Evaluation Report ERC2011-03

Confidor 200 SL containing Imidacloprid

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Overview

Registration Decision for Confidor 200 SL (Imidacloprid)

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of BAY NTN 33893 Technical Insecticide and Confidor 200 SL, containing the technical grade active ingredient imidacloprid, for systemic control of insect pests on deciduous and coniferous trees.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of BAY NTN 33893 Technical Insecticide and Confidor 200 SL.

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[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

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

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

What Is Imidacloprid?

Imidacloprid is a neonicotinoid insecticide that is readily taken up by plants and translocated systemically within the plants. It is active against insects on contact and through ingestion. Various end-use products containing imidacloprid are currently registered for control of insect pests in turf, on various food crops or on companion animals (dogs or cats). Registered uses on plants include foliar sprays, seed treatments and application to soil for uptake by plant roots.

Health Considerations

Can Approved Uses of Imidacloprid Affect Human Health?

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

Potential exposure to imidacloprid may occur when handling and applying Confidor 200 SL. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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

The active ingredient imidacloprid is of high toxicity when given as a single oral dose to rats. Consequently, the words "Danger Poison" are required on the label for the active ingredient.

Imidacloprid did not cause cancer in animals and did not alter genetic material. There was also no indication that imidacloprid impaired reproductive ability. Health effects in animals given daily doses of imidacloprid over long periods of time included effects on the liver, kidney, thyroid gland and eyes. There was evidence that imidacloprid affected the nervous system. When imidacloprid was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to imidacloprid than the adult animal. 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.

Risks in Residential and Other Non-Occupational Environments

Potential exposure and risks to bystanders are expected to be negligible if label directions and precautionary measures are followed.

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

Occupational Risks From Handling Confidor 200 SL

Occupational risks are not of concern when Confidor 200 SL is used according to the label directions, which include protective measures.

Commercial applicators, including city employees, who mix, load or apply Confidor 200 SL by a pressurized tree-trunk injector system have the potential for intermittent dermal and/or inhalation exposure from April to September. Therefore, the label specifies that Confidor 200 SL must only be used with closed application systems and anyone mixing/loading and/or applying Confidor 200 SL must wear a long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, cleaning and repair, and during removal of injection devices from trees. The label also requires that the application sites are not left unattended during the treatment process and applicators must ensure that there is no leakage from the plugged injection holes of host trees after application.

Taking into consideration these label requirements and the expectation of the exposure period for handlers and workers, the risk to these individuals are not a concern.

Environmental Considerations

What Happens When Imidacloprid Is Introduced Into the Environment by Trunk Injection?

In comparison to traditional application methods, trunk injection is expected to reduce environmental exposure. Risk-reduction measures have been implemented to mitigate effects on pollinators that may visit the blossoms of treated trees.

Imidacloprid and its degradates move primarily to the fast growing parts of the tree such as the shoots and leaves. Some residues will also reach other plant parts such as blossoms and buds. Without risk-reduction measures, imidacloprid may impact non-target pollinators, such as bees, foraging on the blossoms of treated trees. At the proposed rate, imidacloprid is not expected to pose a risk to other non-target species.

In comparison to traditional application methods, trunk injection is expected to reduce environmental exposure since imidacloprid is injected directly into selected trees.

Value Considerations

What Is the Value of Confidor 200 SL?

When injected into the trunks of trees, Confidor 200 SL can provide control of various foliage-feeding insect pests and can provide control or suppression of wood-boring beetles.

Confidor 200 SL applied as an injection into the trunks of trees reduces populations of foliage-feeding insect pests below levels that are damaging to the trees. It may also reduce populations of wood-boring beetles substantially, although these pests are more difficult to control and have lower tolerable damage thresholds. Confidor 200 SL provides a new alternative active ingredient for control of foliage-feeding pests of trees and the first pest control product registered for use against wood-boring beetles in Canada. Application by trunk injection helps conserve natural enemies of pests as well as other non-target organisms that would be exposed to foliar applications of insecticides.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Confidor 200 SL to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with workers or bystanders coming into direct contact with Confidor 200 SL on the skin, by inhalation or through ingestion, anyone mixing, loading and applying Confidor 200 SL must: 1) use only closed application systems and 2) wear a long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, cleaning and repair, and during removal of injection devices from trees. The label also requires that the application sites are not left unattended during the treatment process. Applicators must ensure that there is no leakage from the plugged pre-drilled holes of host trees after application.

Environment

For trees that may be visited by pollinators, the label restricts the timing of applications to mitigate the risk to pollinators. Furthermore, the uses are restricted to licensed pest control operators authorized with permits or appropriate license by the government in conjunction with a federal-, provincial- or municipal-government control program.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information by September 1, 2013.

Environment

- Canadian monitoring data on imidacloprid and its transformation products in various parts of treated trees over time, which includes samples of nectar, pollen, guttation water and resinous substances

- Additional information on bee foraging behaviour on blooming trees

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document 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.

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

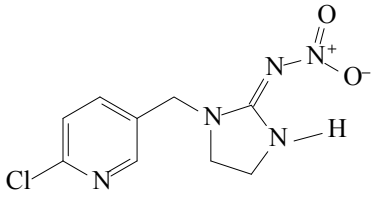
The test data cited in this Evaluation Report (namely, the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). 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).

Science Evaluation

Imidacloprid

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Imidacloprid
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*E*)-1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine
2. Chemical Abstracts Service (CAS)	(2*E*)-1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine
CAS number	138261-41-3
Molecular formula	$C_9H_{10}ClN_5O_2$
Molecular weight	255.67
Structural formula	
Purity of the active ingredient	98% nominal

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

Technical Product—BAY NTN 33893 Technical Insecticide

Property	Result
Colour and physical state	Light yellow solid
Odour	Characteristic odour, weak
Melting point	144°C
Boiling point or range	N/A
Density	1.54 g/cm^3
Vapour pressure at 20°C	4×10^{-7} mPa at 20°C 9×10^{-7} mPa at 25°C
Henry's law constant at 20°C	Relatively non-volatile under field conditions
Ultraviolet (UV)-visible spectrum	pH — λ_{max} (nm) 4 — 270 7 — 270 9 — 270
Solubility in water at 20°C	510 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solvent — Solubility (g/L) dichloromethane — 67 isopropanol — 2.3 toluene — 0.69 n-hexane — <0.1
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 0.57 at 21°C
Dissociation constant (pK_a)	The test substance shows very weak basic properties. Complete protonation can be achieved only in non-aqueous solvents in presence of very strong acids. It is not possible to specify a pK_a value of the test substance in pure aqueous systems.
Stability (temperature, metal)	No exothermic decomposition occurred below 150°C. The absence of any evolution of heat or gas and lack of colour change after 24 hours showed the product to be inert toward reduction by zinc and oxidation by NaOCl.

End-Use Product—Confidor 200 SL

Property	Result
Colour	Clear yellow
Odour	Not specified
Physical state	Liquid
Formulation type	Solution
Guarantee	17.1% nominal (limits: 16.2%–18.0%)
Container material and description	0.5, 1 L to bulk, plastic jug, bottle
Density	1.17 g/mL
pH	6.72 (10% aqueous solution at 25°C)
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Stable for 1 year when stored at ambient temperature in 1 L HDPE/EVOH (High Density Polyethylene / Ethyl Vinyl Alcohol) extruded bottles and 1-gallon HDPE containers, both with and without fluorine gas barrier treatment.
Corrosion characteristics	Not corrosive to the packaging material.
Explodability	The product is not explosive.

1.3 Directions for Use

Confidor 200 SL is formulated for application by trunk injection into deciduous and coniferous trees. The product is to be applied no more than once or three times per year at rates ranging from 0.30 mL to 1.25 mL (0.06-0.25 g a.i.) per cm of trunk diameter at breast height (DBH) for control of a variety of insect pests including aphids, psyllids, scale insects, leafminers, and wood-boring beetles. See also Acceptable Efficacy Claims (Section 5.1.1). Refer to the product label for complete details of the directions for use.

1.4 Mode of Action

Imidacloprid acts as an antagonist by binding to the postsynaptic nicotinic receptors in the insect central nervous system. It is active against insects through contact or ingestion. It is readily taken up by plants and translocated acropetally and also displays translaminar activity when applied as a foliar spray.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in BAY NTN 33893 Technical Insecticide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

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

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for imidacloprid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The database also consisted of several studies conducted with a nitroso metabolite of imidacloprid identified as WAK 3839. 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 pesticide.

Methylene-^{14}C imidacloprid was rapidly absorbed (peak plasma concentration 1-2.5 hours post-dosing) with approximately 90% of the administered dose (AD) being eliminated within 24 hours and 96% within 48 hours. Urinary excretion was the major route of elimination (70-80% of the AD), with a lesser amount eliminated in feces (17-25% of the AD). Biliary excretion was an important contributor to fecal excretion as it accounted for 87% of fecal radioactivity. Only a trace amount (0.033% of the AD) was excreted in expired air. No significant differences were noted between sexes, dose levels, or routes of administration. Total tissue burden 48 hours after dosing accounted for approximately 0.5% of the AD.

In addition to the parent, metabolites were identified in the urine, including the glycine conjugate of 6-chloronicotinic acid, 4 and 5-hydroxyimidacloprid, dehydroimidacloprid (olefinic metabolite), 6-chloronicotinic acid, the glycine conjugate of 6-S-methyl-nicotinic acid, nitroiminodehydroimidazolidine and nitroiminoimidazolidine. A guanidine type metabolite of imidacloprid was also identified in the feces. Two major routes of biotransformation were identified: oxidative cleavage of the parent compound leading to 6-chloronicotinic acid and its glycine conjugate, with subsequent dechlorination to form 6-hydroxy nicotinic acid and its mercapturic acid derivative, and hydroxylation of imidazolidine followed by elimination of water from the parent compound, giving the olefinic metabolite.

Results from acute studies indicate that imidacloprid was highly toxic by the oral route and of low toxicity by the dermal and inhalation routes. Imidacloprid was minimally irritating to the eyes and skin and did not show sensitizing potential.

The end-use product, Confidor 200 SL, was shown to be of low acute toxicity by the oral, dermal and inhalation routes, was non-irritating to the eye and minimally irritating to the skin, and was not considered to be a dermal sensitizer.

In an oral subchronic toxicity study in rats, changes in clinical chemistry and histology indicative of liver injury were noted. Liver effects were also noted in rats in a 28-day inhalation toxicity study. A 21-day dermal toxicity study in rabbits afforded no evidence of toxicity up to the limit dose.

Effects on the kidney and eye, as well as microscopic lesions of the thyroid were noted in the rat chronic toxicity study. These microscopic lesions were described as mineralized particles in the colloid of isolated follicles and were not associated with changes in thyroid hormone levels. Imidacloprid administration to rats and dogs caused increases in liver metabolism enzymes (mixed function oxidase and/or cytochrome P450). The effect on metabolism enzymes was not considered as being adverse. In the mouse oncogenicity study, the main effects of imidacloprid consisted of reduced body weight and food consumption. There was no significant increase in toxicity observed with increased duration of dosing with imidacloprid.

