Evaluation Report ERC2013-04

Amitraz

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Overview

Registration Decision for Amitraz

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 Amitraz Technical and Apivar Strips, containing the technical grade active ingredient amitraz, to control the parasitic mite (*Varroa destructor*) on honey bees.

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 section provides detailed technical information on the human health, environmental and value assessments of Amitraz Technical and Apivar Strips.

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.

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 section of Health Canada's website at healthcanada.gc.ca/pmra.

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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."

What Is Amitraz?

Amitraz is a formamidine contact acaricide and insecticide which is used to kill ectoparasites. It appears to act on the nervous system, leading to overexcitation and consequently paralysis and death in arthropods.

Apivar Strips consist of a plastic polymer strip embedded with amitraz. The strips are placed in the hive with one strip used for every five frames of bees in each brood chamber. The strip is hung between the frames, with the frames separated slightly so that both sides of the strip come into contact with the bees. The bees rub against the strips as they move through the brood chamber, and then pass the chemical on to other bees as they rub up against each other in the hive. The strips should be removed after six weeks.

Health Considerations

Can Approved Uses of Amitraz Affect Human Health?

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

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

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

In laboratory animals, the acute oral toxicity of the technical grade active ingredient amitraz varies widely among species. Amitraz was of low toxicity in mice and of high toxicity in several other test species via the oral route. Amitraz was slightly toxic via the dermal route, of low toxicity via the inhalation route, minimally irritating to the eyes and skin, and was determined to be a potential skin sensitizer.

No acute toxicology data were available for the end-use product, Apivar Strips, and therefore the acute toxicity data for the active ingredient were used to characterize the hazards of the end-use product. Although data indicated that amitraz may be highly acutely toxic via the oral route, this route was not expected to be of concern with the proposed use since the active ingredient is embedded in plastic strips. Overall, Apivar Strips were considered to be slightly acutely toxic via the dermal route, of low acute toxicity via the inhalation route, minimally irritating to the eyes and skin, and capable of causing allergic skin reactions. Consequently the signal words "CAUTION POISON" and "POTENTIAL SKIN SENSITIZER" are required on the product label.

The available toxicology studies indicate the main effects caused by amitraz were related to suppression of the central nervous system, and included sedation, as well as decreases in body temperature, blood pressure, and heart rate. Generally, these effects tended to have a rapid onset, were short-lived, and did not appear to accumulate over time. Amitraz did not damage genetic material and was not considered to pose a cancer risk.

When amitraz was given to pregnant rats, effects on the urinary system of the developing fetus were observed at doses that also caused toxic effects in the mother, indicating that the young do not appear to be more sensitive to amitraz than the adult animal. However, it was not possible to fully describe the effects on young and developing animals, as the full complement of studies required to fully assess these effects was not available. Consequently, an additional protective factor was used in the risk assessment to further reduce the allowable level of human exposure to amitraz. Furthermore, consideration was given to the anticipated low exposure potential resulting from the physical form of the product as well as the dietary and occupational exposure aspects outlined below.

To address this, an extended one-generation reproductive toxicity study, including a neurotoxicity component, is currently being conducted for submission to the Agency.

Residues in Water and Food

Dietary intake estimates (food only) revealed that the general population is expected to be exposed to less than 4.3% of the acceptable daily intake. A dietary intake estimate (food only) for the highest exposed population (children 1-2 years old) used less than 25.42% of the acute reference dose, which is not a health concern. Based on these estimates, the chronic and acute dietary risks from amitraz are not of concern for all population sub-groups.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act.* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Supervised residue trials conducted in France according to the Canadian GAP were found acceptable to support the registration of Apivar Strips in Canada. The MRL for this active ingredient can be found in the Science Evaluation section of this Evaluation Report.

Risks in Residential and Other Non-Occupational Environments

Due to the nature of the application and the treatment location, bystander and residential exposures are not of concern.

Occupational Risks From Handling Apivar Strips

Occupational risks are not of concern when Apivar Strips are used according to the label directions, which include protective measures.

Apivar Strips are sustained-release, hardened plastic strips containing amitraz. For workers handling the strips, exposure via the inhalation route is expected to be minimal, and relative to the dermal exposure incurred, it is expected to be negligible.

The use of amitraz in honey bee colonies potentially represents a risk of concern for chemical handlers of amitraz; however, the mitigation measures recommended on the label, such as the use of chemical resistance gloves (for example, nitrile), should address this risk.

No restricted entry interval is required on the end-use product label for Apivar Strips.

Environmental Considerations

What Happens When Amitraz Is Introduced Into the Environment?

Amitraz is used in the formulation for Apivar Strips for the control of varroa mites on honey bees. Since the end-use product will be used in beehives, the risk to non-target organisms is considered to be negligible, when used according to the label directions. Because of the use pattern, amitraz is unlikely to be introduced to the environment.

