatogenesis with minimal to moderate occurrence of spermatic giant cells in testes
12-month dietary	Beagle Dogs, 4/sex/dose at 0, 25, 150, 750 or 1500 ppm (♂ = 0, 0.7, 4.1, 21 or 42 mg/kg bw/day, ♀ = 0, 0.8, 4.5, 25 or 45 mg/kg bw/day)	NOAEL = 150 ppm (4.1/4.5 mg/kg bw/day, ♂/♀) LOAEL = 750 ppm (21/25 mg/kg bw/day, ♂/♀)	**≥750 ppm (21/25 mg/kg bw/day, ♂/♀)**- transient ↓ in fc (♀) ↑ creatinine, ↑ urea, ↓ ALT, atrophy of seminiferous tubules **1500 ppm (42/45 mg/kg bw/day, ♂/♀)**- transient bw loss (♀), ↓ testis wt, ↓ prothrombin activity (♂), ↓ albumin (♀)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
CHRONIC TOXICITY/ONCOGENICITY			
78-week dietary	Mouse, Tif:MAGf (SPF), 60/sex/dose, plus 10/sex control and high dose for interim sacrifice at 9 months at 0, 5, 20, 500, 1250, 2500 ppm (♂ = 0, 0.7, 2.6, 64, 162 or 354 mg/kg bw/day, ♀ = 0, 0.9, 3.7, 88, 215 or 479 mg/kg bw/day)	NOAEL = 20 ppm (2.6/3.7 mg/kg bw/day, ♂/♀) LOAEL = 500 ppm (64/88 mg/kg bw/day, ♂/♀)	**≥500 ppm (64/88 mg/kg bw/day, ♂/♀)-** ↑ rel liver wt (♀), ↑ incidence of hepatocellular adenoma, ↑ hepatocellular hypertrophy, foci of cellular alteration, necrosis of single hepatocytes, mitotic activity, inflammatory cell infiltration, pigment deposition (♂/♀) and Kupffer cell hyperplasia (♂) **≥1250 ppm (162/215 mg/kg bw/day, ♂/♀) -** ↑ abs/rel liver wt, ↑ hepatocellular adenocarcinoma (♀) **2500 ppm (354/479 mg/kg bw/day, ♂/♀) -** ↓ bwg (♂/♀), ↑ hepatocellular adenocarcinoma (♂), extramedullary hematopoiesis in spleen, epithelial hyperplasia in glandular stomach **Interim sacrifice -** ↑ hepatocellular hypertrophy, necrosis of single hepatocytes, inflammatory cell infiltration and Kupffer cell pigmentation. ↑ in the number of animals with multiple tumours, however, no difference in latency of tumour formation nor in lethality from observed tumours between treated and control groups
2-year dietary	Rat, Tif:RAIf (SPF), 80/sex/dose at 0, 10, 30, 500 or 1500 ppm (♂) and 0, 10, 30, 1000 or 3000 ppm (♀) (50 main study, 10 interim sacrifice, 10 hematology and clinical chemistry and 10 hematology) (♂ = 0, 0.4, 1.3, 21 or 63 mg/kg bw/day, ♀ = 0, 0.5, 1.6, 50 or 155 mg/kg bw/day)	NOAEL = 500 ppm (21 mg/kg bw/day, ♂) NOAEL = 1000 ppm (50 mg/kg bw/day, ♀) LOAEL = 1500 ppm (63 mg/kg bw/day, ♂) LOAEL = 3000 ppm (155 mg/kg bw/day, ♀)	**500 ppm (21 mg/kg bw/day, ♂) -** ↑ incidence of regenerative kidney lesions at interim sacrifice that were not observed at terminal sacrifice (chronic tubular lesions and basophilic proliferation of renal tubules) **1500 ppm (63 mg/kg bw/day, ♂) -** slight ↑ wc, ↑ lymphocytic infiltration of renal pelvis (interim & terminal sacrifice), ↑chronic nephropathy (terminal sacrifice) **3000 ppm (155 mg/kg bw/day ♀) -** ↓ bwg, ↑ severity of hemosiderosis of spleen at interim sacrifice, ↑ foci of cellular alteration in liver, ↑ chronic tubular lesions in kidneys No evidence of oncogenicity in males or females however, evidence suggests that males could have tolerated higher doses
REPRODUCTION / DEVELOPMENTAL TOXICITY			
Range finding reproduction	Rat, Tif:RAIf (SPF), 15/sex/dose at 0, 1000, 2000 or 4000 ppm (♂ = 0, 67, 126 or 241 mg/kg bw/day, ♀ = 0, 75, 136 or 275 mg/kg bw/day)	No NOAEL or LOAEL established by the study author	**≥1000 ppm (67/75 mg/kg bw/day ♂/♀)** - ↓ bwg (pre-mating)(♀) **≥2000 ppm (126/136 mg/kg bw/day ♂/♀) -** ↓ fc during (pre-mating) **4000 ppm (241/275 mg/kg bw/day ♂/♀)-** ↓ bwg (pre-mating)(♂/♀)(lactation, ♀)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Multi-generation reproduction	Rat, Tif:RAIf (SPF), 30/sex/dose at 0, 10, 30, 1000 or 2500 ppm (♂ = 0, 0.6, 1.8, 61 or 158 mg/kg bw/day, ♀ = 0, 0.8, 2.4, 79 or 202 mg/kg bw/day)	**Parental systemic** NOAEL, males = 30 ppm (0.6 mg/kg bw/day) females = 2500 ppm (202 mg/kg bw/day, highest dose tested) LOAEL, parental males = 1000 ppm (61 mg/kg bw/day) **Offspring** NOAEL = 1000 ppm (61/79 mg/kg bw/day, ♂/♀) LOAEL = 2500 ppm (158/ 202 mg/kg bw/day, ♂/♀) **Reproductive** NOAEL = 10 ppm (0.6 mg/kg bw/day) LOAEL = 30 ppm (1.8 mg/kg bw/day)	**≥30 ppm (1.8/2.4 mg/kg bw/day ♂/♀)** - ↑ incidence and severity of tubular atrophy in testes of F_1 **≥1000 ppm (61/79 mg/kg bw/day ♂/♀)** - ↑ incidence of hyaline change in renal tubules (F_0 and F_1 males) and renal tubular casts (F_0 males) **2500 ppm (158/202 mg/kg bw/day ♂/♀)** - slight ↓ parental bwg (F_0 and F_1 males), ↓ pup bwg (all litters) during the lactation period, ↑ incidence of renal tubular casts and ↓ testis wt (F_1 males), hyaline change in renal tubules in one F_1 female Equivocal results in sperm motility (decreased at all doses 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 No treatment-related adverse effects on reproductive indices (mating, gestation, fertility, viability) **Evidence of sensitivity of young** (testis effects observed only after in utero and post-natal exposure)
Multi-generation reproduction	Rat, Tif:RAIf (SPF), 26/sex/dose at 0, 20, 50, 1000 or 2500 ppm (♂ = 0, 1.2, 3.0, 61.7, or 155.6 mg/kg bw/day, ♀ = 0, 1.2, 3.1, 62.2 or 158.9 mg/kg bw/day)	**Parental systemic** NOAEL, males = 50 ppm (3.0 mg/kg bw/day) females = 50 ppm (3.1 mg/kg bw/day) LOAEL, parental males = 1000 ppm (61.7 mg/kg bw/day) females = 1000 ppm (62.2 mg/kg bw/day) **Offspring** NOAEL = 1000 ppm (61.7/62.2 mg/kg bw/day, ♂/♀) LOAEL = 2500 ppm (155.6/158.9 mg/kg bw/day, ♂/♀) **Reproductive** NOAEL = 10 ppm (1.6 mg/kg bw/day) LOAEL = 50 ppm (3.0 mg/kg bw/day)	**≥50 ppm (3.0/3.1 mg/kg bw/day ♂/♀)**- ↓ total sperm and # sperm/ g of testes weight (F1). **≥1000 ppm (61.7/62.2 mg/kg bw/day ♂/♀)**- ↓Pituitary wt (F_0 females), ↑ epididymides wt (F1 males), ↑ testes wt (F1 males), ↑ incidence of renal tubular casts and hyaline droplets (F1 males), **2500 ppm (155.6/158.9 mg/kg bw/day ♂/♀)**-↓ (6-7%) BWG & FC (F_0 males), week 3-4 pup deaths. -↓(12% F0, 7% F1) litter wt , ↑ adrenal wt (F_0 males), ↑seminal vesicle wt (F_0 males), ↑liver wt (F1 males & females), ↓sperm velocity (F1 males). ↑ incidence of abnormal sperm (F0 males), severe germ cell loss or disorganization (F0/F1 males), delayed preputial separation (F1 males) **Evidence of sensitivity of young** (sperm effects observed only after in utero and post-natal exposure)