Most genotoxicity assays conducted with imidacloprid yielded negative results. Only two out of 13 assays were positive and consisted of *in vitro* cytogenic assays conducted with human lymphocytes (clastogenicity) and Chinese hamster ovary cells (sister chromatid exchanges). No positive findings were noted in the *in vivo* assays. The overall weight of evidence for imidacloprid did not suggest that it was mutagenic. Neither the carcinogenicity study in the rat nor the mouse oncogenicity study provided evidence that imidacloprid was carcinogenic.

The reproduction study in rats provided no evidence that imidacloprid was a reproductive toxicant. In that study, only reductions in body weight gains in parental animals (premating) and pups (during lactation) were noted. In a rabbit developmental toxicity study, mortality and reduced body weight, body weight gain and food consumption were noted in dams. Increased abortions and total litter resorptions, decreased fetal weight and a slight increase in skeletal alterations were also noted at high doses that caused significant maternal toxicity (i.e. mortality, body weight loss). In a rat developmental toxicity study, dams had decreased body weight gains while in fetuses there was a slight increase in the incidence of wavy ribs at a maternally toxic dose. Results of the reproduction and developmental toxicity studies did not provide evidence of increased sensitivity in young.

Clinical signs of neurotoxicity (i.e. trembling and severe tremors) were noted early in a 90-day oral dog study but were not observed at all in a 12-month oral dog study, where higher doses were used. The discrepancy between the findings in these two studies was attributed to the different type of feed in which imidacloprid was admixed prior to administration. Despite this discrepancy, the dog appeared to be the species most sensitive overall to the toxic effects of imidacloprid.

Results of acute neurotoxicity studies showed that imidacloprid induced tremors, gait abnormalities, and righting reflex impairments as well as reductions in grip strength, response to stimuli, body temperature and motor/locomotor activity. Reduced grip strength was also noted in male rats in the subchronic neurotoxicity study. In a developmental neurotoxicity study, decreases in locomotor activity and in the thickness of caudate/putamen as well as impaired learning on one trial in the water maze test were noted in offspring at the highest dose level tested. This dose level elicited toxic effects in the maternal animals. Although a NOAEL for the reduced caudate/putamen width was not established as morphometric assessments were not performed on offspring from the low and mid dose groups, there was no indication of adverse functional changes in the young at the low and mid dose levels, and the magnitude of the change in the caudate/putamen width was small (2-5%). As previously noted, this effect occurred at a dose level that was toxic to maternal animals.

WAK 3839 (also identified as NTN 37571), a nitroso metabolite, was not detected as a biotransformation product in the standard metabolism study conducted with imidacloprid. However, in a special study, WAK 3839 was detected in the urine of rats fed a diet containing 1800 ppm of imidacloprid for one year. The toxicology database submitted to support registration of imidacloprid included the following studies conducted with WAK 3839: a metabolism study in the rat, a 12-week drinking water study in the rat, and genotoxicity assays (gene mutations in bacteria, Chinese hamster V79 cells, and Chinese hamster ovary cells; *in vivo* micronucleus assays in mice; chromosome aberrations in Chinese hamster V79 cells and Chinese hamster ovary cells; and unscheduled DNA synthesis in rat hepatocytes). The metabolism study conducted with WAK 3839 revealed a similar pattern of absorption and excretion when compared to imidacloprid, although imidacloprid tended to accumulate in tissues to a greater extent than did WAK 3839. All of the genotoxicity assays conducted with WAK 3839 were negative. The 12-week drinking water study conducted with WAK 3839 provided a NOAEL (13 mg/kg bw/day in males and females) similar to the NOAEL established in the 96-day dietary study in rats conducted with imidacloprid (14/20 mg/kg bw/day in males/females), although the effects observed were not consistent between the two studies. Overall, the metabolite WAK 3839 is not considered to be more toxic than the parent imidacloprid.

Changes were made to the manufacturing process of the technical grade active ingredient after the majority of the toxicological testing was conducted for imidacloprid. The technical imidacloprid produced by the revised manufacturing process, termed “AMP-W”, was found to be negative in the bacterial reverse mutation assay, but two of its impurities, N–[(6-chloro-3-pyridinyl)methyl] -1,2-ethanediamine (PEDA) and N, N’-bis-[6-chloro-3-pyridinyl) methyl] -1,2-ethanediamine (DIPEDA), tested positive. As the impurities were detected at trace levels (<0.1% w/w) in the technical grade active ingredient, they were not considered of toxicological concern.

Results of the acute and chronic tests conducted on laboratory animals with imidacloprid and Confidor 200 SL, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 1, 2, and 3 of Appendix I.

In assessing the occupational risk from potential exposure to Confidor 200 SL, the standard uncertainty factor (UF) of 100-fold has been applied to account for interspecies extrapolation and intraspecies variability.

3.1.1 PCPA Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, the database contains the full complement of required studies including a multigeneration reproduction study in the rat, developmental toxicity studies in the rat and rabbit, and a developmental neurotoxicity study in the rat.

With respect to identified concerns relevant to the assessment of risk to infants and children, there was no indication of increased susceptibility in the offspring compared to parental animals in the reproduction study. In the prenatal developmental toxicity studies in rats and rabbits, developmental effects included abortions, resorptions and skeletal variations; however, these effects occurred in the presence of marked maternal toxicity (i.e. maternal deaths and body weight loss). Thus, the developmental toxicity studies provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to imidacloprid. In the developmental neurotoxicity study, decreases in locomotor activity and in the thickness of caudate/putamen as well as impaired learning on one trial in the water maze test were noted in offspring at the highest dose level tested. A NOAEL for the reduced caudate/putamen width was not established as morphometric assessments were not performed on offspring from the low and mid dose groups. However, the concern regarding the missing measurements was low considering that no effects occurred in the young at lower dose levels (in particular there was no indication of adverse functional changes in the young at the low and mid dose levels), the magnitude of the change in the caudate/putamen width was small (2-5%), and this effect occurred at a dose level that was toxic to maternal animals. Furthermore, the toxicological endpoints selected for risk assessment were considered protective of the slight brain morphometric changes. Therefore, the overall concern for this effect is low. On the basis of this information, the PCPA factor was reduced to 1-fold.

3.2 Occupational and Residential Risk Assessment

3.2.1 Toxicological Endpoints

For short- to intermediate-term dermal and inhalation exposure assessments, the NOAEL of 8 mg/kg bw/day from the 90-day dietary study in the dog was selected. The NOAEL was based on clinical signs suggestive of neurotoxicity (trembling) and slight emaciation at the LOAEL of 22 mg/kg bw/day.

When compared to the rat, the dog was the species most sensitive to neurotoxic effects after short-term exposure. Although no effects were observed up to the limit dose in a 21-day rabbit dermal toxicity study available for imidacloprid, this study did not include any specific assessments for neurotoxicity, such as a functional observational battery (FOB). In oral neurotoxicity studies in the rat, effects on more detailed analyses of neurotoxicity (such as the FOB, motor activity testing, and learning and memory) were noted but at higher doses than the clinical signs of trembling noted in the dog. As such, the 21-day dermal study in the rabbit was not considered suitable for use in the dermal risk assessment.

For occupational risk assessments, a target Margin of Exposure (MOE) of 100 to account for intraspecies variation and interspecies extrapolation is considered appropriate.

For residential assessments, the PCPA factor has been reduced to 1-fold. Therefore, a target MOE of 100 to account for intraspecies variation and interspecies extrapolation is considered appropriate.

The endpoints and target MOE selected for risk assessment provide adequate margins to other endpoints of concern, including the changes in brain morphometrics in rat offspring in the DNT study.

3.2.1.1 Dermal Absorption

In the absence of chemical specific dermal absorption data for Confidor 200 SL Systemic Insecticide, a 100% dermal absorption value was used in the health risk assessment.

3.2.2 Occupational Exposure and Risk

Commercial applicators, including city employees, will conduct host tree injections over a full work day of 8 hours for several weeks intermittently from April to September, when trees are actively transpiring. This exposure would occur indoors or outdoors depending on the location of host trees in commercial (forest and woodlots, indoor/outdoor nurseries, indoor/outdoor plantscapes and greenhouses) or residential (human habitat and recreational) areas. In a greenhouse nursery, the pest problem could occur any time of the year, but trees would be dormant in the winter and it is unlikely that workers would be conducting tree injections in a greenhouse for longer than a few months, as only a single application is required per year.

The workers have the potential for intermittent dermal and/or inhalation exposure when mixing, loading and applying Confidor 200 SL, over a short- to intermediate-term in duration.

Considering the complexity of the pressurized tree trunk injection devices, mixing, loading, application, clean up and repair would take up to several hours to complete. The extent of exposure would depend on the method, rate, skill and experience of a worker conducting tree injections. Although the exposure during a closed tree injection process with these devices is expected to be significantly lower in comparison to the open systems, there is potential for accidental exposure if the device does not work, from handling the pressurized liquid, and clogging of the supply lines and leakage around the injection sites. There is also the potential for exposure while cleaning all parts of the equipment and application area.

3.2.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Tree injection application method specific or imidacloprid specific exposure data are not available. In the generic pesticide handler exposure database (PHED), the mixer/loader (M/L) data for various types of formulations exist, but there is no tree injection application specific exposure scenario subset/data. Therefore, the exposure was estimated using PHED liquid M/L data. This data represents the actual mix/load of the product by a slightly different method, but it may not address the potential applicator exposure during tree injection application. However, the exposure associated with these activities is anticipated to be low compared with the M/L activities due to closed tree injection application systems and personal protective equipment worn by the applicators. Exposure to the whole body would be minimal. Potential exposure for applicators would be limited to incidental exposure during adjustment of tubing/injection tee, set-up, take-down, leakage and clean-up and repair of application equipment. Uncertainties associated with using PHED M/L data can be addressed with the use of conservative data assumptions to conduct the exposure assessment. These assumptions included the maximum application rate, the maximum number of trees that can be treated per day and assuming only one person would carry out all the duties associated with the tree injection. In reality, 2 or 3 individuals would be involved during the treatment process and the number of trees that can be treated per day is limited to the number of tree injectors available, the size of the tree and the severity of the disease. Therefore, the exposure estimates derived for mixer/loader/applicator (M/L/A) using PHED M/L data are considered conservative and adequate to estimate the risks from imidacloprid tree injection applications.

Mixer/loader exposure was estimated using PHED data coupled with information on the amount of imidacloprid handled per day. The amount of imidacloprid handled per day was calculated from the maximum efficacious rate for the pests to be controlled and the number of trees treated per day by a worker depending on the diameter of a tree at breast height (DBH). Fewer trees of larger diameter or a large number of trees of a smaller diameter could be treated in one day. A conservative assumption of 100 trees of 80 cm diameter treated in one day was used for the Confidor 200 SL assessment which was based on the earlier estimated health risks for the emergency uses of Confidor 200 SL. As no imidacloprid specific dermal absorption data are available, the systemic concentrations for a worker were estimated using the default dermal absorption value of 100%. A default body weight of 70 kg was used in the equation for exposure estimation. Margins of exposure were obtained by comparing the combined dermal and

inhalation exposure estimates with the single toxicology endpoint selected for the short- to intermediate-term occupational dermal and inhalation exposures. The target margin of exposure (MOE) is 100 for intra- and inter-species variations, as presented in Appendix I, Table 4.