Value Considerations

What Is the Value of Apivar Strips?

Apivar Strips have value as they control varroa mites (*Varroa destructor*) in honey bee hives.

Varroa mites are the most important parasitic pest of honey bees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestations in a honey bee colony will cause the loss of the infested colonies. Varroa mites are the main cause of honey bee colony loss in Canada.

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 placed on the label of Apivar Strips to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health
Since there is a potential for users to come into direct contact with amitraz on the skin, anyone applying Apivar Strips must wear chemical resistant gloves (for example, nitrile). In addition, the label statements "Do not handle more than 100 pairs of strips per person per day." is required on the label.

Environment
Standard precautionary measures are required to mitigate potential risks to non-target organisms. These include adding precautionary statements to the label regarding environmental hazards and the directions for use.

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 section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated (by September 1, 2013).

Human Health

The following data gaps, which have been identified as part of the ongoing PMRA re-evaluation, will have to be addressed as a condition of registration of the technical active ingredient used in the Apivar Strips:

- DACO 4.5.3 - Prenatal developmental toxicity study in rabbits
- DACO 4.5.1 - Rat reproductive toxicity study
- DACO 4.5.14 - Developmental neurotoxicity study
- DACO 4.5.12 – Acute neurotoxicity*
- DACO 4.5.13 – 90-day neurotoxicity*

*These studies were recently submitted to the Agency, and will be evaluated as part of the re-evaluation activities.

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.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when 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).

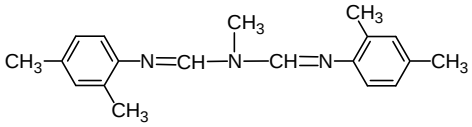
[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Amitraz

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Amitraz
Function	Insecticide/Miticide/Acaricide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*N*,*N*'-[(methylimino)dimethylidyne]di-2,4-xylidine
2. Chemical Abstracts Service (CAS)	*N*'-(2,4-dimethylphenyl)-*N*-[[(2,4-dimethylphenyl)imino]methyl]-*N*-methylmethanimidamide
CAS number	33089-61-1
Molecular formula	$C_{19}H_{23}N_3$
Molecular weight	293.4
Structural formula	
Purity of the active ingredient	97.0%

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

Technical Product—Amitraz Technical

Property	Result
Colour and physical state	White, off-white or pale yellow crystalline powder (Solid)
Odour	Slight odour of amines
Melting range	86.1°C
Boiling point or range	Not applicable
Density	1.128 g/mL
Vapour pressure at 20°C	3.4×10^{-4} Pa
Ultraviolet (UV)-visible spectrum	λmax at 290 nm

Property	Result
Solubility in water at 20°C	< 0.1 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solvent — Solubility Acetone — 30-60 Acetonitrile — 6.0-7.5 Dichloromethane — >60 Dimethylsulphoxide — 12-15 Ethanol — 3.51 Ethyl acetate — 30-60 Hexane — 2.1-2.5 Methanol — 2.01 Propan-2-ol — 2.15 Toluene — 30-60
n-Octanol-water partition coefficient (K_{ow})	Log K_{ow} = 5.5 at 25°C
Dissociation constant (pK_a)	pKa = 4.2 ± 0.1
Stability (temperature, metal)	No detectable decomposition when held in contact with type 316 stainless steel in a dry atmosphere for 24 hours at 23°C.

End-Use Product—Apivar Strips

Property	Result
Colour	Off-white, translucent in appearance
Odour	Not provided but not expected to affect efficacy
Physical state	Solid
Formulation type	SO (Solid)
Guarantee	3.3%
Container material and description	Rigid plastic strips (78 mm × 207 mm × 2.1 mm) Opaque heat sealed multilayer sachet – inner layer is LDPE.
Density	0.88 g/cm^3
pH of 1% dispersion in water	pH cannot be determined since the product is not soluble in water
Oxidizing or reducing action	Tests could not be conducted since the product is not soluble in water. Amitraz is sensitive to oxidation.
Storage stability	The product is stable for 24 months at ambient temperature.
Corrosion characteristics	The strips only contact LDPE and no corrosion was observed over a 24 month period.
Explodability	The product is not potentially explosive.

1.3 Directions for Use

To control varroa mite, hang two Apivar Strips per brood chamber in the hives in the spring or the fall if varroa mite infestations have reached treatment threshold. To place strips, separate the double strip and hang each strip between two comb frames inside the brood area or the bee cluster, with a minimum distance of two frames between strips. Suspend Apivar Strips in the brood chamber in such a way that the bees can walk on both sides of the strips. Leave strips inside the hive for forty-two days, and then remove. In case of movement of the bee cluster inside the beehive far from the strips, reposition the strips into the bee cluster, and leave the strips in place for fourteen more days before removal.