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Range finding developmental toxicity	Rat, Tif:RAIf (SPF), 8 pregnant females/dose at 0, 10, 100, 500 or 1000 mg/kg bw/day from days 6-15 of gestation	NOAEL (maternal) = 100 mg/kg bw/day LOAEL (maternal) = 500 mg/kg bw/day NOAEL (developmental) = 500 mg/kg bw/day LOAEL (developmental) = 1000 mg/kg bw/day	**≥500 mg/kg bw/day -** ↓ maternal bwg during the first half of the dosing period, ↓ fc **1000 mg/kg bw/day -** net loss in body weight during the first half of the dosing period, clinical signs of toxicity during the dosing period (piloerection, hypoactivity, hunched posture), ↓ fetal bw No evidence of teratogenicity
Developmental toxicity	Rat, Tif:RAIf (SPF), 24 pregnant females/dose at 0, 5, 30, 200 or 750 mg/kg bw/day from days 6-15 of gestation	NOAEL (maternal) = 30 mg/kg bw/day LOAEL (maternal) = 200 mg/kg bw/day NOAEL (developmental) = 200 mg/kg bw/day LOAEL (developmental) = 750 mg/kg bw/day	**≥200 mg/kg bw/day -** ↓ maternal bwg (gestation), ↓ fc (gestation) ↑ incidence of transient, reversible, non-adverse skeletal variations (poor ossification of specific digits) **750 mg/kg bw/day -** net loss in bw (gestation),(piloerection, hypoactivity, regurgitation of test material during gestation), ↓ fetal bw, ↑ incidence of skeletal anomalies (asymmetrically shaped sternebrae 6 and irregular ossification of the occipital bone) No evidence of teratogenicity
Range finding developmental toxicity	Rabbit, Russian Chbb:HM, 8 pregnant females/dose at 0, 10, 50, 150 or 500 mg/kg bw/day from days 7-19 of gestation	NOAEL (maternal) = 10 mg/kg bw/day LOAEL (maternal) = 50 mg/kg bw/day NOAEL (developmental) = 50 mg/kg bw/day LOAEL (developmental) = 150 mg/kg bw/day	**≥50 mg/kg bw/day -** ↓ bwg and fc (gestation) **150 mg/kg bw/day -** bw loss (gestation), ↓ mean gravid uterus wt, ↓ fetal body wt **500 mg/kg bw/day -** all animals died between study days 10 and 16 No evidence of teratogenicity
Developmental toxicity	Rabbit, Russian Chbb:HM, 19 pregnant females/dose at 0, 5, 15, 50 or 150 mg/kg bw/day from days 7-19 of gestation	NOAEL (maternal) = 50 mg/kg bw/day LOAEL (maternal) = 150 mg/kg bw/day NOAEL (developmental) = 50 mg/kg bw/day LOAEL (developmental) = 150 mg/kg bw/day	**50 mg/kg bw/day -** ↓ fc **150 mg/kg bw/day -** 3 unscheduled deaths, hemorrhagic uterine contents, hemorrhagic discharge in the perineal area, bw loss, ↓ fc, ↓ fetal body wt, ↑ post-implantation loss, ↑ in the incidence of skeletal anomalies/variations (fused or asymmetrically shaped sternebrae) No evidence of teratogenicity

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
NEUROTOXICITY			
Acute neurotoxicity	Rat, Crl CD SD BR, 10/sex/dose at 0, 100, 500 or 1500 mg/kg bw	NOAEL = 100 mg/kg bw LOAEL = 500 mg/kg bw	**≥500 mg/kg bw** - drooped palpebral closure, ↓ rectal temperature, ↑ forelimb grip strength and ↓ locomotor activity **1500 mg/kg bw** - 3 deaths (days 1 or 2), abnormal body tone, ptosis, impaired respiration, tremors, ↑ latency to first step in open field, crouched-over posture, impaired gait, hypo-arousal, uncoordinated landing in righting reflex test, slight lacrimation (♀ only), ↑ mean average input stimulus in auditory startle response (♂) There were no treatment-related histopathological findings noted in CNS or PNS
Subchronic neurotoxicity	Rat, Crl CD SD BR, 10/sex/dose at 0, 10, 30, 500 or 1500 ppm (♂) and 0, 10, 30, 1000 or 3000 ppm (♀) (♂ = 0, 0.7, 1.9, 32 or 95 mg/kg bw, ♀ = 0, 0.7, 2.1, 73 or 216 mg/kg bw/day)	NOAEL = 1500 ppm (95 mg/kg bw/day, ♂) NOAEL = 3000 (216 mg/kg bw/day, ♀)	There were no treatment-related systemic or neurological effects observed at any dose in this study.
Developmental Neurotoxicity	Rat, Alpk:APfSD (Wistar derived) 30 females/ dose at 0, 50, 400 or 4000 ppm equivalent to (0, 4.2, 34.5, or 298.1 mg/kg bw/day) during gestation and (0, 8.0, 64.0, or 593.5 mg/kg bw/day) during lactation, from gestation day 7 through postnatal day 22.	**Parental systemic** NOAEL, 400 ppm (34.5 mg/kg bw/day, LOAEL, = 4000 ppm (298.1 mg/kg bw/day) **Offspring** NOAEL, 400 ppm (34.5 mg/kg bw/day, LOAEL, = 4000 ppm (298.1 mg/kg bw/day) **Neurotoxicity** NOAEL, 400 ppm (34.5 mg/kg bw/day, LOAEL, = 4000 ppm (298.1 mg/kg bw/day)	**4000 ppm (298.1 mg/kg bw/day)**- ↓ maternal bw (5-6%) , and fc (14-17%) (gestation and lactation periods), bwg (12%) (gestation). ↓ pup bw (lactation (13-14% ♂/♀) and post weaning (8-7% ♂/♀ periods), Delayed sexual maturation (♂). High dose males and females had a variety of brain measurement parameters, including absolute brain weights, less than the respective controls at PND 12 and at termination. Note: The female sexual maturation was confounded by great variability within groups. The Y-Water maze design lacked complexity and as such the results of the water maze were of limited utility.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
GENOTOXICITY			
STUDY	**SPECIES/STRAIN OR CELL TYPE AND CONCENTRATIONS/DOSES EMPLOYED**		**RESULTS**
Gene mutations in bacteria	Salmonella typhimurium strains TA 98, TA 100, TA 102, TA 1535 and TA 1537; E. Coli WP2uvrA 312.5-5000 µg/plate		Negative
Gene mutations in mammalian cells in vitro	Chinese hamster cells V79 61.67-2220 µg/mL without activation 123.33-3330 µg/mL with activation		Negative
Unscheduled DNA Synthesis	Primary rat hepatocytes, isolated from Tif:RAIf (SPF) rats 13.01-1665 µg/mL		Negative
Chromosome Aberrations	Chinese hamster ovary cells CCL 61 283.75-2270 µg/mL without activation 1135-4540 µg/mL with activation		Negative
Micronucleus Assay (in vivo)	Male and female Tif:MAGf (SPF) mice 0, 312.5, 625, 1000 or 1250 mg/kg		Negative
SPECIAL STUDIES*			
Effects on biochemical parameters in the liver	Mouse, Tif:MAGf (SPF), 6/sex/dose at 0, 100, 500 or 2500 ppm (♂ = 0, 17, 74 or 367 mg/kg bw/day, ♀ = 0, 20, 92 or 486 mg/kg bw/day)	N/A	**100 ppm (17/20 mg/kg bw/day)** - slightly ↑ Pentoxyresorufin-O-depentylase (PROD) and Benzyloxyresorufin-O-debenzylase (BROD) activity (♀) **500 ppm (74/92 mg/kg bw/day)** - ↑ PROD and BROD activity (♂/♀), slightly ↑ Ethoxyresorufin-O-deethylase (EROD) (♀) **2500 ppm (367/486 mg/kg bw/day)** - ↑ abs & rel liver wt (♂/♀),↑ microsomal protein content in liver (♀), ↑ in cyt P450 content, ↑ in activity of several microsomal enzymes and cytosolic glutathione-S-transferase
Assessment of hepatic cell proliferation	Mouse, Tif:MAGf (SPF), 25/sex/dose, 5/dose sacrificed on study day 3, 7, 13, 27 or 59, at 0, 100, 500 or 2500 ppm (♂ = 0, 16, 72 or 386 mg/kg bw/day, ♀ = 0, 20, 87 or 463 mg/kg bw/day)	N/A	**100 ppm (16/20 mg/kg bw/day)**- ↑ Bromodeoxyuridine (BrdU) labelling index in females sacrificed day 7 **500 ppm (72/87 mg/kg bw/day)**- ↑ BrdU (♂ sacrificed day 13, 27 and 59 and♀ sacrificed day 7 and 13) **2500 ppm (386/463mg/kg bw/day)**- ↑ abs & rel liver wt (♂/♀), speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation at 59 days, ↑ BrdU labelling (♂/♀) sacrificed day 3, 7, 13 and 59

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Assessment of replicative DNA synthesis in a 28-day dietary toxicity study	Rat, Tif:RAIf (SPF), 5 males per dose at 0, 100, 1000, 2500 or 10000 ppm (Equal to 0, 8.0, 82, 199 or 711 mg/kg bw/day)	N/A	Immunohistochemical staining of liver sections from control and high-dose animals for proliferating cell nuclear antigen gave no indication for a treatment-related increase in the fraction of DNA-synthesizing hepatocytes in S-phase
50-week dietary (PMRA study #1265698)	Male Tif:MAG mice were randomly assigned to one of 35 groups. Groups of 15 mice received CGA 293343 treated diet at concentrations of 0, 50, 200, 500, 2500 or 5000 ppm for 10, 20, 30, 40 or 50 weeks.	**≥500 ppm -** Hepatocellular necrosis, accentuated lobular pattern of the liver and inflammatory cell infiltration **≥1250 ppm -** ↑ AST & ALT **≥2500 ppm -** ↓ bw ,↑ liver wt, ↓kidney wt, ↑ Hepatocellular hypertrophy supplemental	
10-week dietary (PMRA study # 1112530)	6 female Tif:RAIf(SPF) rats/dose in diet, at dose levels of 0, 1000 or 3000 ppm for 10 weeks.		Treatment did not alter the liver protein content and/or function of : Cytochrome P450, 7-methoxy, 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. supplemental
60-day dietary (PMRA study #1112527)	male Tif:MAG mice were given control diet or diet containing 2500 ppm or 5000 ppm of the test material. Groups at each treatment level were sacrificed on days 7, 14, 28 or 60 of the study.		**5000 ppm -** ↓bwg . 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, 8-isoprostane F_{2a} , malondialdehyde). supplemental
50-week dietary (PMRA study #1112529)	10 male Tif:MAG(SPF) mice/dose in diet, at dose levels of 0, 2500 or 5000 ppm for 10, 20, 30, 40, or 50 weeks.		**≥2500 ppm -** ↓ bw, ↑ macroscopical finding "liver: accentuated lobular pattern" were observed at 2500 ppm after 10, 30 and 40 weeks and at 5000 ppm after 10 weeks. Hepatic fatty change, hepatocellular hypertrophy, necrosis, ↑reduced and oxidized glutathione, ↑hepatic γ-glutamylcysteine synthetase activity, ↑hepatic glutathione S-transferase **5000 ppm -** Hepatocellular apoptosis (centrilobular) supplemental