The estimated MOE is above the level of concern for a mixer/loader (> 5000). Although the exposure estimate does not include applicator exposure, the calculated MOE is considered adequate for M/L/A given that the assessment is conducted using conservative assumptions and that exposure for the applicator is likely minimal since a closed application system is used for tree injections. Based on the above information, the calculated MOE is considered acceptable for mixer/loader/applicator provided that a closed application system is used and personal protective equipment (long pants, long-sleeved shirt and chemical resistant gloves) are worn during mixing, loading and application of the product.

In addition, the acceptable occupational exposures from the currently registered uses of imidacloprid were estimated for handling large amounts of imidacloprid in a day (>100 kg a.i./day). Even though there is no unit exposure/kg a.i. handled per day data available for the tree injection application method to compare with the other methods of application, it is highly unlikely that the applicator exposure from the tree injection scenarios in commercial or residential areas would exceed the exposure from the currently acceptable use scenarios.

3.2.2.2 Postapplication Exposure and Risk for Workers Entering Treated Areas

3.2.2.2.1 Inhalation Exposure

The postapplication inhalation exposure and risk were assumed negligible considering the injection of a non-volatile product (low vapour pressure of 2×10^{-10} kPa at 20ºC) directly into a host tree. Therefore, no further assessment of postapplication indoor or outdoor scenarios was required.

3.2.2.2.2 Dermal Exposure

Potential postapplication outdoor or indoor dermal exposure to workers including tree maintenance workers may result from contact with the treated trees in commercial and/or residential areas. This exposure is limited to dermal contact with the outside of the treated trunk, if after injection of the product, the holes drilled in a tree are not plugged and if there is a leakage, or if anyone climbs on a treated tree. The tree maintenance workers may occasionally conduct mechanical pruning or watering of the treated trees. However, for these activities, it is unlikely that this would create a potential for dermal contact with the plugged injection holes in the treated trunk areas.

No dislodgeable indoor or outdoor treated tree surface residue data or transfer coefficients for contact with the treated tree surfaces are available to estimate the postapplication exposure. However, if the exposure occurs, it would likely be less than M/L/A exposure, and can be further mitigated by the label statements.

3.2.3 Residential Exposure and Risk Assessment

3.2.3.1 Residential Handler Exposure and Risk

As the registration is under the Commercial/Restricted class (depending on pest), no residential handler/applicator indoor or outdoor exposure is expected. Thus, only commercial applicators can apply the product to host trees in residential indoor/outdoor landscapes in multifamily residential complexes, commercial buildings, and recreational areas or inside an individual dwelling. However, based on the specified host trees for pests (spruce, ash, birch, elm, black locust, hemlock and ornamental apples), it is unlikely these trees would be grown indoors in containers by homeowners in an individual dwelling.

3.2.3.2 Residential Bystander Postapplication Exposure and Risk

The potential residential postapplication dermal exposure to bystander adults and children may result from contact with the treated trees in residential indoor or outdoor areas. This exposure is limited to dermal contact with the outside of the treated trunk, if after injection of the product, the holes drilled in a host tree are not plugged or if there is a leakage, or if anyone climbs on a treated tree. There is also a potential for incidental exposure to children if application equipment is left unattended. In addition, in the autumn, when leaves containing imidacloprid would fall to the ground in residential areas, children playing in the areas may touch or ingest treated leaves and thus, have potential for exposure to residues in leaves by the route of object to mouth or hand to mouth (after touching treated tree and/or leaves). Also degradation of leaves on the ground would potentially release residues which may become available for exposure to residential/bystanders including children. No postapplication exposure data are available to assess this exposure and risk. The PMRA default method for estimating residential exposure from ingesting plant material assumes negligible exposure from these scenarios.

Imidacloprid is registered for several uses including turf. Therefore, based on the currently acceptable residential postapplication exposure and risks to imidacloprid for adults and children entering treated lawns, it is highly unlikely that the potential postapplication residential exposures from the tree injection scenarios would exceed the exposure to the treated turf. Thus, the potential exposure to bystanders can be considered acceptable and further mitigated by the label statements.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate of imidacloprid in the environment has been discussed previously in Regulatory Note REG2001-11, *Imidacloprid* and Regulatory Note R97-01, *Admire*.

Imidacloprid enters the environment when Confidor 200 SL is injected into the trunks of ornamental and landscape trees in Canada.

Once injected into trees, imidacloprid is translocated by the xylem into branches and into the leaves. In a comprehensive three year USDA monitoring study which was conducted as part of the Asian Longhorned Beetle Eradication Program in New York and Chicago, ash, birch, box elder, elm, horse-chestnut and willow trees injected with imidacloprid were analysed for parent concentration over several years. The study authors indicated that uptake and detection of imidacloprid varied between tree species which is probably due to variation in the physiology of tree vasculature. In general, however, leaf samples tended to have slightly higher concentrations than twig samples and imidacloprid residues tended to be highest at the first sampling period, one month after injection. Residues in trees persisted for at least one year after treatment, although a general decrease in residues in leaves and twigs occurred over time.

As would be expected from a compound that is primarily transported in xylem, plant parts that are primarily nourished by the phloem, such as storage organs, roots and the reproductive parts (seeds, flowers and fruits) had significantly lower concentrations of imidacloprid residues.

The injection of imidacloprid into the trunk of trees is not expected to have a significant impact on the rate of litter degradation in the terrestrial environment. Burning treated leaves is not expected to release imidacloprid residues and/or any transformation products of concern.

In the aquatic environment, the concentration of imidacloprid in leaves dissipates relatively quickly but may continue to persist at low levels. At the current application rate and based on the low mass loading of leaves into aquatic systems, concentrations in the field are expected to be below the level of detection.

In comparison to traditional application methods, trunk injection is expected to reduce environmental exposure since imidacloprid is injected directly into selected trees.

4.2 Environmental Risk Characterization

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

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g., direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

The risk of imidacloprid to terrestrial organisms was based upon the evaluation of toxicity data summarized in Regulatory Note REG2001-11, *Imidacloprid* and Regulatory Note R97-01, *Admire*.

In comparison to traditional application methods, trunk injection is expected to reduce environmental exposure since imidacloprid is injected directly into selected trees. Incidental residues in the surrounding soil and vegetation are expected to be less than those resulting from the existing registered use pattern. Residues are expected to occur, however, in leaves, twigs, pollen and nectar of treated trees. A risk assessment was therefore conducted on earthworms, non-target arthropods, honey bees, birds and mammals. A risk assessment on non-target plants was not required as exposure is unlikely.

4.2.1.1 Earthworms and non-target arthropods

There have been several publications examining the risk to litter-dwelling earthworms and decomposer organisms under laboratory conditions (Kreutzweiser et al. 2007, Kreutzweiser et al. 2008, Kreutzweiser et al. 2008).

In general, these studies show effects on aquatic leaf-shredding insects and litter-dwelling earthworms under laboratory conditions. Based on the low mass loading of leaves into the environment and the reasonable expectation that leaves would be displaced by wind, the amount of imidacloprid that would leach from the fallen leaves into the soil at a particular location in the field is expected to be less than that from the existing use pattern. This is particularly the case if the injected trees are in an urban environment where leaf litter is collected in the fall. The studies cited above indicate that there is a potential for sublethal effects on litter-dwelling earthworms and decomposer organisms when exposed to leaves at realistic concentrations in a contained system under laboratory conditions. Under field conditions where exposure concentrations are expected to be lower, the potential for effects is expected to be limited.

4.2.1.2 Honey bees

The risk assessment for pollinators indicated that there is a potential risk if this product is used on flowering trees that may be visited by insect pollinators.

Although imidacloprid is xylem mobile and accumulates primarily in the leaves, it is possible that some residues may be translocated to the pollen and nectar. Monitoring data indicate that quantifiable residues were present in blossoms 10-12 months after treatment and residues were still detected in blossoms 20 to 24 months after treatment. These values were based on whole blossom analyses. An uncertainty factor of 10 was applied to account for the use of whole blossom data to estimate residue levels in pollen and nectar, the limited number of blossoms analysed and any sublethal or chronic effects on adult bees. An adjustment factor was also applied to account for the difference in the rate that was used in the monitoring study versus the proposed application rate. The values are reported in Appendix I, Table 5.

The honey bee consumption estimate used (20 µL) was based on the amount of sucrose solution that is fed in standard test guidelines.

At the higher application rate, the resulting RQ values were 18.6 and 14.2, one year and two years after application to the tree, respectively. Corresponding RQ values at the lower application rate [0.30 mL/cm diameter at breast height (DBH)] were 4.5 and 3.4.

Additional calculations to further characterise the risk were done using mean residues. The same safety and adjustment factors were applied. At the higher application rate using mean residues, the resulting RQ values were 4.3 and 2.6, one year and two years after application to the tree, respectively. At the lower application rate, the corresponding RQ values were 1.0 and 0.6. It should be noted that a sensitivity analysis was performed to capture the uncertainty with regard to using an estimated LOD in the risk calculation using mean residue values. The calculation was first performed assuming that measured values <LOD were equal to zero and then a second time assuming that measured <LOD were equal to the analytical LOD. The results indicated that the RQ estimates using mean residue values were highly sensitive to assumptions made regarding the LOD values and the results should be interpreted with caution. The results are reported in Appendix I, Table 6.

To further characterise the potential risk to bees, a literature search was conducted on bee exposure to pollen and nectar from the various tree species on the label (Appendix I, Table 7). Exposure was considered relevant if bees were considered pollinators for a tree species and/or if the nectar/pollen from that tree was used as a food source. Exposure through honeydew was not considered relevant since exposure to imidacloprid is toxic to aphids, the source of honeydew. Exposure to imidacloprid through guttation water could not be assessed, but was identified as a potential route of exposure based on the amount of imidacloprid measured in leaves.

The risk was considered to be lower than the level of concern for all tree species at both the higher and lower application rates where pollinator exposure is not expected. The summary is reported in Appendix I, Table 7.

The above risk assessment was conducted using a limited number of blossom samples and was extrapolated from whole blossoms concentrations to pollen and nectar. Any chronic or sublethal effects on adult bees were assumed to be accounted for in the uncertainty factor. In addition residue estimates were adjusted for the difference in the application rates between the USDA monitoring data and the proposed application rate. The risk assessment did not address any effects on larval or hive health.

To address the uncertainties identified in the risk assessment and to better characterise the potential exposure to pollinators, additional information on bee foraging behaviour on blooming trees and estimated concentrations in pollen and nectar have been requested. In addition, precautionary statements are recommended on the product label.