1.4 Mode of Action

Amitraz is a formamidine non-systemic contact acaricide and insecticide which is used as an ectoparasiticide. It appears to act by alpha-adrenergic agonist activity, interaction with octopamine receptors of the nervous system and inhibition of monoamine oxidases and prostaglandin synthesis, leading to overexcitation and consequently paralysis and death in arthropods.

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 Amitraz Technical 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.

2.3 Methods for Residue Analysis

High performance liquid chromatography with ultraviolet detection (HPLC-UV) method API002, gas chromatography with electron capture detection (GC-ECD) method API005 and gas chromatography mass spectrometry (GC-MS) method TMP-20, Version 2 were developed and proposed for data generation in honey samples. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the lowest limit of method validation. Acceptable recoveries (70–120%) were obtained in honey. No extraction efficiency data was provided. FDA PAM II contains two methods (I and II) which were deemed adequate as enforcement methods for animal and plant commodities.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Amitraz is currently under re-evaluation by the PMRA. At this juncture in the re-evaluation, which is based largely on available United States Environmental Protection Agency (USEPA) documentation, a number of gaps in the toxicology data package have been identified including a multigeneration reproduction study, a non-rodent developmental toxicity study, an acute neurotoxicity study, a subchronic neurotoxicity study, and a developmental neurotoxicity study. With respect to these data gaps, reproductive toxicity studies as well as developmental toxicity studies were available, but some were found to have major deficiencies and/or did not meet current standards for toxicity testing. In addition, while acute and repeat-dose neurotoxicity studies were recently submitted to the Agency, these studies were not evaluated within the context of this registration and therefore, continue to be identified as data gaps that will be addressed through the re-evaluation activities.

The following provides a summary of the toxicological profile for amitraz, an α_2-adrenergic receptor agonist, based on previous PMRA reviews, as well as readily available public literature. Amitraz manifests its principal effects in laboratory animals as sedation, hypothermia (decreased body temperature), hypotension (decreased blood pressure) and bradycardia (decreased heart rate). Generally, the acute onset and transient nature of the clinical effects observed with amitraz suggest good correlation between the pharmacological effects of amitraz and plasma concentrations. The acute oral toxicity of amitraz varies widely among species, with LD_{50} values ranging from 100 mg/kg bw (in dogs and pigs) to > 1600 mg/kg bw (in mice). Non-rodents tended to be more sensitive than rodent species. Amitraz was slightly toxic via the dermal route (LD_{50}>1600 mg/kg bw in the rat), and was of low acute toxicity via the inhalation route (LC_{50} =2.4 mg/L). Amitraz was minimally irritating to the eyes and skin and was determined to be a potential dermal sensitizer.

No acute toxicology data were available for the end-use product, Apivar Strips, containing amitraz embedded in plastic strips, and therefore the acute toxicity data for the active ingredient were used to characterize the hazards of the end-use product. Although data indicated that amitraz may be highly acutely toxic via the oral route, this route was not expected to be of concern with the proposed use due to the formulation type of the end-use product (i.e. active ingredient embedded in plastic strips). Overall, Apivar Strips were considered to be slightly acutely toxic via the dermal route, of low acute toxicity via the inhalation route, minimally irritating to the eyes and skin, and a potential dermal sensitizer.

Major effects noted in the available toxicology studies conducted with laboratory animals included sedation, hypothermia, hypotension and bradycardia, consistent with the mode of action of amitraz as described above. The central nervous system (CNS) effects were not cumulative, but were shown to be a response to a daily dose. In 90-day and 24-month dietary studies conducted with the dog, effects at the LOAEL included CNS depression, decreased body temperature and pulse rate. The effects in these studies defined the most sensitive parameters in the animal database.

In a prenatal developmental toxicity study in rats, there was no evidence of sensitivity of the young as increased incidences of hydro-ureter and renal pelvic cavitation were observed in fetuses at doses producing decreases in maternal body weight. Evidence of susceptibility of the young following pre-natal exposure to rabbits and with regards to reproductive toxicity in rats could not be fully ascertained due to deficiencies in either the study designs and/or study reports. There was no evidence that amitraz has genotoxic potential, there were no treatment-related tumours noted in the 24-month rat dietary chronic/oncogenicity study, and no tumours were observed in an initial mouse carcinogenicity study. In a repeat mouse study, there was evidence of a tumorigenic response in the livers of females at the highest dose level; however, this response occurred at excessive doses and was therefore not considered to be biologically significant. Overall, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.