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
60-day dietary (PMRA study #1112528)	10 male Tif:MAG (SPF) mice each were treated for 7, 14, 28 and 60 days with CGA 293343 tech. at dietary concentrations of 0, 2500 and 5000 ppm, corresponding to mean daily doses of 0, 448 and 976 mg/kg body weight,		**≥2500 ppm -**↓ protein ,↑ y-glutamylcysteine synthetase activity, ↓glutathione reductase (82.5% of control), ↑glutathione S-transferase activity Treatment had no effect on the activity of glucose-6-phosphate dehydrogenase. The increased activity of γ-glutamylcysteine synthetase, the rate limiting enzyme of glutathione synthesis, is in accordance with the increased hepatic glutathione concentration observed in the same animals supplemental
7-day dietary (PMRA study #1076460)	In an in vivo experiment, two groups of mice (5 per group) were placed on a diet containing 2000 ppm CGA652307 for 7 days		CGA265307 inhibited nitric oxide synthase to a similar extent as the selective iNOS inhibitor L-NAME. Thiamethoxam and other metabolites were not as effective at inhibiting iNOS. The reduction in iNOS or NO *in vivo* was not demonstrated in this experiment. Mice fed a diet containing 2000 ppm CGA265307 for 7 days and then injected with 10 ul/kg CCl_4 had even greater serum levels of aminotransferase activity than animals given the 10 ul/kg CCl_4 treatment alone. Microscopy analysis of livers supported the increased liver toxicity following exposure to both CGA265307 and 10 ul/kg CCl_4. Mice fed diet containing 2000 ppm CGA265307 for 7 days did not demonstrate evidence of liver toxicity in the absence of exposure to 10 ul/kg CCl_4.
50-week dietary (PMRA study #1089137)	15 female Tif:RAIf(SPF) rats/dose in diet at dose levels of 0,1000 or 3000 ppm (0, 58.9 or 180.9 mg/kg bw/day) for up to 50 weeks.		**3000 ppm (180.8 mg/kg bw/day) -** clinical signs of morbidity prior to being sacrificed. ↑ mortality, ↓bwg, fe
20-week dietary (PMRA study #1082670)	17 male Tif:MAGf or CD-1 mice were fed either control diet or diets containing 2500ppm CGA 293343, 2000ppm CGA 322704 or 500ppm CGA 265307 for up to 20 consecutive weeks.		**2000 ppm CGA 322704 -** ↓bw, fe., ↑ mortality, ↓ kidney wt, ↑liver wt **2500 ppm CGA 293343 -** ↓bw, fe, ↓ protein, albumin & cholesterol, ↑ALT, ↓ kidney wt, ↑liver wt The results indicate a similar range of liver toxicity in 2 strains of mice, mainly attributed to Thiamethoxam, not its main metabolites.
40-week dietary (PMRA study #1081655)	15 male mice in the diet at dose levels of 0, 200, 500, or 1250 ppm for 40 weeks.		**≥500 ppm -** ↑hepatocellular mitotic index It is incertain if an increase in mitotic index of 2-3x can explain the occurrence of hepatocellular tumours in mice of these dose levels following chronic treatment.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
20-week dietary (PMRA study #1081654)	Thiamethoxam(2500 ppm), CGA322704 (2000 ppm) or CGA265307 (500 ppm) were administered to groups of 12 male mice in diet for 1, 10, or 20 weeks. In a second study, male mice (12 per group) were fed diets containing 0, 500 or 1000 ppm CGA33050 for 1 or 10 weeks. In a third study female rats (17 per group) were fed diets containing 0, 500 or 1000 ppm CGA 33050 for 1 week.		**2500 ppm Thiamethoxam -** ↓cholesterol, ↓protein (week 1 onward), ↑ ALT (week 10 onward)& ↑ AST (week 20). Hepatocellular hypertrophy, necrosis & apoptosis(week 10 onwards), inflammatory cell infiltration (week 20). **CGA322704 or CGA265307 -** no evidence of liver toxicity. **≥500 ppm CGA33050 -** ↑ ALT and AST (week 1**)** **1000 ppm CGA33050 -** ↓cholesterol, ↓protein, ↑ hepatocellular hypertrophy, necrosis , apoptosis & inflammatory cell infiltration.
7-day dietary (PMRA study #1081205)	6 male weanling or adult Tif:MAG mice in the diet at dose levels of 0, 500, 1250 or 2500 ppm for 7 days.		≥ 500 ppm - ↓Cholesterol (adult). ≥1250 ppm - ↓Cholesterol (weanling) Liver enzymes were not changed in weanlings or adult mice. Concentrations of parent and the main metabolites were noted to be higher in all weanling animals than their corresponding adult dosed animals. This difference in plasma levels of test material may be due to a higher food intake in weanling animals than the adults (food consumption not measured). However, the increase in serum levels of test material, in the absence of an increased liver toxicity demonstrates that weanling animals are not more sensitive to the liver effects of the compound.
Review Document (PMRA study #1099831)	The current study attempted to review the cholesterol data from a number of rodent studies to identify patterns of effect		The plasma cholesterol reductions were reproducible between mice studies and dosing routes, they were dose dependent and they persisted over the duration of a 50 week study. The changes were seen in two strains of mouse, but they were not seen in rats fed on diets containing up to 3000 ppm thiamethoxam for 50 weeks. Although the changes in plasma cholesterol occurred in a dose dependent manner, and were noted at similar doses as those which elicited the development of liver tumours in mice, there was not definitive linkages demonstrated to confirm the change in plasma cholesterol as being an underlying step in the development of liver tumours in mice.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Review Document (PMRA study #1112526)	In this retrospective investigation, hepatic apoptosis in mice treated with dietary concentrations of 0, 100, 500, and 2500 ppm thiamethoxam (CGA 293343 tech.) for 3, 7, 13, 27, and 59 days and for 9 months (0 and 2500 ppm only)		Significantly increased numbers of apoptotic figures were seen at 500 and 2500 ppm after 59 days and at 2500 ppm after 9 months of treatment. The apoptosis were mostly localized centrilobularly, often adjacent to central veins, thereby corresponding to the location of histopathologically recognized necrosis and apoptosis. No significant increase was seen at 100 ppm or before day 59. The data support the hypothesis that mice fed thiamethoxam treated diets for prolonged periods, demonstrate liver toxicity as manifested by necrotic and apoptotic events at doses which resulted in tumour formation following chronic exposure.
50-week dietary (PMRA study # 1112531)	Male Tif:MAG mice were randomly assigned to one of 35 groups. Groups of 15 mice received CGA 293343 treated diet at concentrations of 0, 50, 200, 500, 2500 or 5000 ppm for 10, 20, 30, 40 or 50 weeks.		The mean body weight was reduced at 2500 and 5000 ppm. Increased AST and ALT were noted at 1250, 2500 and 5000 ppm (116/139%, 122/207% and 169/256% of control, for AST and ALT respectively). The mean relative liver weight was increased at 2500 ppm (116%) and at 5000 ppm (129%). The mean absolute kidney weight was decreased at 2500 ppm (87%) and at 5000 ppm (79%). Hepatocellular necrosis, accentuated lobular pattern of the liver and inflammatory cell infiltration were increased in incidence at 500, 1250, 2500 and 5000 ppm. The majority of these lesions were histopathologically correlated with hepatic fatty change. Hepatocellular hypertrophy was increased in incidence at 2500 and 5000 ppm
60-day dietary (PMRA study #1112527)	Male Tif:MAG mice were given control diet or diet containing 2500 ppm or 5000 ppm of the test material. Groups at each treatment level were sacrificed on days 7, 14, 28 or 60 of the study.		Treatment at 5000 ppm resulted in reduced body weight gain throughout the whole treatment period. During the 60 day experiment 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, 8-isoprostane F_{2a}, malondialdehyde).
Relevance of a2u-Globulin: A series of papers were submitted to address kidney effects in male rats. These papers are combined below, since they were used collectively in the database interpretation.			