4.2.1.3 Birds and small wild mammals

The risk of imidacloprid to birds and small wild mammals was based upon the evaluation of toxicity data submitted previously in Regulatory Note REG2001-11, *Imidacloprid* and Regulatory Note R97-01, *Admire*. The data used in this assessment are presented in Appendix I, Table 8, Table 9, Table 10, and Table 11.

The screening level risk assessment for birds and small wild mammals assessed the dietary exposure to imidacloprid in potential food items from treated trees after application of 1.25 mL/cm DBH (Appendix I, Table 12 and 13). The EEC value of 10.2 ppm was estimated using the 95th percentile residue value on leaves obtained from the 2000-2003 USDA monitoring survey data (3.9 ppm), adjusted to account for the difference in the rate used in the monitoring study versus the rate on the label (2.65×). All screening level risk quotient values for acute, short-term and long-term effects were less than the level of concern (Appendix I, Table 14 and Table 15).

4.2.2 Risks to Aquatic Organisms

The risk of imidacloprid to aquatic organisms was based upon the evaluation of toxicity data summarized in Regulatory Note REG2001-11, *Imidacloprid* and Regulatory Note R97-01, *Admire*.

In comparison to traditional application methods, trunk injection is expected to reduce environmental exposure since imidacloprid is injected directly into selected trees. Since residue concentrations in water are expected to be less than those resulting from the existing registered use pattern, a risk assessment on aquatic organisms was not required.

4.2.3 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

As of April 1, 2010, the PMRA is not aware of any Canadian incident reports related to adverse effects on wildlife or natural vegetation from imidacloprid. One incident is reported in the USEPA's Ecological Incident Information System (EIIS) for imidacloprid. This incident is highly probable and involved bumble bee mortality resulting from exposure to trees treated with imidacloprid by soil injection. A significant number of dead bees were observed at the bottom of the treated trees in the season following treatment in two subsequent years. Residue analysis of the dead bees confirmed exposure at concentrations above the laboratory derived LD_{50} value. The PMRA reviewed the information contained in the USEPA incident report and incorporated it as a consideration in the risk assessment.

5.0 Value

5.1 Effectiveness Against Pests

Submitted efficacy data for wood-boring beetles indicate that treatment of trees by trunk injection of Confidor 200 SL may reduce populations of these insects substantially, although the data are insufficient to demonstrate a consistently high level of control. Only one trial for Asian longhorned beetle tested the proposed application rate and insect populations within the trees were not assessed in that trial; two other trials with different application rates produced inconsistent results. The proposed application rate was effective against brown spruce longhorn beetle, but was tested only in a single trial, no other application rates were tested, and imidacloprid concentrations measured in the phloem were generally low and quite variable. Two trials demonstrated efficacy of the proposed application rate against emerald ash borer, although only one of those trials showed a lower application rate to be less effective. In contrast, a much lower application rate was effective against the congeneric bronze birch borer, but was tested only in a single trial. Collectively, the proposed application rate of 1.25 mL product (0.25 g a.i.) per cm DBH for Asian longhorned beetle, brown spruce longhorn beetle, and emerald ash borer can be supported based in part on the submitted efficacy data. Although the data alone are not sufficient to justify the proposed application rate, the highly destructive nature of these pests and their invasive status warrants the use of a relatively high rate in order to maximize the probability of success of the treatment. On the other hand, the lower application rate of 0.3 mL product (0.06 g a.i.) per cm DBH proposed for bronze birch borer can be supported for this native and relatively minor pest. Still, a precautionary statement that treatment may provide suppression only is required to reflect the limitations of the available efficacy data for wood-boring beetles.

A single trial report was submitted for each of six different insect pests that feed on foliage and/or twigs and small branches of trees, including a psyllid, a scale insect, two taxonomically unrelated leafminers (one beetle, one sawfly), an aphid, and an adelgid. Each of these trials tested two application rates (usually 0.15 and 0.30 mL/cm DBH) and the proposed label rate for each pest was one or the other (or in one case both, as a range) of the application rates tested. In no case was there a statistically significant difference in efficacy between the two application rates tested, but in most cases the higher rate yielded numerically superior results. Collectively, these trials provide support for label claims against foliage-feeding insects and indicate that a single application rate of 0.3 mL product (0.06 g a.i.) per cm DBH would be effective against all of the proposed foliage and/or twig feeding pests.

5.1.1 Acceptable Efficacy Claims

Pest	Host Trees	Application Rate (mL/cm DBH)
Asian longhorned beetle*	Birch Elm Hackberry Horsechestnut Maple Mountain ash Poplar Silk tree Sycamore / London plane tree Willow	1.25
Brown spruce longhorn beetle*	Spruce	
Emerald ash borer*	Ash	
Bronze birch borer*	Birch	0.30
Cottony ash psyllid	Ash	
European elm scale	Elm	
Locust leafminer	Black locust	
Elm leafminer	Elm	
Woolly apple aphid	Apple (ornamental)	
Hemlock woolly adelgid	Hemlock	

*Treatment with Confidor 200 SL may provide only suppression of wood-boring beetles

Notes: Trees with vascular tissue damage caused by boring larvae will not translocate the active ingredient in Confidor 200 SL as well as undamaged trees, resulting in lower efficacy. Applications at the rate of 1.25 mL/cm DBH should be made with high pressure injection systems (50-200 psi); applications at the rate of 0.30 mL/cm DBH may be made with lower pressures (30 psi or less). Injections should be made when trees are actively transpiring, generally April – September. For trees that may be visited by pollinators (such as ash, elm, black locust and ornamental apple), applications must be made post-bloom.

5.2 Economics

No economic analysis was conducted for this product evaluation; however, the only other active ingredient currently registered in Canada for application to trees by trunk injection is acephate, which is not registered for use against any wood-boring beetles; there are no pest control products currently registered in Canada for use against wood-boring beetles in trees.

5.3 Sustainability

5.3.1 Survey of Alternatives

No other pest control products are currently registered in Canada for use against wood-boring beetles. Only two products are currently registered for application to trees by trunk injection, both of which contain acephate as the active ingredient. There are five alternative active ingredients registered in Canada for control of woolly apple aphid; for each of the other foliage-feeding insects on the label of Confidor 200 SL, there is one alternative active ingredient registered.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Confidor 200 SL is compatible with current management practices and is well suited for integrated pest management. With the application method of trunk injection, only insects feeding on the trees are exposed to the insecticide, allowing for conservation of natural enemies and other non-target organisms that would be exposed to foliar applications of insecticides.

5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

According to Whalon et al. (2004-2010), resistance to imidacloprid has been reported in at least 11 insect species representing a variety of different orders and families, but none of the pest species on the label of Confidor 200 SL has been reported to show resistance to any insecticide except woolly apple aphid (a single report of resistance to an organochlorine insecticide in 1965). The label for Confidor 200 SL includes the recommended statements for resistance management as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

5.3.4 Contribution to Risk Reduction and Sustainability

The application method of trunk injection provides a way of targeting treatment to pests of the trees while minimizing exposure of humans and the environment to the product.
Confidor 200 SL provides a new alternative active ingredient for use against those pests for which other pest control products are registered.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

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

The Toxic Substances Management Policy (TSMP) was assessed previously in Regulatory Note REG2001-11, *Imidacloprid* and Regulatory Note R97-01, *Admire*. No new information on imidacloprid was submitted with this data package that would affect the previous assessment.

- Imidacloprid does not meet Track 1 criteria, and is not considered a Track 1 substance.

- Imidacloprid is not expected to form any transformation products that are Track 1 substances.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[4]. The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[6], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Imidacloprid and the end-use product Confidor 200 SL do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for imidacloprid is adequate to define the majority of toxic effects that may result from exposure to imidacloprid. In subchronic and chronic studies on laboratory animals, the primary targets were the liver, kidney, thyroid gland, eye and nervous system. There was no evidence of carcinogenicity in rats or mice after long-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies.

Target margins of exposure were achieved for occupational exposure scenarios from mixing/loading the formulation in closed application tree injection systems. In addition, the occupational exposure and risks from tree injections scenarios are not expected to exceed the exposures and risks from the currently acceptable uses of imidacloprid. The postapplication exposures for workers and all bystanders are expected to be much lower than the handlers, and considering the postapplication occupational and residential exposures from the currently acceptable uses of imidacloprid, the risks are not of concern.

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4 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

5 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

6 DIR2006-02, PMRA Formulants Policy.

Thus, mixers, loaders and applicators handling Confidor 200 SL and workers reentering treated areas are not expected to be exposed to levels of Confidor 200 SL that will result in an unacceptable risk when Confidor 200 SL is used according to label directions. The personal protective equipment on the product label is adequate to protect workers. Residential exposure to individuals contacting treated areas is not expected to result in unacceptable risk when Confidor 200 SL Systemic Insecticide is used according to label directions.

7.2 Environmental Risk

There are no concerns about the use of imidacloprid as a tree-injection affecting earthworms, birds, wild mammals, fish, terrestrial plants, amphibians, aquatic invertebrates, algae, or aquatic vascular plants.

Risks to pollinators that may forage on treated trees when in bloom could not be ruled out. For trees that may be visited by pollinators, the label restricts the timing of applications to mitigate the risk to pollinators. Furthermore, the uses are restricted to licensed pest control operators authorized with permits or appropriate license by government in conjunction with a federal, provincial or municipal government control program.

7.3 Value

Confidor 200 SL has value for control of various foliage-feeding insect pests of trees and for control or suppression of certain wood-boring beetles when injected into the trunks of deciduous or coniferous trees.