In the overall characterization of the toxicity profile of amitraz, gaps were identified in the toxicology database, as noted above, some of which resulted from the fact that the data did not meet current standards for toxicity testing, and thus were not considered sufficiently robust to be included in the risk assessment. In this regard, an extended one-generation reproductive toxicity study, including a neurotoxicity component, is currently being conducted. Additional studies assessing acute and subchronic neurotoxicity in adult animals have also recently been submitted. For the current evaluation of amitraz use in the Apivar Strips product, a database uncertainty factor of 10-fold was applied to the risk assessment as an added measure of protection in view of the toxicology data gaps. Consideration was also given to the low anticipated occupational exposure (since the end-use product consists of amitraz embedded in plastic strips), the mitigation measures that will be put in place, as well as the limited contribution of amitraz residues in honey to the overall dietary risk. Notwithstanding these considerations, the toxicology data gaps identified through re-evaluation will also have to be addressed as a condition of registration of the Apivar Strips product.

The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 2.

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. Information on the reporting of incidents can be found on the Pesticides and Pest Management section of Health Canada's website. Incidents in the PMRA database were searched and reviewed for the active ingredient amitraz. As of October 11, 2012, there were no human incidents, and seven domestic animal incidents involving this active ingredient reported to the PMRA. All of these incidents were related to a product applied as a collar for use on dogs to control ticks, and are therefore not relevant to the current use pattern.

In 2009, the USEPA published a summary of human incident reports related to amitraz use between the years 2002 and 2009 in the United States. This summary indicated that five amitraz-related incidents had been reported to the USEPA, and that another 10 cases were reported to the Centers for Disease Control and Prevention's NIOSH SENSOR database during that time. These

cases were reported to be of low to moderate severity, and most included neurological, gastrointestinal, ocular, dermal, cardiovascular and respiratory symptoms. The cases reported to the USEPA were associated with flea treatment products, while those reported in the NIOSH SENSOR database (which collects information regarding occupational incidents relating to pesticide exposures) were associated with professional applicator exposures (involving the use of dip products to treat dogs), as well as unintentional ingestions; in a few of the cases the source of the exposure was not documented. Overall, based on the low number of reported incidents and on the low to moderate severity of those that were reported, the USEPA concluded that there did not appear to be a risk concern for amitraz.

According to information from the California Pesticide Illness Database, five amitraz-related human incidents were reported in California during the period of 1992-2009, all of which were associated with the use of amitraz on cotton crops. In these incidents, dermal (itching, red and or burning rashes), ocular (red, burning, itching and/or irritation) and gastrointestinal (upset stomach) symptoms were reported.

The above information regarding incident reports relating to amitraz was considered in this evaluation and did not affect the risk assessment.

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 threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, as well as to concerns relating to pre- and post-natal toxicity, a prenatal developmental toxicity study in rats demonstrated an increased incidence of hydro-ureter as well as renal pelvic cavitation in fetuses at a dose which produced decreased body weight gain in the dams, indicating that the young animal was not more sensitive than the adult to amitraz toxicity. A prenatal developmental toxicity study in rabbits and a rat reproductive toxicity study, conducted according to current standards for toxicity testing, as well as a developmental neurotoxicity study have been identified as outstanding data requirements. Until the data have been received and reviewed by the agency, it is difficult to fully characterize the potential prenatal and postnatal toxicity of amitraz.

Since the resulting residual uncertainty with respect to prenatal and postnatal toxicity has been addressed through the application of a database uncertainty factor of 10-fold, the 10-fold factor required under the *Pest Control Products Act* was reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

To estimate acute dietary risk for the general population, the common and lowest NOAEL values in the database of 0.25 mg/kg bw/day from the 90-day and 24-month dietary studies in the dog were selected. Effects at the study LOAEL (1.0 mg/kg bw/day) included CNS depression, as well as decreased body temperature and pulse rate. The effects at the NOAELs were observed after a single dose with onset of toxic signs within a few hours of dosing, and were generally found to rapidly reverse and recur after each daily dose. They were therefore considered relevant for an acute exposure scenario. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 10-fold database uncertainty factor was applied to account for the toxicology data gaps. As explained above, the 10-fold PCPA factor was reduced to 1-fold, as this factor was subsumed by the 10-fold database uncertainty factor that was applied to account for the toxicology data gaps. **The composite assessment factor (CAF) is 1000.**

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.25 \text{ mg/kg bw}}{1000} = 0.0003 \text{ mg/kg bw of amitraz}$$

3.3 Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the common NOAEL values of 0.25 mg/kg bw/day from the dog 90-day and 24-month dietary studies were selected. Effects at the study LOAEL (1.0 mg/kg bw/day) included CNS depression, as well as decreased body temperature and pulse rate. As previously mentioned, the NOAEL of 0.25 mg/kg bw/day was the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 10-fold database uncertainty factor was applied to account for the toxicology data gaps. As explained above, the 10-fold PCPA factor was reduced to 1-fold, as this factor was subsumed by the 10-fold database uncertainty factor that was applied to account for the toxicology data gaps. **The composite assessment factor (CAF) is 1000.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.25 \text{ mg/kg bw/day}}{1000} = 0.0003 \text{ mg/kg bw/day of amitraz}$$

Cancer Assessment

There was no evidence in the available genotoxicity studies suggesting that amitraz has genotoxic potential and the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

For this specific assessment, only dermal endpoints were necessary to characterize risk.