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
1222935, **1224686**, **1224687**, **1224688** Weber, E. (2000a, b, c, d). **1239980** MacInnes, J.I., et al. (1986) **1236148** Swenberg, J.A. and Lehman-McKeeman, L.D. (1999), **1236147** Swenberg, J.A. (1989). **1237566** Borghoff, S.J., et al. (1990), **1237571** Charbonneau, M., et al. (1989), **1239984** Neuhaus, O.W. (1986), **1239983** Neuhaus, O. W., et al. (1981), **1239982** Motwani, N.M, et al. (1984), **1237568** Caldwell, D.J., et al. (1999), **1237567** V.L. Burnett (1989), **1236155** Alden, C. (1986). **1240003** Lehman-Mckeeman, L.D., et al. (1991) **1240002** Lehman-Mckeeman, L.D., et al. (1990) **1247128** Stonard, M.D., et al. (1986). **1247126** Short, B.G., et al. (1986) **1247127** Short, B.G., et al. (1987) **1236154** Alden, C.L. et al, (date unknown) **1236151** Yamamoto, I. et al. (1995). **1239987** Roy, A.K., et al. (1966).**1239988** Roy, A.K., and Neuhaus, O.W. (1966). **1239996** H. Hildebrand et al, (1997). **1240001** Kurtz, D. (1981)			The series of papers detail the main points of the body of literature relating to male rat specific α2u- globulin toxicity. The inference being the lack of correlation between rat and man for these indicators of kidney toxicity. This interpretation of the literature is generally accepted, and further documentation of this work was not considered to be required. The following is a listing of the papers submitted related to this topic, with the PMRA workbook document IDs attached for future reference.
General Animal Anatomy/Physiology: A series of papers were submitted to aid in the interpretation of endocrine effects in the database. These papers are combined below, since they were used collectively in the database interpretation.			
1228237 Seely, J.C. (2000). **1228235** Sara Lloyd (2004). **1228238** Lloyd, S., and Peffer, R. (2004). **1236153** Yang-Dar Yuan, (1991). **1237570** Chapin, R.E., et al. (1993). **1237569** Chapin, R.E., et al. (1993). **1237555** C-K. Atterwill and J.D Flack (Date unknown). **1237572** Creasy, D.M, and Foster, P.M., (Date unknown). **1239985** Niemand, H.G. & Suter, P.F. (1989). **1239986** Fox, J.G., et al. (1984). **1239992** Garside, D.A, and Harvey, P.W. (Date unknown). **1239997** IARC No: 147 (1999). **1239990** Scharer, K. (1977). **1247125** Senoo, H. (Date unknown). **1240004** Levin, S. Et al. (1993). **1239989** Russfield, A.B. (1967). **1239993** Gopinath, C., et al. (Date unknown). **1239994** Greaves, P. (1990). **1239999** Kawakami, E. Et al. (1991). **1239995** Heiderstadt, K.M. et al. (2000).			This series of papers were primarily submitted to address the possibility of Thiamethoxam effects on endocrine tissues. Several papers discussed the common physiology and development of endocrine organs, while other papers discussed the effects of feed restriction on the same target tissues. While these papers served as a valuable reference, they were not of critical importance in the interpretation of the animal database. The following is a listing of the papers submitted related to this topic, with the PMRA workbook document IDs attached for future reference.
Chemistry of Thiamethoxam: A series of papers were submitted to aid in the identification of treatment related effects in the database. These papers are combined below, since they were used collectively in the database interpretation.			
1236149 Tomizawa, M. et al. (2000). **1236150** Tomizawa, M. and Casida, J.E. (2003). **1236152** Yamamoto, I. and Casida, J.E. (Date unknown). **1239981** Maienfisch, P. et al. (2001). **1239991** Earley, F.G. et al. (2002). **1237556** Blythe, J. et al, (2002). **1240000** Kayser, H., et al. (Date unknown)			This series of papers generally refer to the mode of action for Thiamethoxam and related neonicotinoids. These papers did not factor heavily into the overall database interpretation or end point selection. As such, these papers were not individually detailed in this document. The following is a listing of the papers submitted related to this topic, with the PMRA workbook document IDs attached for future reference.
Risk Assessment Interpretation:			
1228239 Peffer, R., and Lloyd, S. (2004). **1239998** Meek, M.E. et al. (2003).			A series of papers were submitted to aid in the interpretation of tumour data captured in the chronic rodent studies. These papers are combined below, since they were used collectively in the database interpretation.
Compound-Induced Mortality: No treatment-related mortality in short-term or chronic toxicity studies. Three unscheduled maternal deaths were observed at 150 mg/kg bw/day in the rabbit teratology study, and all 8 animals died at 500 mg/kg bw/day in the range finding rabbit teratology study.			
Recommended ARD: The ARD is 0.12 mg/kg bw, based on the NOAEL of 34.5 mg/kg bw established in the developmental neurotoxicity study, with a 300-fold factor.			

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Recommended ADI: The ADI is 0.004 mg/kg bw/day, based on the NOAEL of 1.2 mg/kg bw/day established in the 2-generation rat reproduction study, with a 300-fold factor.			

* Since many of the studies captured in this review were literature papers or special studies which did not correspond to a typical toxicity study classification, many of the citations noted use the PMRA UKID number for identification.

Appendix II Residues

DIRECTIONS FOR USE OF PESTICIDE ON POTATO AND POME FRUIT						
Crop	**Formulation/ type**	**Interval (day)**	**Rate g a.i./ha**	**#/Season**	**Maximum Rate**	**PHI (days)**
Potato	Actara 25 WG	7	26	2 foliar applications per year	52 g a.i./ha	7
Potato	Actara 240 SC	N/A	1.06 g a.i./100 m row	1 in-furrow application	Assuming a 90 cm row spacing, 117 g a.i./ha	N/A (At plant app.)
Label Restrictions (Actara 25 WG): Do not make a foliar application of Actara 25 WG following a soil application of Actara 240 SC Insecticide in the same crop. Do not apply by air. Label Restrictions (Actara 240 SC): Do not follow a soil application of Actara 240 SC Insecticide with a foliar application of Actara 25 WG Insecticide. Do not apply by air.						
Apple and crabapples	Actara 25 WG	10	40-96	Spotted tentiform leafminer and Rosy apple aphid - 2 foliar applications per year Apply as one pre and postbloom or two post bloom application	192 g a.i./ha	60
Label Restrictions: Do not apply Actara 25 WG Insecticide during bloom. Do not apply by air.						
Pear and Oriental Pear	Actara 25 WG	10	76-96	2 postbloom applications only	192 g a.i.	60
Label Restrictions: Do not apply Actara 25 WG Insecticide during bloom. Do not apply by air.						

PHYSICOCHEMICAL PROPERTIES	
Water solubility at 20°C (g/L)	4.1
Solvent solubility at 20°C	Acetone 48 g/L Dichloromethane 110 g/L Ethyl Acetate 7 g/L Hexane < 1 mg/L Methanol 13 g/L Octanol 620 mg/L Toluene 680 mg/L
Octanol/water partition coefficient (Log K_{ow}) at 25°C	Log K_{ow} = -0.13
Dissociation constant (pKa)	No Dissociation within the range pH 2 to pH 12
Vapour pressure	Temp (°C) — v.p. (Pa) 20 — 2.7×10^{-9} 25 — 6.6×10^{-9}
Relative density at 20°C (g/cm^3)	1.57
Melting point °C	139.1

UV/Visible absorption spectrum	No significant adsorption at wavelength over 300 nm in neutral acidic and basic solutions.

ANALYTICAL METHODOLOGY			
Parameters	**Plant matrices**		**Animal matrices**
Method ID	**AG-675**	**MS-269**	**AG-675**
Type	Data-gathering and Enforcement	Data-gathering	Data-gathering and Enforcement
Analytes	Thiamethoxam and CGA 322704	Thiamethoxam and CGA 322704	Thiamethoxam and CGA 322704
Instrumentation	HPLC-UV or HPLC-MS	HPLC-MS/MS	HPLC-UV or HPLC-MS
LOQ	0.01 ppm for all crop matrices except fruit juices (0.005 ppm), grass (0.05 ppm) and cured tobacco (<0.1 ppm)	0.01 ppm for each analyte	0.01 ppm in meat, poultry and eggs and 0.005 ppm in milk
Standard	Not stated	An external standard was used.	Not stated
ILV	Successfully validated by ILV	Successfully validated by ILV	Successfully validated by ILV in eggs, milk and beef liver
Extraction/ clean-up	HPLC-UV: – Extracted with ACN: water – Reversed-phase SPE – Normal-phase SPE HPLC-MS: – Extracted with ACN: water – Strong anion exchange SPE – Phenyl SPE – Normal-phase SPE column	– Polytron extraction with ACN: water – C-18 SPE and ENV SPE	– Extracted with ACN: water – Reversed-phase SPE – Normal-phase SPE
Radiovalidation	Adequately radiovalidated	None	Adequately radiovalidated
Multiresidue method	Recovery of Thiamethoxam was 50-60% using Protocol D and <30% using Protocol E. Using Protocol C, Thiamethoxam obtained adequate detector responses to Section 302 CG5 and DG13 gas liquid chromatography (GLC) systems. Metabolite CGA 322704 and CGA 265307 were tested using Protocol C but did not yield adequate detector responses to any of the Section 302 DG5, DG13 and DG18 GLC systems; no further testing was conducted for the metabolites. The MRMs are not adequate for enforcement of the proposed MRLs in any commodity.		

NATURE OF THE RESIDUE IN PLANTS—PEAR	
Radiolabel position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings
Test site	Orchard
Treatment	Foliar application
Rate	150 or 1500 g a.i./ha
Seasonal rate	300 or 3000 g a.i./ha
PHI	15 days
Most of the radioactivity remained on the foliage. Most of the radioactivity on the fruit was removed with a surface wash of acetonitrile.	