7.4 Unsupported Uses

All uses proposed by the applicant were supported with some modification of the label claims.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of BAY NTN 33893 Technical Insecticide and Confidor 200 SL, containing the technical grade active ingredient imidacloprid, for systemic control of insect pests on deciduous and coniferous trees.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant to address uncertainties regarding the exposure and risk to bees under field conditions. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information by September 1, 2013.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Environment

- Canadian monitoring data on imidacloprid and its transformation products in various parts of treated trees over time, which includes samples of nectar, pollen, guttation water and resinous substances

- Additional information on bee foraging behaviour on blooming trees

List of Abbreviations

µg	microgram(s)
µL	microlitre(s)
a.i.	active ingredient
AD	administered dose
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetre(s)
d	day(s)
DBH	diameter at breast height
DIPEDA	N, N'-bis-[6-chloro-3-pyridinyl) methyl] -1,2-ethanediamine
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
EDE	estimated daily exposure
EEC	estimated environmental concentration
EP	end-use product
EVOH	ethyl vinyl alcohol
F	female
FIR	food ingestion rate
FOB	functional observational battery
g	gram(s)
HDPE	high density polyethylene
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
kPa	kilopascal(s)
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LPM	litres per minute
M	male
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
M/L	mixer/loader
M/L/A	mixer/loader/applicator
MOE	margin of exposure
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

OECD	Organisation for Economic Co-operation and Development
PCPA	*Pest Control Products Act*
PEDA	N–[(6-chloro-3-pyridinyl)methyl] -1,2-ethanediamine
PHED	Pesticide Handler Exposure Database
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post natal day
PPE	personal protective equipment
ppm	parts per million
psi	pounds per square inch
RQ	risk quotient
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
ww	wet weight

Appendix I Tables and Figures

Table 1 Acute Toxicity of Imidacloprid and Its Associated End-use Product (Confidor 200 SL)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Imidacloprid				
Oral	Rat	LD_{50} (M) = 424 mg/kg bw LD_{50} (F) = 450-475 mg/kg bw	High Toxicity	1155724
Dermal	Rat	LD_{50} > 5000 mg/kg bw	Low Toxicity	1155729
Inhalation	Rat	LC_{50} > 0.069 mg/L aerosol; 5.32 mg/L dust	Low Toxicity	1155720
Skin irritation	Rabbit	MAS = 0 MIS = 1 at 1 hour	Minimally Irritating	1155733
Eye irritation	Rabbit	MAS = 0 MIS = 6 at 1 hour	Minimally Irritating	1155731
Skin sensitization	Guinea pig	No sensitization response	Not a skin sensitizer	1155747
Acute Toxicity of End-Use Product – Confidor 200 SL				
Oral	Rat	LD_{50} (F) > 2000 mg/kg bw	Low Toxicity	1429523
Dermal	Rat	LD_{50} > 4000 mg/kg bw	Low Toxicity	1429525
Inhalation	Rat	LC_{50} > 3.15 mg/L	Low Toxicity	1429526
Skin irritation	Rabbit	MAS = 0 MIS = 0	Non Irritating	1429527
Eye irritation	Rabbit	MAS = 3.6 MIS = 8.7 at 1 hour	Minimally Irritating	1429531
Skin sensitization	Guinea pig	No sensitization response	Not a skin sensitizer	1429540

MAS = maximum average score for 24, 48 and 72 hours
MIS = maximum irritation score

Table 2 Toxicity Profile of Imidacloprid

Study Type	Species	Results[7] (mg/kg/day in M/F)	Reference
21-day dermal	Rabbit	**NOAEL** > 1000 mg/kg bw/day. **LOAEL** not established as no adverse effects were noted up to the highest dose tested.	1155690
28-day inhalation	Rat	**NOAEL:** 8.4 mg/kg bw/day **LOAEL:** 51.8 mg/kg bw/day, based on liver enzyme induction, reduced triglyceride levels, and increased coagulation time.	1155689

[7] Effects observed in males as well as females unless otherwise reported.

Study Type	Species	Results[7] (mg/kg/day in M/F)	Reference
96-day dietary	Rat	**NOAEL:** 14/20.3 mg/kg bw/day in M/F. **LOAEL:** 60.9/83.3 mg/kg bw/day in M/F, based on reduced body weight in males, reduced leukocytes in females, and reduced serum calcium levels in both sexes.	1155682
12-week drinking water WAK 3893	Rat	**NOAEL:** 13 mg/kg bw/day in M & F. **LOAEL:** 35/39 mg/kg bw/day in M/F, based on increased lymphocytes and decreased polymorphonuclear cells.	1155695
28-day dietary	Dog	A NOAEL and LOAEL were not established as this was a dose range-finding study. No effects were noted at 7.3 mg/kg bw/day. Effects at the next highest dose of 31 mg/kg bw/day included transient reductions in food consumption, liver enzyme induction, increased liver weight in one F, hepatocellular hypertrophy, pigmentation of the Kupffer cells, and thyroid follicular cell atrophy.	1155691
90-day dietary	Dog	**NOAEL:** 7.7/8.0 mg/kg bw/day in M/F. **LOAEL:** 22.1/24.8 mg/kg bw/day in M/F, based on trembling noted during the first week of dosing and slight emaciation.	1155681
1-year dietary	Dog	**NOAEL** > 40/72 mg/kg bw/day in M/F. **LOAEL** not established as no adverse effects were noted up to the highest dose tested.	1155758
Carcinogenicity (2-year dietary)	Mouse	**NOAEL:** 208/272 mg/kg bw/day in M/F. **LOAEL:** 414/424 mg/kg bw/day in M/F, based on an increased incidence of squeaking and twittering, reduced body weight after week 13, reduced body weight gain, decreased food and water consumption, decreased food conversion efficiency in F, and decreased absolute and relative spleen weights in F.	1155697 1155705
Chronic/ Carcinogenicity (2-year dietary)	Rat	**NOAEL (M):** 5.7 mg/kg bw/day. **LOAEL (M):** 61.9 mg/kg bw/day, based on and increased incidence of mineralized particles in the colloid of isolated thyroid follicles. **NOAEL (F):** 24.9 mg/kg bw/day. **LOAEL (F):** 73.0 mg/kg bw/day, based on decreased body weight and body weight gain, and an increased incidence of mineralized particles in the colloid of isolated thyroid follicles.	1155757 1155760 1155761

Study Type	Species	Results[7] (mg/kg/day in M/F)	Reference
Two-generation reproduction		**Parental toxicity:** **NOAEL:** 16.5/18.9 mg/kg bw/day in M/F. **LOAEL:** 47.3/52.3 mg/kg bw/day in M/F, based on decreased body weight gain and food consumption. **Offspring toxicity:** **NOAEL:** 16.5/18.9 mg/kg bw/day in M/F. **LOAEL:** 47.3/52.3 mg/kg bw/day in M/F, based on reduced body weight during lactation. **Reproductive toxicity:** **NOAEL** > 47.3/52.3 mg/kg bw/day. **LOAEL** not established as no adverse effects were noted.	1155687 1155688
Developmental toxicity	Rat	**Maternal:** **NOAEL:** 10 mg/kg bw/day. **LOAEL:** 30 mg/kg bw/day, based on reduced body weight gain and food consumption. **Developmental:** **NOAEL:** 30 mg/kg bw/day. **LOAEL:** 100 mg/kg bw/day, based on a slight increase in the incidence of wavy ribs.	1155698
Developmental toxicity	Rabbit	**Maternal:** **NOAEL:** 8 mg/kg bw/day. **LOAEL:** 24 mg/kg bw/day, based on a slight, transient decrease in body weight and food consumption. Effects at the next higher dose (72 mg/kg bw/day) included two deaths, one abortion, two total litter resorptions, and body weight loss during dosing. **Developmental:** **NOAEL:** 24 mg/kg bw/day. **LOAEL:** 72 mg/kg bw/day, based on increased resorptions and postimplantation loss, decreased number of live pups per litter, decreased fetal and litter weight, a slight increase in skeletal malformations (fused, asymmetric, missing and abnormally ossified sternebrae and shortened tail).	1155699
Acute neurotoxicity	Rat	**NOAEL** not established as effects were noted at the lowest dose tested. **LOAEL:** 20 mg/kg bw, based on reduced motor and locomotor activity in M.	1039613 1039650
Subchronic neurotoxicity	Rat	**NOAEL:** 9.3/10.5 mg/kg bw/day in M/F. **LOAEL:** 63.3/69.3 mg/kg bw/day in M/F, based on reduced body weight and body weight gain in both sexes, and reduced grip strength in M.	1039643 1039652

Study Type	Species	Results[7] (mg/kg/day in M/F)	Reference
Developmental neurotoxicity	Rat	**Maternal:** **NOAEL:** 20 mg/kg bw/day. **LOAEL:** 55 mg/kg bw/day, based on reduced body weight gain and food consumption. **Offspring:** **NOAEL:** 20 mg/kg bw/day. **LOAEL:** 55 mg/kg bw/day, based on reduced body weight and body weight gain, decreased overall locomotor activity in both sexes on PND 17 and in F on PND 21, increased errors and time to complete trial 1 in the water maze test in M, and decreased thickness of the caudate/putamen in F.	591475
Reverse gene mutation assay	*Salmonella typhimurium, E. coli*	Negative in two studies	1155710 1155714
Reverse gene mutation assay – AMP-W manufacturing process	*Salmonella typhimurium*	Negative	1167318 1181377
Reverse gene mutation – PEDA (impurity)	*Salmonella typhimurium*	Positive	1181390
Reverse gene mutation – DIPEDA (impurity)	*Salmonella typhimurium*	Positive	1181354 1181365
Reverse gene mutation – WAK 3839 (metabolite)	*Salmonella typhimurium, E. coli*	Negative	1155715
Gene mutations in mammalian cells *in vitro*	Chinese hamster ovary cells	Negative	1155706
Gene mutations in mammalian cells *in vitro* – WAK 3839 (metabolite)	Chinese hamster V79 lung cells	Negative	1155702 1155707
In vivo mammalian chromosome aberration	Hamster bone marrow cells	Negative	1155701
In vivo mammalian chromosome aberration	Mouse spermatogonia	Negative	1155700
In vitro mammalian chromosomal aberration	Human lymphocyte cells	Positive at cytotoxic doses	1155711
In vitro mammalian chromosomal aberration – WAK 3839 (metabolite)	Chinese hamster V79 lung cells	Negative	1155703
In vitro mammalian chromosomal aberration – WAK 3839 (metabolite)	Chinese hamster ovary cells	Negative	1155738

Study Type	Species	Results[7] (mg/kg/day in M/F)	Reference
In vivo micronucleus	Mouse bone marrow cells	Negative	1155755
In vivo micronucleus	Mouse bone marrow cells	Negative following oral and intraperitoneal administration in two pilot studies and two main studies	1155751 1155753 1155708 1155709
In vivo sister chromatid exchange	Hamster bone marrow cells	Negative	1155712
In vitro sister chromatid exchange	Chinese hamster ovary cells	Negative in one study, positive in a second study	1155694 1155756
Mitotic recombination	*Saccharomyces cerevisiae*	Negative	1155718
DNA repair	*Bacillus subtilis*	Negative	1155717
In vitro unscheduled DNA synthesis	Rat hepatocytes	Negative	1155754
In vitro unscheduled DNA synthesis – WAK 3839 (metabolite)	Rat hepatocytes	Negative	1155713
Metabolism		**Absorption:** Rapidly absorbed with approximately 90% of the administered dose being eliminated within 24 hours. **Distribution:** Total tissue burden 48 hours after dosing accounted for approximately 0.5-1.0% of the administered dose, with major sites of accumulation being the liver, kidney, lung, skin and plasma and minor sites being the brain, muscle and testes. **Excretion:** Urinary excretion was the major route of elimination (70-90% of the administered dose), with a lesser amount eliminated in feces (17-25% of the administered dose). Biliary excretion was a major contributor to fecal radioactivity, with only 5% of the administered dose being excreted in feces in bile-fistulated animals. Only a trace amount of radioactivity was excreted in expired air. **Metabolism:** Biotransformation involved oxidative cleavage of the parent compound to yield 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite produced 6-hydroxynicotinic acid and its mercapturic derivative. Another route of biotransformation occurred via hydroxylation of imidazolidine followed by elimination of water from the parent compound to give NTN 35884.	1155769 1155781 1155782

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Imidacloprid (Confidor 200 SL)

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	Target MOE
Short- to intermediate-term dermal & inhalation	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100

Table 4 Occupational Exposure and Risks from Mixing and Loading Confidor 200 SL

PHED	Dermal Unit Exposure[a] (µg/kg a.i. handled)	Inhalation Unit Exposure[a] (µg/kg a.i. handled)	kg a.i. handled per day[b]	Systemic Exposure[c] (dermal + inhalation) (mg a.i./kg bw/day)	MOE[d] Target: 100
Liquid M/L	51.14	1.6	2.0	0.0015	5300

[a] Best-fit dermal or inhalation liquid mix/load unit exposures from PHED, Scenario 3a for a single layer of clothing and gloves as the proposed PPE.