For occupational dermal risk assessments of all durations, the common NOAEL values from the 90-day and 24-month dietary studies in the dog were selected, as no acceptable repeat-dose dermal studies were available in the database. The NOAELs in these studies were 0.25 mg/kg bw/day. Effects at the study LOAELs (1.0 mg/kg bw/day) included CNS depression, as well as decreased body temperature and pulse rate. These effects were observed after a single dose, with onset of toxic signs within a few hours of dosing, and were generally found to rapidly reverse and recur after each daily dose. They were therefore considered relevant for all durations of exposure.

The target MOE is 1000. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 10-fold database uncertainty factor was applied to account for the toxicology data gaps.

3.4.1.1 Dermal Absorption

A 13% Dermal Absorption Factor was selected based upon previous dermal absorption reviews. In 1995, the USEPA evaluated the available data and approved a dermal absorption factor of 13.8% for use in their evaluation of amitraz. In 2006, a dermal absorption of 8% was supported by the USEPA in their Tolerance Reassessment Progress and Risk Management Decision for amitraz. Both of these values were selected for the liquid formulation. In the absence of formulation-specific dermal absorption data, the value of 13% is deemed appropriate.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Apivar Strips are sustained-release, hardened plastic strips containing amitraz. For workers handling the strips, exposure via the inhalation route is expected to be minimal, and relative to the dermal exposure incurred, it is expected to be negligible.

To address the data deficiency of assessing the exposure incurred by chemical handlers of Apivar Strips in honey bee colonies, an appropriate study was submitted in support of the registration of Apivar Strips in Canada.

This study was chemical-specific and involved the use of the end-use product (i.e., Apivar Strips) by a ‘worker’ wearing two pairs of chemical-resistant gloves who applied 250 pairs of strips in a controlled laboratory setting. Each strip was hung between two frames in keeping with label instructions. The study included two sets of two pairs of gloves: latex (as per the original product label) and nitrile. No other Personal Protective Equipment is recommended on the product label.

The study authors concluded that nitrile gloves appear to be more effective than latex gloves in reducing the amount of amitraz residues that are transferred to the hands of the applicator during the installation of Apivar strips.

Several limitations, such as conducting a study with one worker that is not reflective of the current PMRA standards, prevent the Agency from applying the results of the study in a quantitative manner; however, the results are indicative of the protective capacity of nitrile gloves, which is largely accepted and well documented (USEPA 1993; Purdue 2003). Specifically, nitrile is recognized as providing good protection against pesticides in dried form, and at least some protection against all categories of liquid pesticides (see Appendix 1, Table 6). In the submitted study, nitrile appeared to be more effective than latex gloves in reducing the residue of amitraz that are transferred to the hands of the applicator during the installation of Apivar Strips.

Based on the above, a weight of evidence approach is utilized in support of the registration of Apivar Strips, which takes into account the following:

1. While limited, the submitted study does suggest that amitraz is transferred to the hands of the applicator during strip installation;
2. The portion of the study related to the glove wash indicates that:
    - The amitraz residue that penetrates the interior of a nitrile glove during strip manipulation is minimal;
    - The amitraz residue that penetrates the interior of a nitrile glove during strip manipulation is also less in comparison to the residues that penetrate the interior of a latex glove during strip manipulation.
3. Keeping in mind the accepted and known properties of nitrile as a material for Personal Protective Equipment, the results of the study are consistent with this body of evidence in that it supports the use of nitrile as an effective barrier against dried amitraz residues.

The registration decision also takes into consideration that:

- The use of Apivar Strips is widely supported by Canadian stakeholders; provinces have identified the need for mite control in honey bee colonies and have supported Apivar Strips as a potential solution.
- There is no history, to date, of the development of resistance to amitraz among Canadian mite populations.
- The lack of incident reports related to human and animal health (Section 3.5).
- The acceptability of the risk also depends on the risk mitigation measures such as limiting the number of strips handled to not more than 100 pairs of strips per person per day.

3.4.2.2 Exposure for Workers Entering Treated Areas

The risk of concern for post-application exposure is likely negligible and further mitigated by the requirement to wear chemical resistant gloves (for example, nitrile) whenever the strips are handled.

Post-application exposure activities are limited to the removal and disposal of the strips from a minimum of 42 days up to a maximum of 56 days after application. Since Apivar Strips are sustained-release, it is expected that the remaining transferable residue at the time of removal will be significantly less than the amount available during application. It is therefore assumed that due to the similarities in the two tasks, exposure incurred during the application of the new strips should greatly exceed the exposure incurred during the removal of the used strips.

No restricted entry interval is required on the end-use product label for Apivar Strips.

3.4.3.3 Bystander Exposure and Risk

Bystander exposure is not of concern.