Metabolites identified	Major metabolites (>10% TRRs)	Minor metabolites (<10% TRRs)
Pear fruit	Thiamethoxam, CGA 322704	CGA 322704 glucose conjugate, CGA 353968, Desmethyl-CGA 353968, CGA 265307, CGA 355190, NOA 407475, CGA 349208, NOA 405217, CGA 382191, NOA 421275
NATURE OF THE RESIDUE IN PLANTS—POTATO		
Radiolabel position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Test site	Outdoor field plots	
Treatment	Seed treatment	
Rate	6.1 or 6.3 g/100 kg seed and 26.4 or 33.4 g/100 kg seed	
Seasonal rate	6.1 or 6.3 g/100 kg seed and 26.4 or 33.4 g/100 kg seed	
PHI	84 and 106 days	
Total residues were substantially higher in foliage than tubers, suggested translocation of residues to foliar tissue during plant growth.		
Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Potato tuber	Thiamethoxam	CGA 322704, CGA 322704 glucose conjugate, CGA 353968, Desmethyl-CGA 353968, CGA 265307, CGA 355190, CGA 340575, CGA 282149, CGA 353042, NOA 407475, CGA 349208, NOA 405217, CGA 382191, NOA 421275, NOA 421276, NOA 436944, N-Glucoside of CGA 353968, Glucoside of CGA 349208, Hydroxylamine Glucoside of NOA 421276, Malonyl Glucoside of CGA 349208
CONFINED ROTATIONAL CROP STUDY—Turnips, mustard (spinach), wheat		
Radiolabel position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Test Site	Separate plots	
Formulation used for trial	Not specified	
Application rate and timing	100 (Study 1) or 200 g a.i./ha (Study 2) applied to bare soil 30, 120 and 365 days before seeding rotational crops	
Metabolites identified	**Major metabolites (> 10% TRRs)**	**Minor metabolites (<10% TRRs)**
Radiolabel Position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Study 1		
Turnips PBI 30	Thiamethoxam, CGA 322704	CGA 353968
PBI 120	Thiamethoxam, CGA 322704, CGA 359683	CGA 353968
PBI 365	Thiamethoxam, CGA 322704, CGA 359683	None
Mustard PBI 30	Thiamethoxam, CGA 322704	CGA 265307, CGA 353968, CGA 359683
PBI 120	Thiamethoxam, CGA 322704, CGA 353968	None
Spinach PBI 365	CGA 322704	Thiamethoxam, CGA 265307, CGA 353968, CGA 359683

Wheat	PBI 30	Thiamethoxam, CGA 322704, CGA 265307	CGA 353968, CGA 355190, Desmethyl-CGA 353968
	PBI 120	Thiamethoxam, CGA 322704, CGA 265307	CGA 353968
	PBI 365	CGA 322704, CGA 359683	CGA 265307, Desmethyl-CGA 353968
Study 2			
Lettuce	PBI 30	Thiamethoxam, CGA 322704, NOA 405217	NOA 407475, NOA 421275, CGA 382191
	PBI 120	Thiamethoxam, CGA 322704	None
	PBI 365	Not analysed	Not analysed
Radish	PBI 30	Thiamethoxam, CGA 322704	CGA 322704, NOA 407475, NOA 421275, CGA 265307, CGA 353968, Desmethyl-CGA 353968, CGA 355190, CGA 382191
	PBI 120	None	Thiamethoxam, CGA 322704, CGA 265307
	PBI 365	Not analysed	Not analysed
Spring wheat	PBI 30	CGA 322704, NOA 421275	Thiamethoxam, CGA 322704, CGA 265307, NOA 407475, NOA 421275, Desmethyl-CGA 353968
	PBI 120	CGA 322704	Thiamethoxam, CGA 322704, CGA 265307, NOA 421275, NOA 407475, NOA 405217, CGA 382191, Desmethyl-CGA 353968
	PBI 365	None	CGA 322704, CGA 265307

NATURE OF THE RESIDUE IN LAYING HEN			
Species	Dose Level	Length of Dosing (d)	Sacrifice
Hen	97.6 or 111 mg/kg/day once daily	3	6 hours after last dose

Of the total radioactive dose, approximately 80% was excreted in the urine and faeces, 0.1% was secreted in the eggs. Radioactivity remaining in edible tissues accounted for 1.3-1.5% of the dose.

Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Radiolabel Position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Egg white	CGA 322704, CGA 265307, NOA 404617	Thiamethoxam, NOA 404617, Desmethyl-CGA 353968, NOA 405217, CGA 355190, 8U
Egg yolk	Thiamethoxam, CGA 322704, CGA 265307	NOA 407475, NOA 405217, NOA 421275, 8U
Liver	CGA 322704, CGA 265307, NOA 421275, MU3	Thiamethoxam, Desmethyl-CGA 353968, NOA 402988, NOA 405217, NOA 404617, NOA 421275, 8U
Muscle	Thiamethoxam, NOA 421275, MU3	CGA 322704, NOA 407475, CGA 265307, NOA 405217, NOA 421275, CGA 355190, 8U
Skin/fat	Thiamethoxam, CGA 265307	CGA 322704, NOA 407475, NOA 421275, NOA 404617, MU3, Desmethyl-CGA 353968, 8U, CGA 355190

NATURE OF THE RESIDUE IN RUMINANT			
Species	Dose Level	Length of Dosing (d)	Sacrifice
Goat (lactating)	100.6 or 111.9 ppm once daily	3	6 hours after the last dose

For both ^{14}C test substances, the dosed radioactivity was eliminated primarily in the urine (44-49%) and faeces (8-12%). Approximately 1% was secreted in the milk. Radioactivity remaining in edible tissues at sacrifice accounted for 3.4-3.7% of the dose. Minor amounts of radioactivity (0.6%) were detected in blood and bile and 18-26% was present in the gastrointestinal tract and rumen at sacrifice.

Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Radiolabel Position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Milk	Thiamethoxam, CGA 322704, CGA 265307	Desmethyl-CGA 353968, NOA 405217
Liver	NOA 407475, NOA 421275, NOA 421276, L14	Thiamethoxam, CGA 322704, CGA 265307, NOA 404617, MU12, Desmethyl-CGA 353968, CGA 355190, CGA 353968, CGA 309335, CGA 359683, N5, NOA 405217
Kidney	Thiamethoxam, NOA 421275, NOA 421276, N5	CGA 322704, NOA 407475, CGA 265307, NOA 404617, L14, MU12, Desmethyl-CGA 353968, CGA 355190, CGA 353968, CGA 359683, NOA 405217
Muscle	Thiamethoxam, NOA 421276, MU12	CGA 322704, NOA 407475, CGA 265307, NOA 421275, NOA 421276, L14, MU12, Desmethyl-CGA 353968, NOA 405217
Fat	Thiamethoxam, CGA 322704, NOA 421275, NOA 421276	CGA 265307, NOA 404617, Desmethyl-CGA 353968, NOA 405217, MU12

CROP FIELD TRIALS—APPLES

Eight field trials were conducted throughout Canada (1, 1A, 5, 5B and 11) during the 2002 growing season. The number and location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Apples were treated with 79 g a.i./ha or 192 g a.i./ha; 0.4× or 1.0× the proposed Canadian rate, respectively.

Commodity	Total Rate g a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Apple fruit	79	110-154	Thiamethoxam + CGA 322704	16	<0.02	<0.02	<0.02	<0.02/ 0.02	NA
	192	35		2	NQ (0.016)	NQ (0.020)	NQ (0.018)	NQ (0.018)/ 0.02	NA
	192	59-61		16	NQ (0.013)	<0.02	<0.02	NQ (0.017)/ 0.02	0
	192	66-114		22	<0.02	<0.02	<0.02	<0.02	NA

CROP FIELD TRIALS—PEARS

Five field trials were conducted throughout Canada (1A, 5 and 11) during the 2002 growing season. The number and location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Pears were treated with 79 g a.i./ha or 192 g a.i./ha; 0.4× or 1.0× the proposed Canadian rate, respectively.

Commodity	Total Rate g a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Pear fruit	79	97-147	Thiamethoxam + CGA 322704	10	<0.02	<0.02	<0.02	<0.02/ 0.02	NA
	192	59-61		8	NQ (0.008)	<0.02	<0.02	NQ (0.016)/ 0.02	0.01
	192	67-109		10	NQ (0.014)	<0.02	<0.02	NQ (0.017)/ 0.02	0

CROP FIELD TRIALS—POTATOES

Twelve field trials were conducted throughout Canada (1, 1A, 5, 5A, 5B, 7A, 12 and 14) during the 2002 growing season. The location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Potatoes were treated with either an in-furrow 116 g a.i./ha application or a foliar 52 g a.i./ha application; 1.0× the proposed Canadian rate.

Commodity	Total Rate g a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Potato tubers	116	79-106	Thiamethoxam + CGA 322704	24	NQ (0.007)	0.022	0.021	NQ (0.014)/ 0.02	0
	52	3		2	<0.02	<0.02	<0.02	<0.02/ 0.02	NA
	52	38905		24	NQ (0.013)	<0.02	<0.02	0.020/ 0.02	0
	52	38970		24	<0.02	<0.02	<0.02	<0.02/ 0.02	NA
	52	39096		24	NQ (0.008)	<0.02	<0.02	NQ (0.019)/ 0.02	0
	52	21		2	<0.02	<0.02	<0.02	<0.02/ 0.02	NA

RESIDUE DECLINE—APPLES AND POTATOES

Residue decline studies were conducted on apple and potatoes. In both studies, Thiamethoxam residue data was less than the combined LOQ (0.02 ppm; Thiamethoxam + CGA 322704) when trials were conducted at GAP. No residue decline information could be obtained when apple or potato samples were harvested at or near the proposed preharvest interval.

MAXIMUM RESIDUE LIMITS

Apples and pears: 0.02 ppm was the maximum residue found for both commodities. Therefore, a MRL of 0.02 ppm for the pome fruit crop group is recommended to cover Thiamethoxam residues.

Potatoes: 0.022 ppm was the maximum residue found in potato tubers. Consequently, a MRL of 0.03 ppm for potato tubers is recommended to cover Thiamethoxam residues.