[b] Maximum rate 0.25 g a.i./cm DBH × 100 trees/day × 80 cm DBH trees/1000 (conversion from g to kg).

[c] Where total systemic exposure in mg a.i./kg bw/day = [(dermal unit exposure × 100% dermal absorption) + inhalation unit exposure] × kg a.i. handled/day / 70 kg bw × 1000 µg/mg. Used light inhalation rate (17 LPM). Route specific dermal and inhalation exposures were combined as the same NOAEL was identified for both routes of exposure.

[d] MOE = NOAEL/Systemic exposure, based on a NOAEL of 8 mg a.i./kg bw/day from a sub chronic dog study for intermediate-term dermal or inhalation occupational exposures. The target MOE is 100.

Table 5 Estimated Environmental Concentrations in Pollen and Nectar based on monitoring data on whole blossoms the USDA Environmental Monitoring Report, 2003

Application Rate	Time after Application (months)	Adjustment Factor	Maximum Residue	Average Residue[c]
221.4 mg ai/1 inch DBH[a]	10-12	N/A	0.13	0.03
	20-24		0.10	0.02
1.25 mL/cm DBH[b]	10-12	2.65	0.30	0.07
	20-24		0.23	0.04
0.30 mL/cm DBH	10-12	0.64	0.07	0.02
	20-24		0.05	0.01

[a] Data from the USDA 2003 Monitoring Report (442.8 mg ai/2 inches DBH). The rate is equivalent to 0.087 a.i./cm DBH

[b] Equivalent to 0.23 g ai/cm DBH assuming a specific gravity of 1.08-1.20 g/mL and 17.1% a.i.

[c] Where the LOQ and LOD values were estimated using the following formula: calculated LOQ = 0.5× (measured LOQ-measured LOD) /2 +measured LOD and the calculated LOD = 0.5× measured LOD

Table 6 Screening Level Risk Assessment on Non-Target Species: Pollinator Risk Assessment using available Monitoring Data

Application Rate	EEC[a] (mg a.i./kg ww)	Toxicity endpoint[d] (mg a.i./kg)	Uncertainty Factor	RQ
Maximum residues				
1.25 mL/cm DBH (10-12 months after treatment)	0.34	0.185	10	18.6
1.25 mL/cm DBH (20-22 months after treatment)	0.26	0.185	10	14.2
0.30 mL/cm DBH (10-12 months after treatment)	0.08	0.185	10	4.5
0.30 mL/cm DBH (20-22 months after treatment)	0.06	0.185	10	3.4
Mean Residues[b]				
1.25 mL/cm DBH (10-12 months after treatment)	0.08 (0.05-2.22)[c]	0.185	10	4.3 (2.8-120)[c]
1.25 mL/cm DBH (20-22 months after treatment)	0.05 (0.01-1.05)	0.185	10	2.6 (0.8-57)
0.30 mL/cm DBH (10-12 months after treatment)	0.02 (0.01-0.53)	0.185	10	1.0 (0.7-29)
0.30 mL/cm DBH (20-22 months after treatment)	0.01 (0.00-0.25)	0.185	10	0.6 (0.2-14)

[a] EEC values were adjusted for the difference in rate between the monitoring study and the proposed application rate on the label (2.65× for the 1.25 mL/cm DBH) and 0.64× for the 0.3 mL/cm DBH).

[b] Mean residues were calculated assuming measured values <LOD = 1/2 analytical LOD and <LOQ = (analytical LOQ-analytical LOD)/2 + analytical LOD.

[c] The sensitivity analysis results are presented in brackets ( ) for EEC and RQ values. These values were calculated using LOD=0 and LOD=LOD.

[d] The honey bee consumption estimate used (20 µL) was based on data from PMRA Document Number 1086433 and the amount of sucrose solution that is fed according to standard test guidelines (OECD Guideline 213 and OEPP/EPPO Bulletin 22, 203-215 (1992)). Conversion of the toxicity endpoint to a dose endpoint based on an estimated 20 µL consumption value: 0.0037 µg/bee / [20 uL solution × 0.998 g/mL (specific gravity of water)] = 0.185 mg a.i./kg (LD_{50} dose)

Table 7 Refined Risk Assessment: Confidor 200 SL use pattern in relation to potential exposure to pollinators

Tree Species	Pest	Rate (mL/cm DBH)	Potential Pollinator Exposure/Risk
Birch	Asian longhorned beetle	1.25	No
Spruce	Brown spruce longhorn beetle	1.25	No
Birch	Bronze birch borer	0.30	No
Hemlock	Hemlock woolly adelgid	0.30	No
Ash	Cottony ash psyllid	0.30	Yes (white ash only)
Elm	Soft scales European elm scale	0.30	Yes
	Elm leafminer	0.30	Yes
Black Locust	Leafminer	0.30	Yes
Ornamental Apple	Woolly apple aphid	0.30	Yes
Ash	Emerald ash borer	1.25	Yes (white ash only)
Mountain Ash	Asian longhorned beetle	1.25	Yes
Maple	Asian longhorned beetle	1.25	Yes
Elm	Asian longhorned beetle	1.25	Yes
Hackberry	Asian longhorned beetle	1.25	Yes
Horsechestnut	Asian longhorned beetle	1.25	Yes
Poplar	Asian longhorned beetle	1.25	Yes
Silk tree	Asian longhorned beetle	1.25	Yes
Sycamore or London Plane Tree	Asian longhorned beetle	1.25	No
Willow	Asian longhorned beetle	1.25	Yes
Oak	Asian longhorned beetle	1.25	Yes
Ash	Asian longhorned beetle	1.25	Yes (white ash only)

Table 8 Toxicity to Non-Target Species

Test organism	Study type	Substance	Endpoint	Reference
Apis mellifera (honey bees)	Oral	Imidacloprid technical	LD_{50}: 0.0037 µg a.i./bee	1086433
	Contact	Imidacloprid technical	LD_{50}: 0.0129 µg a.i./bee	1086420
Bombus terrestris L. (bumble bee)	Contact	Imidacloprid technical	The LD_{50} could not be accurately calculated, but results indicated that bees showed serious effects at 0.1 µg and higher.	1086422
	Oral	Imidacloprid technical	LD_{50} (24 hrs): 0.33 µg a.i./bee LD_{50} (48 hrs): 0.22 µg a.i./bee LD_{50} (72 hrs): 0.15 µg a.i./bee	1086421
Coturnix virginianus (bobwhite quail)	Acute oral	Imidacloprid technical	LD_{50}: 152 mg a.i./kg bw	1155842
	Short-term dietary	Imidacloprid technical	LC_{50}: 1420 mg a.i./kg bw	1155843
	Reproduction	Imidacloprid technical	NOEC: 120 mg a.i./kg bw	1155846
Anas platyrhynchos (mallard duck)	Short-term dietary	Imidacloprid technical	LC_{50}: 5000 mg a.i./kg bw	1155844
	Reproduction	Imidacloprid technical	NOEC: 120 mg a.i./kg bw	1155847 1155848 1155849
Passer domesticus (house sparrow)	Acute oral	Imidacloprid technical	LD_{50}: 41 mg a.i./kg bw	1157921
Serinus canarius (canary)	Acute oral	Imidacloprid technical	LD_{50}: 25-50 mg a.i./kg bw	1157923
Coturnix cot. japonica (Japanese quail)	Acute oral	Imidacloprid technical	LD_{50}: 31 mg a.i./kg bw	1157924
	Short-term dietary	Imidacloprid technical	LC_{50}: 473.7 mg a.i./kg	1157925
Columba livia (pigeon)	Acute oral	Imidacloprid technical	LD_{50}: 25-50 mg a.i./kg bw (M), 25 mg a.i./kg bw (F)	1157922

Test organism	Study type	Substance	Endpoint	Reference
Rat	Acute oral	Imidacloprid technical	LD_{50}: 424 mg a.i./kg bw	1155724
	Reproduction	Imidacloprid technical	NOEL: 18.3 mg a.i./kg bw	1155688
	Developmental toxicity gavage	Imidacloprid technical	NOEL: 10 mg a.i./kg bw/d	1155698

Table 9 Endpoints used for risk assessment and the uncertainty factors applied

Taxonomic group	Exposure	Endpoint	Uncertainty factor
Bees	Acute	LD_{50}	10
Birds	Acute oral	LD_{50}	10
	Dietary	LD_{50}	10
	Reproduction	NOEL	1
Mammals	Acute oral	LD_{50}	10
	Chronic	NOEL	1

Table 10 Calculation of the Toxicity Endpoints used in the Screening level risk assessment on non-target birds for Confidor 200 SL

Study type	Dose-based endpoint	Toxicity endpoint (mg a.i./kg bw/d)	Uncertainty factor	Value used for the risk assessment (mg a.i./kg bw/d)
Acute oral	LD_{50}	25	10	2.5
Acute dietary	LD_{50}	151	10	15.1
Reproduction	NOEL	6.8	1	6.8

Table 11 Calculation of the Toxicity Endpoints used in the Screening level risk assessment on non-target wild mammals for Confidor 200 SL

Study type	Dose-based endpoint	Toxicity endpoint (mg a.i./kg bw/d)	Uncertainty factor	Value used for the risk assessment (mg a.i./kg bw/day)
Acute oral	LD_{50}	424	10	42.4
Reproduction	NOEL	10	1	10

Table 12 Estimated dietary exposure of imidacloprid to birds resulting from a single application rate of 0.24 g a.i./cm DBH, based on the 95th percentile monitoring residue value in leaves and adjusted for the difference in application rate (2.3×)

Generic body weight (kg)	FIR (kg ww diet/day)	Food Guild (food item)	On-field	
			EEC (mg a.i./kg diet)	EDE[a] (mg a.i./kg bw)
0.02	0.0051	Insectivore (small insects)	10.2	2.6
0.02	0.0051	Granivore (grain and seeds)	10.2	2.6
0.02	0.0051	Frugivore (fruit)	10.2	2.6
0.1	0.0199	Insectivore (small insects)	10.2	2.0
0.1	0.0199	Insectivore (large insects)	10.2	2.0
0.1	0.0199	Granivore (grain and seeds)	10.2	2.0
0.1	0.0199	Frugivore (fruit)	10.2	2.0
1	0.0581	Insectivore (small insects)	10.2	0.6
1	0.0581	Insectivore (large insects)	10.2	0.6
1	0.0581	Granivore (grain and seeds)	10.2	0.6
1	0.0581	Frugivore (fruit)	10.2	0.6
1	0.0581	Herbivore (short grass)	10.2	0.6
1	0.0581	Herbivore (long grass)	10.2	0.6
1	0.0581	Herbivore (forage crops)	10.2	0.6
1	0.0581	Herbivore (leafy foliage)	10.2	0.6