Bystander exposure is expected to be negligible as the potential for drift is expected to be minimal. Application is limited to honey bee colonies using a sustained-release plastic strip. Taking into consideration the application method and locale, there is minimal risk of drift to areas of human habitation or activity such as houses, cottages, schools, and recreational areas.

3.5 Incident Reports Related to Human and Animal Health

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 Health Canada website. As of May 2012, no amitraz incidents related to human health, bee health, or the environment have been reported.

3.6 Food Residues Exposure Assessment

3.6.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant commodities has been revised as amitraz and the metabolites containing the 2,4-dimethylaniline moiety (N-(2,4-dimethylphenyl)-N′-methyl formamidine (BTS 27271) and N-(2,4-dimethylphenyl)formamide (BTS 27919)), expressed as amitraz equivalents. The data gathering analytical methods are valid for the quantitation of residues of amitraz equivalents in honey matrices. The residues of amitraz, metabolite BTS 27271 and metabolite BTS 27919 are stable in honey when stored in a freezer at -20°C for four months. Residues of amitraz are unstable in honey when stored at 25°C and 60% relative humidity for one month. Supervised residue trials conducted in France according to the Canadian GAP were adequate in assessing the expected amitraz residues in honey.

3.6.2 Dietary Risk Assessment:

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.6.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions and/or data were made in the very refined chronic dietary exposure analysis: default processing factors, monitoring data for plant commodities, half-LOD for animal commodities and percentages of domestic production of crops/commodities versus importation. The very refined chronic dietary exposure from all supported amitraz food uses (alone) for the total population, including infants and children, and all representative population subgroups are 1.7% of the ADI. The highest exposure and risk estimate is for children 1–2 years old at 4.3% (0.000013 mg/kg bw/day) of the ADI.

3.6.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were made in the very refined acute analysis: default processing factors, maximum values of monitoring data for plant commodities, LOD for animal commodities and percentages of domestic production of crops/commodities *vs* importation. The very refined acute dietary exposure (food alone) for all supported amitraz registered commodities is estimated to be 11.82% (0.000035 mg/kg/day) of the ARfD for the general population (95^{th} percentile, deterministic). The highest exposure and risk estimate is for children of 1–2 years old at 25.42% (0.000076 mg/kg bw/day) of the ARfD.

3.6.3 Maximum Residue Limits

Table 3.6.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Honey	0.1

For additional information on Maximum Residue Limit (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 4 and 5.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The properties and environmental fate characterization of amitraz have been previously reviewed and reported in the Decision Document: *Amitraz* for the historical use of Amitraz in commercial pear orchards (E95-02), and are summarized as follows:

Amitraz is considered to be of low-to-intermediate mobility in fine and medium-textured soils, but may be of higher mobility in coarse-textured soils. Laboratory studies indicate that amitraz and its major transformation products are moderately persistent in natural sediment/water, with reported DT_{50}s ranging from 14–32 days at 25ºC and 48–65 days at 8ºC. Results from terrestrial

field dissipation studies indicate that there is a possibility of accumulation and carryover of amitraz residues in treated soil.

When used according to label directions, use of Apivar Strips in bee hives will result in very limited environmental exposure. The amount of amitraz on the strips is not expected to be a significant environmental input if they are disposed of in accordance with provincial requirements.

4.2 Environmental Risk Characterization

4.2.1 Risks to Terrestrial Organisms

The potential environmental impacts of amitraz on terrestrial organisms have been previously reviewed and reported in Decision Document: *Amitraz* (E95-02) and are summarized as follows:

Amitraz is not toxic to earthworms, slightly toxic to birds on an oral acute basis and practically non-toxic to birds on a dietary basis; however, there may be a potential for dietary chronic toxicity to birds. Amitraz is also toxic to mammals. Amitraz is moderately toxic to bees on an oral basis, but relatively non-toxic on a contact basis.

Negligible risk to non-target terrestrial organisms, including bees in the treated hives, is expected from the use of Apivar Strips, when used according to label directions.

4.2.2 Risks to Aquatic Organisms

The potential environmental impacts of amitraz on aquatic organisms have been previously reviewed and reported in Decision Document: *Amitraz* (E95-02) and are summarized as follows:

Amitraz is highly toxic to fish and very highly toxic to aquatic invertebrates.

Negligible risk to non-target aquatic organisms is expected from the use of Apivar Strips, when used according to label directions.

5.0 Value

5.1 Effectiveness Against Pests

Five efficacy trials were reviewed in support of Apivar Strips: one conducted in Alberta, three conducted in France, and one conducted in Turkey. The reviewed data demonstrated that Apivar Strips provided control of varroa mite when applied at a rate of two strips per brood box for a period of 42 days. No adverse effects on treated hives were observed in the reviewed studies whether treated in the spring or fall. One known issue with Apivar Strips is that if the bees cluster in an area away from the strips, the mites will not be adequately treated. It is important that the mites are not exposed to sub-lethal levels of amitraz in order to reduce the chance of resistance development and to ensure effective control of the pest. Therefore, the application direction to apply two strips per brood box has value as it ensures that all brood boxes receive

equal treatment and reduce the opportunity for bees to cluster away from a strip. If bees are found to cluster away from the strips, the strips should be repositioned into the bee cluster and left in place for 14 more days before removal.