FIELD ACCUMULATION IN ROTATIONAL CROPS—WHEAT, LETTUCE, TURNIPS

Rotational field trials were conducted in Fresno County, CA, Indian River County, FL and Champaign County, IL on soil textures ranging from sand to silty clay loam. Peppers, leaf lettuce and mustard greens were planted as primary crops. At each test site, Thiamethoxam was applied to the primary crop as an in-furrow application at planting (leaf lettuce and mustard greens) or as a transplant drench (peppers) followed by a broadcast foliar application 30 to 51 days later for a seasonal application of ~200 g a.i./ha. At each test site, control and treated plots were planted with leaf lettuce, turnips and wheat as representative rotational crops at PBIs of approximately 30, 120 and 180 days after the final application of Thiamethoxam.

Commodity	Total Rate g a.i./ha	PBI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Wheat forage	200	30	Thiamethoxam + CGA 322704	2	0.04	0.04	0.04	0.04/0.04	N/A
		120		3	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
Wheat hay		30		2	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
		120		3	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
Lettuce		30		2	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
		120		3	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
Turnip tops		30		2	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
		120		3	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
Turnip roots		30		2	<0.02	<0.02	<0.02	<0.02/<0.02	N/A
		120		3	<0.02	<0.02	<0.02	<0.02/<0.02	N/A

PROCESSED FOOD AND FEED—APPLES AND POTATOES

Fraction	Mean Residue Levels (ppm)	Concentration factor
Apple—RAC (291 g a.i./ha)	0.09	N/A
Wet apple pomace (291 g a.i./ha)	0.12	1.6
Apple juice (291 g a.i./ha)	0.08	0.75
Potato tubers—RAC (571 g a.i./ha)	0.03	N/A
Potato culls (571 g a.i./ha)	0.05	1.2
Potato wet peel and trimmings (571 g a.i./ha)	0.03	1
Potato granules (571 g a.i./ha)	0.04	1.2
Potato chips (571 g a.i./ha)	0.03	1.9

MAXIMUM RESIDUE LIMITS
The combined residues of Thiamethoxam and CGA 322704 concentrated slightly in wet apple pomace and were reduced slightly in apple juice. Based upon the 1.6× concentration factor and the HAFT of 0.02 ppm for apple, the combined residues of Thiamethoxam and CGA 322704 would be expected to reach 0.032 ppm in wet apple pomace. Thiamethoxam residues in/on apple juice will be covered under the recommended MRL of 0.02 ppm for pome fruit. The combined residues of Thiamethoxam and CGA 322704 concentrated in potato chips and slightly in potato culls, granules and wet peel and trimmings. Based upon the 1.9× concentration factor and the HAFT of 0.021 ppm for potato tuber, the combined residues of Thiamethoxam and CGA 322704 would be expected to reach 0.039 ppm in potato chips. Consequently, a MRL of 0.04 ppm is recommended to cover Thiamethoxam residues in/on potato chips. Thiamethoxam residues in/on potato granules will be covered under the recommended MRL of 0.03 ppm for potato RAC.

LIVESTOCK FEEDING			
Soybean, potato, apples, wheat, barley, canola and corn are the feed items on the Canadian label. Poultry feed items on the Canadian label include corn, canola and barley and swine feed items include potato and barley. The estimated MTDB is 0.16 ppm for beef cattle, 0.10 ppm for dairy cattle, 0.02 ppm for poultry and 0.02 ppm for swine.			
Tissues/Matrices	Feeding level	Mean residue levels (ppm)	Anticipated residues (ppm)
Whole milk	2	0.012	0.0006
	6	0.045	0.0008
	20	0.16	0.0008
Beef kidney	2	<0.02	<0.02
	6	<0.02	<0.02
	20	0.036	0.0003
Beef liver	2	0.055	0.0044
	6	0.148	0.0004
	20	0.326	0.0026
Meat	2	<0.02	<0.02
	6	<0.02	<0.02
	20	0.045	0.0004

PROPOSED MRLs (as per MRL calculator)	
potato	0.03 ppm
potato chips	0.04 ppm
pome fruit crop group 11 (apple; crabapple; loquat; mayhaw; pear; pear, oriental; quince)	0.02 ppm

Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT **Primary Crops** **Rotational Crops**	The sum of Thiamethoxam and CGA 322704
METABOLIC PROFILE IN DIVERSE CROPS	Similar in five diverse crops (corn, cucumber, pear, potato and lettuce)

ANIMAL STUDIES - Poultry and Ruminant			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT		The sum of Thiamethoxam and CGA 322704	
METABOLIC PROFILE IN ANIMALS		Quantitative and qualitative differences in poultry and ruminants, but does not affect overall profile assessment.	
FAT SOLUBLE RESIDUE		NO, based on Log K_{ow} = -0.13	
DIETARY RISK from food and water			
Chronic Non-Cancer Dietary Risk **ADI =0.004 mg/kg bw** **PGW water number = 1.516 µg/L** **Refined includes STMRs, experimental or default processing factors**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Refined Food	**Refined Food + Water**
	All infants < 1 yr old	17.7	20.3
	Children 1 to 2 yrs	25.6	26.8
	Children 3 to 5 yrs	19.6	20.7
	Children 6 to 12 yrs	10.6	11.4
	Youth 13 to 19 yrs	5.7	6.2
	Adults 20 to 49 yrs	4.7	5.5
	Adults 50+ yrs	5	5.8
	Females 13 to 49 yrs	4.8	5.6
	Total Population	7.1	7.9
Acute Dietary Exposure Analysis, 95th percentile EEC = 7.19 µg/L (level 2)	**POPULATION**	**ESTIMATED RISK (% of ARfD)**	
		Basic Food (MRL)	**Basic Food + EEC**
ARfD = 0.115 mg/kg bw **Basic includes MRLs and US tolerances, experimental or default processing factors**	**All infants < 1 yr old**	9.05	9.43
	Children 1 to 2 yrs	10.25	10.36
	Children 3 to 5 yrs	7.97	8.19
	Children 6 to 12 yrs	4.9	5.09
	Youth 13 to 19 yrs	2.87	3.01
	Adults 20 to 49 yrs	2.42	2.59
	Adults 50+ yrs	2.36	2.52
	Females 13 to 49 yrs	2.41	2.57
	Total Population	3.82	3.97

Appendix III Environmental assessment

Table 5.7.1 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Thiamethoxam (CGA 293343)	t½ pH 5: stable t½ pH 7: 572 - 643 days t½ pH 9: 4.2 - 8.4 days	Hydrolysis will not be an important route for transformation or dissipation of Thiamethoxam in the terrestrial environment at environmentally relevant pH.
Phototransformation on soil	Thiamethoxam (CGA 293343)	DT_{50} = 79 - 97 days on soil	Phototransformation will not be an important route for transformation of Thiamethoxam on soil.
Phototransformation in air			No studies submitted
Biotransformation			
Biotransformation in aerobic soil	Thiamethoxam (CGA 293343)	DT_{50}: 101 - 353 days in soil	Thiamethoxam is classed as moderately persistent to persistent in soil under aerobic conditions.
Biotransformation in anaerobic soil	Thiamethoxam (CGA 293343)		No studies submitted
Mobility			
Adsorption or desorption in soil	Thiamethoxam (CGA 293343)	Ads. K_{oc} : 33 - 177 mL/g carbon Des. K_{oc} : 72 - 698 mL/g carbon	Thiamethoxam has a moderate to very high potential for mobility in the soil.
	CGA 355190	Ads. K_{oc} : 40 - 188 mL/g carbon Des. K_{oc} : 77 - 379 mL/g carbon	CGA 355190 has a high to very high potential for mobility in the soil.
	NOA 404617	Ads. K_{oc} : 11 - 73 mL/g carbon Des. K_{oc} : 27 - 152 mL/g carbon	NOA 404617 has a very high potential for mobility in the soil.
	NOA 407475	Ads. K_{oc} :434 - 1553 mL/g carbon Des. K_{oc} : 455 - 1666 mL/g carbon	NOA 407475 has a low to moderate potential for mobility in the soil.
	CGA 322704	Ads. K_{oc} : 74 - 382 mL/g carbon Des. K_{oc} : 118 - 673 mL/g carbon	CGA 322704 has a moderate to high potential for mobility in the soil.
	CGA 353042	Ads. K_{oc} : 199 - 1451 mL/g carbon Des. K_{oc} : 200 - 1278 mL/g carbon	CGA 353042 has a low to moderate potential for mobility in the soil.
Soil leaching (ageing)		K_d : 2.01 - 197.53 mL/g soil	Thiamethoxam will be less mobile in soil after ageing.
Volatilization			No studies submitted

Property	Test substance	Value	Comments
Field studies			
Field dissipation (Canada)	Thiamethoxam (CGA 293343)	DT_{50}: 48 - 239 d, for broadcast use	Thiamethoxam is moderately persistent to persistent in soil under field conditions, *when used as broadcast spray.*
Field dissipation (U.S.)	Thiamethoxam (CGA 293343)	DT_{50}: 34.7 d for broadcast use DT_{50}: 35.2 d, for in-furrow use	Thiamethoxam is slightly persistent in soil under certain field conditions *when used as broadcast or in-furrow soil treatment.*

Table 5.7.2 Summary of transformation products formed in the terrestrial environment

Fate process	Test material	Major transformation products	Minor transformation products
Hydrolysis	Thiamethoxam (CGA-293343)	CGA-355190 NOA-404617	CGA-309335 (formed by hydrolysis of NOA-404617)
Phototransformation on soil	Thiamethoxam (CGA-293343)	None Not an important route of transformation	None
Biotransformation in aerobic soil	Thiamethoxam (CGA-293343)	In clay loam soil: CGA-355190 In sandy loam soil: None found	Several found in clay loam and sandy loam soils
Biotransformation in anaerobic soil (flooded soil)	No studies submitted		
Field dissipation	Thiamethoxam (CGA-293343)	Foliar use: CGA322704[a] (U.S. site) In-furrow use: CGA322704 (U.S. site)	CGA 355190 (Manitoba site) CGA 322704 (Ontario and PEI sites)

[a] CGA-322704 is the chemical code for the active ingredient clothianidin.