[a] Estimated Daily Exposure (EDE) = $FIR_{ww}/BW \times EEC$, where Estimated Environmental Concentration (EEC) in fresh diet (mg a.i./kg fresh weight diet)

Table 13 Estimated dietary exposure of imidacloprid to wild mammals resulting from a single application rate of 0.24 g a.i./cm DBH, based on the 95th percentile monitoring residue value in leaves and adjusted for the difference in application rate (2.3×)

Generic Body weight (kg)	FIR (kg ww diet/day)	Food Guild (food item)	On-field	
			EEC (mg a.i./kg diet)	EDE[a] (mg a.i./kg bw)
0.015	0.0022	Insectivore (small insects)	10.2	1.5
0.015	0.0022	Granivore (grain and seeds)	10.2	1.5
0.015	0.0022	Frugivore (fruit)	10.2	1.5
0.035	0.0045	Insectivore (small insects)	10.2	1.3
0.035	0.0045	Insectivore (large insects)	10.2	1.3
0.035	0.0045	Granivore (grain and seeds)	10.2	1.3
0.035	0.0045	Frugivore (fruit)	10.2	1.3
0.035	0.0045	Herbivore (short grass)	10.2	1.3
0.035	0.0045	Herbivore (long grass)	10.2	1.3
0.035	0.0045	Herbivore (forage crops)	10.2	1.3
0.035	0.0045	Herbivore (leafy foliage)	10.2	1.3
1	0.0687	Insectivore (small insects)	10.2	0.7
1	0.0687	Insectivore (large insects)	10.2	0.7
1	0.0687	Granivore (grain and seeds)	10.2	0.7
1	0.0687	Frugivore (fruit)	10.2	0.7
1	0.0687	Herbivore (short grass)	10.2	0.7
1	0.0687	Herbivore (long grass)	10.2	0.7
1	0.0687	Herbivore (forage crops)	10.2	0.7
1	0.0687	Herbivore (leafy foliage)	10.2	0.7

[a] Estimated Daily Exposure (EDE) = $FIR_{ww}/BW \times EEC$ where Estimated Environmental Concentration (EEC) in fresh diet (mg a.i./kg fresh weight diet); Food Ingestion Rate of indicator species in wet weight (FIR); Bodyweight (BW) (kg)

Table 14 Screening level risk assessment on non-target birds for Confidor 200 SL assuming an application rate of 0.24 g a.i./cm DBH based on the 95th percentile monitoring residue value in leaves and adjusted for the difference in application rate (2.3×)

Study type	Toxicity endpoint (mg a.i./kg bw/d)	Feeding guild (food item)	EDE (mg a.i./kg bw)	RQ
Small bird (0.02 kg)				
Acute	2.50	Insectivore (small insects)	2.27	1.0
Reproduction	6.80	Insectivore (small insects)	2.27	0.4
Medium sized bird (0.1 kg)				
Acute	2.50	Insectivore (small insects)	1.77	0.8
Reproduction	6.80	Insectivore (small insects)	1.77	0.3
Large sized bird (1 kg)				
Acute	2.50	Herbivore (short grass)	0.52	0.2
Reproduction	6.80	Herbivore (short grass)	0.52	0.1

Table 15 Screening level risk assessment on non-target wild mammals for Confidor 200 SL assuming an application rate of 0.24 g a.i./cm DBH based on the 95th percentile monitoring residue value in leaves and adjusted for the difference in application rate (2.3×)

Study type	Toxicity (mg ai/kg bw/d)	Feeding Guild (food item)	EDE (mg ai/kg bw)	RQ
Small mammal (0.015 kg)				
Acute	42.40	Insectivore (small insects)	1.31	<0.1
Reproduction	10.00	Insectivore (small insects)	1.31	0.2
Medium sized mammal (0.035 kg)				
Acute	42.40	Herbivore (short grass)	1.14	<0.1
Reproduction	10.00	Herbivore (short grass)	1.14	0.1
Large sized mammal (1 kg)				
Acute	42.40	Herbivore (short grass)	0.61	<0.1
Reproduction	10.00	Herbivore (short grass)	0.61	<0.1

Table 16 Alternative Active Ingredients Registered in Canada for Pests on the Label of Confidor 200 SL

Pest	Active Ingredient	Product(s) Available
Asian longhorned beetle	None	n/a
Brown spruce longhorn beetle	None	n/a
Emerald ash borer	None	n/a
Bronze birch borer	None	n/a
Cottony ash psyllid*	Acephate	1 commercial class product
European elm scale	Mineral oil	1 commercial class product
Locust leafminer	Acephate	1 commercial class product
Elm leafminer	Potassium salts of fatty acids	1 commercial class product 1 domestic class product
Woolly apple aphid	Carbaryl	5 commercial class products 2 domestic class product
	Diazinon	3 commercial class products
	Endosulfan	2 commercial class products
	Lambda-cyhalothrin	2 commercial class products
	Malathion	1 commercial class product
Hemlock woolly adelgid*	Acephate	1 commercial class product

*Considered to be included under generic label claims.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number: 1429518
Reference: 2004, Product chemistry of Confidor 200 SL, Data Numbering Code: 3.0, 3.1, 3.1.1, 3.1.2, 3.1.3, 3.1.4, 3.2, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2, 3.4, 3.4.1, 3.4.2, 3.5, 3.5.1, 3.5.11, 3.5.12, 3.5.13, 3.5.15

PMRA Document Number: 1429519
Reference: 2004, Product chemistry of Confidor 200 SL, Data Numbering Code: 3.2, 3.2.1, 3.2.2, 3.2.3, 3.3.1, 3.3.2 Confidential Business Information

PMRA Document Number: 1429521
Reference: 2006, Product chemistry of Merit Tree Injection Insecticide, Data Numbering Code: 3.5.10, 3.5.14

PMRA Document Number: 1438624
Reference: 1994, Technical chemistry file - BAY NTN 33893 Technical, Data Numbering Code: 2.1, 2.2, 2.3, 2.4, 2.5, 2.6 Confidential Business Information

PMRA Document Number: 1438628
Reference: 1995, Technical chemistry file - BAY NTN 33893 Technical, Data Numbering Code: 2.1, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 Confidential Business Information

PMRA Document Number: 1438653
Reference: 1996, Technical chemistry file – Water solubility and partition coefficient of UREA compound (project NTN 33893), Data Numbering Code: 2.14.12, 2.14.7 Confidential Business Information

PMRA Document Number: 1438655
Reference: 1996, Technical chemistry file – Water solubility and partition coefficient of DESNITRO compound (project NTN 33893) supplemental, Data Numbering Code: 2.14.12, 2.14.7 Confidential Business Information

PMRA Document Number: 1438697
Reference: 1997, Technical chemistry file - Supplementary chemistry requirements for the registration of BAY NTN 33893 Technical, Data Numbering Code: 2.1, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 Confidential Business Information

PMRA Document Number: 1438815
Reference: Technical chemistry file – National Registration Authority for Agricultural and Veterinary Chemicals – Public Release Document, Imidacloprid in the product Confidor Insecticide, Data Numbering Code: 2.99

2.0 Human and Animal Health

PMRA Document Number: 591475
Reference: 2001, A developmental neurotoxicity screening study with technical grade imidacloprid in Wistar rats, Data Numbering Code: 4.5.12, 4.5.14

PMRA Document Number: 1039613
Reference: 1994, An acute oral neurotoxicity screening study with technical grade imidacloprid (NTN 33893) in rats, Data Numbering Code: 4.5.12

PMRA Document Number: 1039643
Reference: 1994, A subchronic dietary neurotoxicity screening study with technical grade imidacloprid (NTN 33893) in Fischer 344 rats, Data Numbering Code: 4.5.13

PMRA Document Number: 1039650
Reference: 1994, An acute oral neurotoxicity screening study with technical grade imidacloprid (NTN 33893) in rats, Data Numbering Code: 4.5.12

PMRA Document Number: 1039652
Reference: 1994, A subchronic dietary neurotoxicity screening study with technical grade imidacloprid (NTN 33893) in Fischer 344 rats, Data Numbering Code: 4.5.13

PMRA Document Number: 1155681
Reference: NTN 33893 Technical: Subchronic toxicity study on dogs in oral administration (thirteen-week feeding study) (100176; 18732) (Imidacloprid/ Admire), Data Numbering Code: 4.3.1

PMRA Document Number: 1155682
Reference: NTN 33893: Subchronic toxicity study on Wistar rats (administration in the feed for 96 days) (100036; 18187) (Imidacloprid/ Admire), Data Numbering Code: 4.3.1

PMRA Document Number: 1155687, 1155688
Reference: NTN 33893 Technical: (proposed C.N. imidacloprid), multiple generation reproduction study in rats (100647; R5097; RCC087063; T 7025163) (Admire), Data Numbering Code: 4.5.1

PMRA Document Number: 1155689
Reference: NTN 33893 (proposed common name: imidacloprid) subacute inhalation toxicity study on the rat according to OECD Guideline No.412 (100262; 18199; T 3027635) (Amire), Data Numbering Code: 4.3.6

PMRA Document Number: 1155690
Reference: NTN 33893 Technical: study for subacute dermal toxicity in the rabbit (100688; 19152) (Imidacloprid/ Admire), Data Numbering Code: 4.3.4,4.3.5

PMRA Document Number: 1155691
Reference: 28-day oral range-finding toxicity (feeding) study with NTN 33893 Techn. in the dog (99656; RCC084993; T 6025018; R 4196) (Imidacloprid/ Admire), Data Numbering Code: 4.3.1

PMRA Document Number: 1155694
Reference: Final report, Sister chromatid exchange assay in Chinese hamster ovary cells (99676; 1149; T8302.334) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155695
Reference: WAK 3839 subchronic toxicological study on rats (twelve-week administration in drinking water) (101949; 21140; T 5033324) (Imidacloprid/ Admire), Data Numbering Code: 4.3.1

PMRA Document Number: 1155697
Reference: NTN 33893 carcinogenicity study on B6C3R1 mice (administration in the food for 24 months) (100693; 19931) (Imidacloprid/ Admire), Data Numbering Code: 4.4.1,4.4.2

PMRA Document Number: 1155698
Reference: Embryotoxicity study (including teratogenicity) with NTN 33893 Technical in the rat, Part I revised edition (98571; 083496; 148004; T 5032695) (Imidacloprid/ Admire), Data Numbering Code: 4.5.2