5.1.1 Acceptable Efficacy Claims

Based on reviewed value information, a claim that Apivar Strips when applied at a rate of two strips per brood box for a period of 42 days is acceptable. If it is observed the honey bee cluster has moved inside the beehive far from the strips, the strips should be repositioned strips into the bee cluster and left in place for 14 more days before removal. Strips must be removed after a maximum of 56 days, and must not be re-used.

5.2 Economics

Varroa mites are the most economically important parasitic pest of honey bees, and have a severe economic impact on the Canadian beekeeping industry. Significant varroa mite infestations in a honey bee colony will cause the loss of the infested colonies. Varroa mites are the main cause of honey bee colony loss in Canada, and without effective control of this pest beekeeping would not be an economically viable activity in many regions of Canada. Amitraz is an effective product for control of this pest.

5.3 Sustainability

5.3.1 Survey of Alternatives

Active ingredients currently registered in Canada for control of varroa mites include formic acid, oxalic acid, fluvalinate-tau, coumaphos, and thymol. Cultural control methods for varroa mites include drone brood trapping and use of sticky-boards or screened bottom boards to trap mites and keep them from returning to the honey bees.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Apivar Strips are compatible with current management practices and integrated pest management programmes. Since 1993 when the first varroa mite pest control strip product (fluvalinate-tau) was registered in Canada, beekeepers have integrated impregnated strip type products into their varroa control regimen. With the widespread occurrence of resistance to the two other active ingredients (fluvalinate-tau and coumaphos) available as varroa control strip products, Apivar Strips provide an effective alternative.

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

There have been no reports of amitraz resistant varroa mites in Canada. However, the development of resistance to pest control products is a major concern with varroa mites. Varroa mites in Canada have already developed widespread resistance to both coumaphos and

fluvalinate-tau. The development of resistance is a certain risk for amitraz without careful product stewardship, including alternation with other varroa pest control methods and products. While there have been some reports of possible resistance in other jurisdictions, resistance is not known to be a widespread problem at this time.

5.3.4 Contribution to Sustainability

By providing an additional mode of action for control of varroa mite, amitraz will contribute to the sustainable management of this pest.

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*].

During the review process, amitraz and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Amitraz does not meet all Track 1 criteria, and is not considered a Track 1 substance

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*[5]. The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[7], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act*

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

5 *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.*

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

7 DIR2006-02, PMRA Formulants Policy.

(substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade amitraz and the end-use product Apivar Strips 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

Key findings in the available toxicology studies included sedation, hypothermia, hypotension and bradycardia. The CNS effects of amitraz were not cumulative, but were shown to be a response to a daily dose. The toxicology database available for amitraz is lacking a number of studies, prompting the use of a database uncertainty factor. The data gaps were viewed in consideration of the low level of anticipated occupational exposure associated with handling of the product (as amitraz is embedded in plastic strips) and the mitigation measures to be put in place, as well as the limited contribution of amitraz residues in honey to the overall dietary risk. These gaps, which have been identified as part of the ongoing Agency re-evaluation, will have to be addressed as a condition of registration of the technical active ingredient used in the Apivar Strips.

The nature of the residue in plants (orchard crops) is adequately understood. The residue definition in plants, for enforcement and risk assessment purposes, is amitraz and the metabolites containing the 2,4-dimethylaniline moiety (N-(2,4-dimethylphenyl)-N′-methyl formamidine (BTS 27271) and N-(2,4-dimethylphenyl)formamide (BTS 27919)), expressed as amitraz equivalents. The proposed use of amitraz in beehives prior to honey production does not constitute unacceptable acute and chronic dietary risks (food only) to any segment of the population, including infants, children, adults and seniors. Sufficient honey residue data have been reviewed to recommend that the following maximum residue limit be specified for residues of amitraz equivalents in/on honey:

- 0.1 ppm

Applicators handling Apivar Strips and workers re-entering treated areas are not expected to be exposed to levels of amitraz that will result in unacceptable risk when Apivar Strips are used according to the proposed label directions. The Personal Protective Equipment on the product label is adequate to protect workers.

7.2 Environmental Risk

Since amitraz and the end-use product, Apivar Strips, will be used in beehives, the risk to non-target organisms is considered to be negligible, when used according to the label directions.