Table 5.8.1 Fate and behaviour in the aquatic environment

Property	Test material	Value	Comments
Abiotic transformation			
Hydrolysis	Thiamethoxam (CGA 293343)	t½ pH 5: stable t½ pH 7: 572 - 643 days t½ pH 9: 4.2 - 8.4 days	Hydrolysis will not be an important route for transformation or dissipation of Thiamethoxam in the terrestrial environment at environmentally relevant pH.

Property	Test material	Value	Comments
Phototransformation in water	Thiamethoxam (CGA 293343)	DT_{50} = 2.3 - 3 days in water	Phototransformation may be a route for transformation or dissipation of Thiamethoxam in the photic zone of clear natural water.
Biotransformation			
Biotransformation in aerobic water systems	Thiamethoxam (CGA 293343)	DT_{50} at 25°C: 9.5 - 22 days in water DT_{50} at 25°C: 16 days in water/sediment	Thiamethoxam is classed as slightly persistent in water and sediment under aerobic conditions.
Biotransformation in anaerobic water systems	Thiamethoxam (CGA 293343)	DT_{50} at 25°C: 25 - 50 days in water/sediment	Thiamethoxam is classed as moderately persistent in water under anaerobic conditions.
		DT_{50} at 5°C: 12 - 44 days in water/sediment	Thiamethoxam is classed as moderately persistent in water under anaerobic conditions at lower temperature.
Partitioning			
Adsorption or desorption in sediment	Thiamethoxam (CGA 293343)	Ads. K_{oc} : 33 - 177 mL/g carbon Des. K_{oc} : 72 - 698 mL/g carbon	Thiamethoxam has a low potential for partitioning into sediment.
Field studies			
Field dissipation			No studies submitted

Table 5.8-2 Summary of transformation products formed in the aquatic environment

Fate process	Test material	Major transformation products	Minor transformation products
Hydrolysis	Thiamethoxam (CGA 293343)	CGA 355190 NOA 404617	CGA 309335 (formed by hydrolysis of NOA 404617)
Phototransformation in water	Thiamethoxam (CGA 293343)	CGA 353042 (guanidine label) Carbonyl sulfide (volatile product from thiazolyl label)	Several unidentified minor transformation products formed
Biotransformation in aerobic water	Thiamethoxam (CGA 293343)	CGA 355190 NOA 404617	CGA 353968 & one unidentified
Biotransformation in aerobic water/sediment	Thiamethoxam (CGA 293343)	NOA 407475 CGA 355190 NOA 404617	None

Fate process	Test material	Major transformation products	Minor transformation products
Biotransformation in anaerobic water/sediment at 25°C	Thiamethoxam (CGA 293343)	NOA 407475	CGA 355190
Biotransformation in anaerobic water/sediment at 5°C	Thiamethoxam (CGA 293343)	NOA 407475 CGA 355190 NOA 404617	None
Field dissipation			No studies submitted

Table 5.9.2-1 Major groundwater and surface water model inputs for assessment of Thiamethoxam and CGA-322704.

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	potato, apple/crabapple, pear and oriental pear
	Maximum allowable application rate per year (kg a.i./ha)	apple: 0.192 potato: 0.052 (foliar), 0.117 (in-furrow)
	Maximum rate each application (kg a.i./ha)	Thiamethoxam: apple: 0.079 (pre-bloom), 0.096 (post-bloom) potato: 0.026 (foliar), 0.117 (in-furrow) CGA 322704: 21% of Thiamethoxam application rates, for drinking water modelling
	Maximum number of applications per year	apple: 2 potato: 2 (foliar), 1 (in-furrow)
	Minimum interval between applications (days)	apple: 10 potato: 7 (foliar), NA (in-furrow)
	Method of application	foliar spray (apple and potato-foliar) or in-furrow spray during planting (potato in-furrow) using conventional ground application equipment
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Thiamethoxam: 643 CGA 322704: stable
	Phototransformation half-life in water (days)	Thiamethoxam: 97 CGA 322704: 0.14
	Adsorption K_{oc} (mL/g)	Thiamethoxam: 38 CGA 322704: 84
	Aerobic soil biotransformation half-life (days)	Thiamethoxam: 337 CGA 322704: 870
	Aerobic aquatic biotransformation half-life (days)	Thiamethoxam: 21.9 CGA 322704: 1732
	Anaerobic aquatic biotransformation half-life (days)	Thiamethoxam: 28.6 CGA 322704: 27

Table 5.9.2-2 Level 1 aquatic ecoscenario modelling results (µg/L) for Thiamethoxam.

EEC (µg a.i./L)					
Peak	**96-hour**	**21-day**	**60-day**	**90-day**	**Yearly**
4.98	4.79	4.11	3.05	2.55	0.96

Table 5.9.2-3 Level 2 estimated environmental concentrations (µg/L) of Thiamethoxam (T) and CGA 322704 ©) in potential surface water sources of drinking water.

Crop	Method	Province	Date	Peak[1] (acute)		Yearly[1] (chronic)		Comment
				T	C	T	C	
Reservoir								
Apple	Foliar	QC	07 Jun	**6.9**	0.288	**0.912**	0.0303	highest parent and transformation product total
Potato	Foliar	ON	14 Jul	2.33	**0.433**	0.315	**0.044**	highest CGA 322704
Dugout								
Potato	Foliar	MB	01 Jul	1.65	**0.419**	**0.382**	0.112	
Potato	Foliar	MB	25 Jun	1.62	0.375	0.299	**0.118**	
Potato	Foliar	MB	20 Jun	**2.12**	0.416	0.37	0.109	

[1]The 90th percentile of the value (peak or yearly average) over all years in the simulation

Table 5.9.2-4 Level 2 estimated environmental concentrations (µg/L) of Thiamethoxam (T) and CGA 322704 ©) in potential groundwater sources of drinking water

Crop	Province	Daily [1]		Yearly[2]		Comment
		T	C	T	C	
Apple	QC	**17.2**	6.18	**15.8**	6.17	highest parent and transformation product total
Apple	ON	8.73	**8.18**	8.44	**8.18**	highest CGA 322704

[1] 90th percentile of yearly peak concentrations
[2] 90th percentile of yearly average concentrations

Table 5.9.3 Maximum EEC in vegetation and insects, based on 2 foliar applications (10 days apart) at the proposed Canadian label rate for apple and pear, of 96 g a.i./ha of Actara 25 WG (equivalent to a cumulative application rate of 174.75 g a.i./ha on the day of the second application).

Matrix	EEC (mg a.i./kg fw)[a]	Fresh to dry weight ratios	EEC (mg a.i./kg dw)
Short range grass	37.39	3.3[b]	123.41
Leaves and leafy crops	19.57	11[b]	215.3
Long grass	17.12	4.4[b]	75.35
Forage crops	20.97	5.4[b]	113.23
Small insects	9.08	3.8[c]	34.53
Pods with seeds	1.87	3.9[c]	7.3
Large insects	1.5	3.8[c]	5.91
Grain and seeds	1.55	3.8[c]	5.91
Fruit	2.34	7.6[c]	17.8

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[b] Fresh to dry weight ratios from Harris (1975)
[c] Fresh to dry weight ratios from Spector (1956)

Table 6.1.1 Effects on terrestrial organisms

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Invertebrates				
Earthworm	Acute	Thiamethoxam	LC_{50} > 1000 mg a.i./kg soil NOEC = 1000 mg a.i./kg soil	Non-toxic
Bee	Acute Oral	Thiamethoxam	LD_{50} = 0.005 µg a.i./bee	Highly toxic
	Acute Contact	Thiamethoxam	LD_{50} = 0.024 µg a.i./bee	Highly toxic
	Contact	Thiamethoxam residues	NOEL = 0.004 µg a.i./bee	Highly toxic
Predatory arthropod (*Coccinella septempunctata*)	Contact	Thiamethoxam	LR_{50} = 12.4 g a.i./ha NOEC = 25 g a.i./ha (reproduction capacity)	Moderately harmful
Predatory arthropod (*Typhlodromus pyri*)	Contact	Thiamethoxam	LR_{50} = 41 g a.i./ha NOEC = 6.3 g a.i./ha (Fecundity)	Slightly harmful
Parasitic arthropod (*Aphidius rhopalosiphi*)	Contact	Thiamethoxam	LR_{50} = 0.131 g a.i./ha NOEC = 0.063 g a.i./ha (reproduction capacity)	Harmful