PMRA Document Number: 1155699
Reference: Embryotoxicity study (including teratogenicity) with NTN 33893 Technical in the rabbit, Part I revised edition (98572; 083518) (Imidacloprid/ Admire), Data Numbering Code: 4.5.2

PMRA Document Number: 1155700
Reference: Mouse germ-cell cytogenetic assay with NTN 33893 (Imidacloprid/ Admire) (102654; R 5063), Data Numbering Code: 4.5.4

PMRA Document Number: 1155701
Reference: NTN 33893 *in vivo* cytogenetic study of the bone marrow in Chinese hamster to evaluate for induced clastogenic effects (100021; 18557; T 8032562) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155702
Reference: WAK 3839 mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay *in vitro* (17757; 100661; T 7030167) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155703
Reference: Chromosome aberration assay in Chinese hamster V79 cells *in vitro* with WAK 3839 (100666; T4849; CCR 151200) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155705
Reference: NTN 33893 carcinogenicity study in B6C3F1 mice (supplementary MTD Testing For study T 5025710 with adminstration in diet over a 24-month period) (101929; 20769; T 4029986) (Imidacloprid/ Admire), Data Numbering Code: 4.4.1,4.4.2

PMRA Document Number: 1155706
Reference: NTN 33893 mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay *in vitro* (98587; 17578; T 5029536) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155707
Reference: WAK 3839 mutagenicity study for the detection of induced forward mutations in the V79-HGPRT assay *in vitro* (100662; 18281) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155708
Reference: WAK 3839 micronucleus test on the mouse after oral application (100663; 184060) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155709
Reference: WAK 3839 or NTN 37571 micronucleus test on the mouse after intraperitoneal injection (100664; 18407) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155710
Reference: NTN 33893 Salmonella/ microsome test to evaluate for point mutagenic effects (98570; 17577; T 6030111) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155711
Reference: NTN 33893 *in vitro* cytogenetic study with human lymphocytes for the detection of induced clastogenic effects (99262; 18092; T 6029654) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155712
Reference: NTN 33893 sister chromatid exchange in bone marrow of Chinese hamsters *in vivo* (99257; 18093; T 8030302) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155713
Reference: Unscheduled DNA synthesis in primary hepatocytes of male rats *in vitro* with WAK 3839 (100665; R4746; CCR 137002) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155714
Reference: NTN 33893 reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) (101276; 90A032) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155715
Reference: WAK 3839 reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) (100668; 90A015; RA90035) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155717
Reference: NTN 33893 REC-assay with spores in the bacterial system (101275; 90A013) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155718
Reference: NTN 33893 test on *S. cerevisiae* D7 to evaluate for induction of mitotic recombination (102653; 16832) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155720
Reference: NTN 33893 study for acute inhalation toxicity in the rat in accordance with OECD Guideline No. 403 (99806; 16777) (Imidacloprid/ Admire), Data Numbering Code: 4.2.3

PMRA Document Number: 1155724
Reference: NTN 33893 study for acute oral toxicity to rats (100040; 18594)(Imidacloprid/ Admire), Data Numbering Code: 4.2.1

PMRA Document Number: 1155729
Reference: NTN 33893 (C.N. imidacloprid (proposed)), Study for acute dermal toxicity to rats (100041; 18532) (Admire), Data Numbering Code: 4.2.2

PMRA Document Number: 1155731
Reference: NTN 33893 study for irritant/corrosive potential on the eye (rabbit) according to OECD Guideline No. 405 (99679; 16456; T 8025515) (Imidacloprid/ Admire), Data Numbering Code: 4.2.4

PMRA Document Number: 1155733
Reference: NTN 33893 study for irritant/corrosive potential on the skin (rabbit) according to OECD Guideline No.404 (99804; 16455) (Imidacloprid/ Admire), Data Numbering Code: 4.2.5

PMRA Document Number: 1155738
Reference: NTN 37571 *in vitro* cytogenetic assay measuring chromosome aberrations in CHO-K1 cells (100678; RP880088) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155747
Reference: NTN 33893 technical study for skin sensitising effect on guinea pigs (maximization test) (99800; 16533; T 9025651) (Imidacloprid/ Admire), Data Numbering Code: 4.2.6

PMRA Document Number: 1155751
Reference: NTN 37571 micronucleus test on the mice after oral treatment pilot study (100680; RS88040) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155753
Reference: NTN 37571 micronucleus test on the mice after I.P. treatment pilot study (100679; RS88041) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155754
Reference: Mutagenicity test on NTN 33893 in the rat primary hepatocyte unscheduled DNA synthesis assay (98573; HLA 10237-0-447; T6027610; 4631), Final report (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155755
Reference: NTN 33893 micronucleus test on the mouse to evaluate for clastogenic effects (102652; 16837) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155756
Reference: Clastogenic evaluation of NTN 33893 in an in vitro cytogenetic assay measuring sister chromatid exchange in Chinese hamster ovary (Cho) cells (102655; R 4407) (Imidacloprid/ Admire), Data Numbering Code: 4.5.4

PMRA Document Number: 1155757
Reference: NTN 33893 (proposed common name: imidacloprid) chronic toxicity and carcinogencity studies on Wistar rats (administration in food over 24 months) supplementary MTD study for two-year study T 1025699 (101931; 20541; T3030055; T 1025699), Data Numbering Code: 4.4.1, 4.4.2

PMRA Document Number: 1155758
Reference: 52-week oral toxicity (feeding) study with NTN 33893 Technical in the dog (085004; T 7025019; T 4856; 100015) (Imidacloprid/ Admire), Data Numbering Code: 4.4.1

PMRA Document Number: 1155760, 1155761
Reference: NTN 33893 (proposed common name: imidacloprid) chronic toxicity and carcinogenicity studies on Wistar Rats (administration in food over 24 months) (100652; 19925) (Admire), Data Numbering Code: 4.4.1, 4.4.2

PMRA Document Number: 1155769
Reference: Methylene- [^{14}-C] imidacloprid: metabolism part of the general metabolism study in the rat (101999; M 182 0176-5) (Admire), Data Numbering Code: 6.4

PMRA Document Number: 1155771
Reference: [^{14}-C] NTN 33893: Investigations on the distribution of the total radioactivity in the rat by whole-body autoradiography (87264; M 181 0177-5) (Imidacloprid/ Admire), Data Numbering Code: 6.4

PMRA Document Number: 1155781
Reference: Imidacloprid- WAK 3839: comparison of biokinetic behaviour and metabolism in the rat following single oral dosage and investigation of the metabolism after chronic feeding of imidacloprid to rats and mice (100645; PF 3432; M 71810016), Data Numbering Code: 4.5.9

PMRA Document Number: 1155782
Reference: [Imidazolidine-4,5-^{14}C] imidacloprid: investigation of the biokinetic behaviour and metabolism in the rat (102617; PF 3629; M 31819004) (Admire), Data Numbering Code: 4.5.9

PMRA Document Number: 1167318
Reference: NTN 33893 AMP Salmonella/ microsome test (101266; 20090), Data Numbering Code: 4.5.8

PMRA Document Number: 1181354
Reference: Salmonella/ microsome test with LZR 6548 using TA 100 (20173; T9038071; 107438), Data Numbering Code: 4.5.4

PMRA Document Number: 1181365
Reference: LZR 6548 Salmonella/ microsome test (20313; T0037000; 107439), Data Numbering Code: 4.5.4

PMRA Document Number: 1181377
Reference: NTN 33893 AMP W Salmonella/ microsome test (21775; T1039126; 107440), Data Numbering Code: 4.5.4

PMRA Document Number: 1181390
Reference: Salmonella/ microsome test with PEDA (20387; T2037002; T4038085; T8039664; 107441), Data Numbering Code: 4.5.4

PMRA Document Number: 1429523
Reference: 2004, NTN 33893 200 SL acute toxicity in the rat after oral administration, Data Numbering Code: 4.6.1

PMRA Document Number: 1429525
Reference: 2004, NTN 33893 200 SL acute toxicity in the rat after dermal application, Data Numbering Code: 4.6.2

PMRA Document Number: 1429526
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PMRA Document Number: 1429527
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Reference: 2004, NTN 33893 - study for the skin sensitization effect in guinea pigs (guinea pig maximization test according to Magnusson and Kligman), Data Numbering Code: 4.6.6

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Reference: 2007, Occupational safety assessment of imidacloprid resulting from the tree injection of Confidor 200 SL Systemic Insecticide, Data Numbering Code: 5.2, 5.3, 5.4

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PMRA Document Number: 1633695
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PMRA Document Number: 1155687, 1155688
Reference: NTN 33893 Technical: (proposed C.N. imidacloprid), multiple generation reproduction study in rats (100647; R5097; RCC087063; T 7025163) (Admire), Data Numbering Code: 4.5.1

PMRA Document Number: 1155698
Reference: Embryotoxicity study (including teratogenicity) with NTN 33893 Technical in the rat, Part I revised edition (98571; 083496; 148004; T 5032695) (Imidacloprid/ Admire), Data Numbering Code: 4.5.2

PMRA Document Number: 1155724
Reference: NTN 33893 study for acute oral toxicity to rats (100040; 18594) (Imidacloprid/ Admire), Data Numbering Code: 4.2.1

PMRA Document Number: 1155842
Reference: Technical NTN 33893: An acute oral LD_{50} with bobwhite quail, Data Numbering Code: 9.6.2.1

PMRA Document Number: 1155843
Reference: Technical NTN 33893: Subacute dietary LC_{50} with bobwhite quail, Data Numbering Code: 9.6.2.4

PMRA Document Number: 1155844
Reference: Technical NTN 33893: A subacute dietary LC_{50} with mallard ducks (100238; N3720801) (Imidacloprid/ Admire), Data Numbering Code: 9.6.2.4

PMRA Document Number: 1155846
Reference: Technical NTN 33893: A one generation reproduction study with bobwhite quail (101203; N3741701) (Imidacloprid/ Admire), Data Numbering Code: 9.6.3.1

PMRA Document Number: 1155847
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PMRA Document Number: 1155848
Reference: Technical NTN 33893: A one generation reproduction study with mallard ducks (103813; N3740802) (Imidacloprid/ Admire), Data Numbering Code: 9.6.3.1

PMRA Document Number: 1155849
Reference: Supplemental Report: Technical NTN 33893: A one generation reproduction study with mallard ducks (103813-1; N3740802) (Imidacloprid/ Admire), Data Numbering Code: 9.6.3.1

PMRA Document Number: 1157921
Reference: NTN 33893 2.5g: An acute oral LD_{50} with house sparrows (*Passer domesticus*) (N3711402; 101324) (Admire), Data Numbering Code: 9.6.2.1

PMRA Document Number: 1157922
Reference: Bird toxicity oral/ pigeon (*Columbia livia*) (GMU11194.doc; 106611; VT-113) (Admire), Data Numbering Code: 9.6.2.1

PMRA Document Number: 1157923
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PMRA Document Number: 1157924
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PMRA Document Number: 1157925
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