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Birds				
Bobwhite quail	Acute	Thiamethoxam	LD_{50} = 1552 mg a.i./kg bw NOEL = 125 mg a.i./kg bw	Slightly toxic
	Dietary	Thiamethoxam	LC_{50} > 5200 mg a.i./kg diet NOEC = 1300 mg a.i./kg diet	Non-toxic
	Reproduction	Thiamethoxam	NOEC = 900 mg a.i./kg diet LC_{50} not determined	No significant treatment-related effects
Mallard duck	Acute	Thiamethoxam	LD_{50} = 576 mg a.i./kg bw NOEL not determined	Slightly toxic
	Dietary	Thiamethoxam	LC_{50} > 5200 mg a.i./kg diet NOEC = 163 mg a.i./kg diet	Non-toxic
	Reproduction	Thiamethoxam	NOEC = 300 mg a.i./kg diet LC_{50} not determined	No significant treatment-related effects
Mammals				
Rat	Acute Oral	Thiamethoxam	LD_{50} = 1552 mg a.i./kg bw NOEL = 125 mg a.i./kg bw	Slightly toxic
	Dermal	Thiamethoxam	LD_{50} > 2000 mg a.i./kg bw NOEL not determined	Low toxicity
	Inhalation	Thiamethoxam	LC_{50} > 3.72 mg a.i./L NOEC not determined	Low toxicity
	Oncogenicity	Thiamethoxam	NOEL = 21 mg a.i./kg bw/day LD_{50} not determined	Trend for increase in oncogenic effects
	Multi-generations Reproduction	Thiamethoxam	NOEL = 202 mg a.i./kg bw/day LD_{50} not determined	No treatment-related adverse effects
	Teratogenicity	Thiamethoxam	LD_{50} and NOEL not determined	Non-teratogenic
Mouse	Acute Oral	Thiamethoxam	LD_{50} = 871 mg a.i./kg bw NOEL not determined	Moderately toxic
	Oncogenicity	Thiamethoxam	NOEL = 2.6 mg a.i./kg bw/day LD_{50} not determined	Trend for increase in oncogenic effects
Rabbit	Acute Neurotoxicity	Thiamethoxam	NOEL = 100 mg a.i./kg bw LD_{50} not determined	Neurotoxic
	Teratogenicity	Thiamethoxam	LD_{50} and NOEL not determined	Non-teratogenic
Beagle Dog	Sub-chronic Oral	Thiamethoxam	NOEL = 32.6 mg a.i./kg bw/day (♀) 31.6 mg a.i./kg bw/day (♂) LD_{50} not determined	Toxic

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Vascular plants				
Vascular plant	Seedling emergence	No studies submitted		
	Vegetative vigour	No studies submitted		

[a] Atkins *et al.* (1981) for bees, Hassan et al (1994) for other beneficial arthropods, and the U.S. EPA classification for others, where applicable.

Table 6.2.1 Effects on aquatic organisms

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Freshwater species				
Crustacean *(Daphnia magna)*	Acute	Thiamethoxam	EC_{50} > 105.8 mg a.i./L NOEC = 36.5 mg a.i./L	Practically non-toxic
	Chronic	Thiamethoxam	EC_{50} > 100.5 mg a.i./L NOEC = 100.5 mg a.i./L	Practically non-toxic
Midge *(Chironomid riparius)*	Acute	Thiamethoxam	EC_{50} = 35 µg a.i./L NOEC = 13 µg a.i./L	Very highly toxic
	Chronic	Thiamethoxam	EC_{50} = 11 µg a.i./L NOEC = 5 µg a.i./L	Very highly toxic
Rainbow trout	Acute	Thiamethoxam	LC_{50} > 100 mg a.i./L NOEC = 100 mg a.i./L	Non-toxic
	Chronic (early life stage)	Thiamethoxam	NOEC = 20 mg a.i./L	Non-toxic
Bluegill sunfish	Acute	Thiamethoxam	LC_{50} > 114 mg a.i./L NOEC = 114 mg a.i./L	Non-toxic
	Chronic	No studies submitted		
Freshwater alga (*Selenastrum capricornutum*)	Acute	Thiamethoxam	EC_{50} > 100 mg a.i./L NOEC = 100 mg a.i./L	Practically non-toxic
Vascular plant (*Lemna gibba*)	Dissolved	Thiamethoxam	EC_{50} > 90.2 mg a.i./L NOEC = 90.2 mg a.i./L	
	Over spray	No studies submitted		
Marine species				
Crustacean (*Mysidopsis bahia*)	Acute	Thiamethoxam	LC_{50} = 6.8 mg a.i./L EC_{50} = 5.4 mg a.i./L (sub-lethal effects) NOEC < 2.0 mg a.i./L	Moderately toxic
	Chronic	No studies submitted		

Organism	Exposure	Test substance	End point value	Degree of toxicity[a]
Mollusk (*Crassostrea virginica*)	Acute	Thiamethoxam	EC_{50} > 119 mg a.i./L NOEC = 119 mg a.i./L	Practically non-toxic
	Chronic	No studies submitted		
Salmonid	Acute (Sheephead minnow)	Thiamethoxam	LC_{50} = 111 mg a.i./L EC_{50} > 111 mg a.i./L (sub-lethal effects) NOEC = 111 mg a.i./L	Non-toxic
	Salinity challenge	No studies submitted		
Marine alga	Acute	No studies submitted		

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

Table 6.4.1 PMRA's Risk Quotient Classification

Risk Quotient (RQ)	Risk Category
< 0.1	Negligible Risk
≥ 0.1 < 1	Low Risk
≥ 1 < 10	Moderate Risk
≥ 10 < 100	High Risk
≥ 100 < 1000	Very High Risk
≥ 1000	Extremely High Risk

Table 6.4.2 Risk to terrestrial organisms

Organism	Exposure	End point value (NOEC / NOEL / LD50)	EEC	RQ	Risk
Invertebrates					
Earthworm	Acute	1000 mg a.i./kg	0.08 mg a.i./kg	8.4×10^{-5}	Negligible risk
Bee	Acute Oral	0.005 µg a.i./bee (= 5.6 g a.i./ha)	96 g a.i./ha	17.14	High risk
	Acute Contact	0.024 µg a.i./bee (= 26.8 g a.i./ha)	96 g a.i./ha	3.58	Moderate risk
	Contact with residues	0.004 µg a.i./bee (= 4.48 g a.i./ha)	96 g a.i./ha	21.42	High risk
Predatory beetle	Contact	25 g a.i./ha	96 g a.i./ha	3.84	Moderate risk
Predatory mite	Contact	6.3 g a.i./ha	96 g a.i./ha	15.23	High risk
Parasitic wasp	Contact	0.063 g a.i./ha	96 g a.i./ha	1523.8	Extremely high risk

Organism	Exposure	End point value (NOEC / NOEL / LD50)	EEC	RQ	Risk
Birds					
Bobwhite quail	Acute	125 mg a.i./kg bw	30.6 mg a.i./kg	0.02	Negligible risk
	Dietary	1300 mg a.i./kg diet	30.6 mg a.i./kg	0.02	Negligible risk
	Reproduction	900 mg a.i./kg diet	1.3 mg a.i./kg bw/d	0.016	Negligible risk
Mallard duck	Acute	57.6 mg a.i./kg bw	30.6 mg a.i./kg	0.004	Negligible risk
	Dietary	163 mg a.i./kg diet	30.6 mg a.i/kg	0.03	Negligible risk
	Reproduction	300 mg a.i./kg diet	1.1 mg a.i./kg bw/d	0.08	Negligible risk
Mammals					
Small mammal (body weight 0.015 kg)	Acute (mouse study)	871 mg a.i./kg bw	87.63 mg a.i./kg diet	0.014	Negligible risk
Medium mammal (body weight 0.035 kg)	Acute (mouse study)	871 mg a.i./kg bw	87.63 mg a.i./kg diet	0.012	Negligible risk
Large mammal (body weight 1.0 kg)	Acute (mouse study)	871 mg a.i./kg bw	87.63 mg a.i./kg diet	0.007	Negligible risk
Vascular plants					
Vascular plant	Seedling emergence	No data submitted			
	Vegetative vigour	No data submitted			

Table 6.4.3-a Risk to aquatic organisms from direct over spray

Organism	Exposure	End point value (NOEC)	EEC	RQ	Risk
Freshwater species					
Crustacean (*Daphnia magna*)	Acute	36.5 mg a.i./L	0.02 mg a.i./L	0.0005	Negligible risk
	Chronic	100.5 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
Midge (*Chironomus riparius*)	Acute	13 µg a.i./L	0.02 mg a.i./L	1.6	Moderate risk
	Chronic	5 µg a.i./L	0.02 mg a.i./L	4	Moderate risk
Rainbow trout	Acute	100 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
	Chronic (early life-stages)	20 mg a.i./L	0.02 mg a.i./L	0.001	Negligible risk

Organism	Exposure	End point value (NOEC)	EEC	RQ	Risk
Bluegill sunfish	Acute	114 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
	Chronic	No studies submitted			
Amphibians	Early life-stages of rainbow trout as surrogate	20 mg a.i./L	0.11 mg a.i./L	0.005	Negligible risk
Freshwater alga	Acute	100 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
Vascular plant	Dissolved	90.2 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
	Overspray	No studies submitted			
Marine species					
Crustacean (*Mysidopsis bahia*)	Acute	2 mg a.i./L	0.02 mg a.i./L	0.01	Negligible risk
	Chronic	No studies submitted			
Mollusk	Acute	119 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
	Chronic	No studies submitted			
Salmonid (sheepshead minnow)	Acute	111 mg a.i./L	0.02 mg a.i./L	0.0002	Negligible risk
	Salinity challenge	No studies submitted			
Marine alga	Acute	No studies submitted			

Table 6.4.3-b Risk to *Chironomus riparius* using refined EEC in water*

Organism	Exposure	End point value (NOEC)	EEC	RQ	Risk
Freshwater species					
Midge (*Chironomus riparius*)	Acute	13 µg a.i./L	4.8 µg a.i./L	0.37	Negligible risk
	Chronic	5 µg a.i./L	4.2 µg a.i./L	0.84	Negligible risk

* EECs based on Level 1 aquatic ecoscenario runoff modelling for 96 h for acute and 21 days for chronic exposure.