7.3 Value

Apivar Strips control varroa mite in honey bee colonies when applied at a rate of two strips per brood box for a period of 42 days. If it is observed the honey bee cluster has moved inside the beehive far from the strips, the strips should be repositioned strips into the bee cluster and left in place for 14 more days before removal. Strips must be removed after a maximum of 56 days, and must not be re-used.

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 Amitraz Technical and Apivar Strips, containing the technical grade active ingredient amitraz, to control the parasitic mite (*Varroa destructor*) on honey bees.

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. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below (by September 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.

Human Health

The following gaps, which have been identified as part of the ongoing Agency re-evaluation, will have to be addressed as a condition of registration of the technical active ingredient used in the Apivar Strips:

- DACO 4.5.3 – Prenatal developmental toxicity study in rabbits
- DACO 4.5.1 – Rat reproductive toxicity study
- DACO 4.5.14 – Developmental neurotoxicity study
- DACO 4.5.12 – Acute neurotoxicity*
- DACO 4.5.13 – 90-day neurotoxicity*

*As mentioned previously, these studies were recently submitted to the Agency, but were not evaluated within the context of this registration.

List of Abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CAF	composite assessment factor
CAS	Chemical Abstracts Service
cm	centimetres
CNS	central nervous system
DACO	data code
DPT	days post-treatment
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
ECD	electron capture detector
FDA	*Food and Drugs Act*
g	gram
GAP	good agricultural practices
GC	gas chromatography
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	n–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose 50%
LDPE	low density polyethylene
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
mg	milligram
mL	millilitre
mm	millimetre
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NAFTA	North American Free Trade Agreement
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operative Development
Pa	pascal
PCPA	*Pest Control Products Act*
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
PPE	personal protective equipment

ppm	parts per million
SD	standard deviation
SENSOR	Sentinel Event Notification System for Occupational Risk
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
uv	ultraviolet

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analytes	Method Type	LOQ	Reference
Honey	API002	Amitraz	HPLC-UV	0.010 ppm	PMRA # 2213007 ≡ 2212994
	API005	Amitraz + BTS 27271 + BTS 27919 as BTS 24868 (2,4-dimethylaniline)	GC-ECD	0.050 ppm	PMRA # 2213011 ≡ 2212996; 2216754
	TMP-20, Version 2		GC-MS	0.03 ppm	PMRA # 1937893-1937894; 2213013 ≡ 2212998; 2213016 ≡ 2213001

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Amitraz

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	90-day and 24-month dog dietary	NOAEL = 0.25 mg/kg bw/day CNS depression, decreased body temperature and pulse rate following a single dose.	1000
	ARfD = 0.0003 mg/kg bw		
Repeated dietary	90-day and 24-month dog dietary	NOAEL = 0.25 mg/kg bw/day CNS depression, decreased body temperature and pulse rate.	1000
	ADI = 0.0003 mg/kg bw		
Dermal – all durations[2]	90-day and 24-month dog dietary	NOAEL = 0.25 mg/kg bw/day CNS depression, decreased body temperature and pulse rate.	1000
Cancer	Overall, the weight of evidence supported the conclusion that carcinogenicity was not an endpoint of concern for risk assessment.		

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

[2]Since an oral NOAEL was selected, a dermal absorption factor of 13% was used in a route-to-route extrapolation.

Table 3 Integrated Food Residue Chemistry Summary

STORAGE STABILITY	**PMRA # 1937891; 2216754**
Residues of amitraz and metabolites BTS 27271, BTS 27919 and BTS 24868 (i.e. 2,4-dimethylaniline) were shown to be stable at -20°C for four months in honey. However, residues of amitraz were shown to be unstable at 25°C and 60% relative humidity in honey for one month.	
FIELD TRIALS ON HONEY (FRENCH TRIALS)	**PMRA # 1937886; 1937891; 2213007 ≡ 2212994; 2213011 ≡ 2212996; 2216754**

Ten beehives were treated in France during the spring of 1993 at one-fold the use pattern for Apivar Strips (i.e. two strips per hive). The Apivar strips were placed inside the hives for 42 consecutive days. Supers were added to each beehive on Day 42. Samples of honey were collected during treatment with the Apivar Strips (Day 21 and Day 42) and after removal of strips (Days 45, 49, 56, 65 and 70 or 3, 7, 14, 21 and 30 DPT). Residues of amitraz were all less than LOQ (< 10 ppb) at all sampling times (Days 21, 42, 45 and 49). Samples of honey collected on Days 56, 63 and 70 were not analysed as no measurable residues of amitraz were found in the other samples.

Eight beehives, in France, which had undergone a long-term use of Apivar Strips (i.e. two treatments per year for three consecutive years) were treated during the spring of 1998 at one-fold the use pattern for Apivar Strips (i.e. two strips per hive). The Apivar Strips were suspended between the frames of the hives for 42 consecutive days. Honey supers were added to five of the eight hives at Day 30 of treatment. Samples of honey were collected from each hive during treatment (Days 21 and 42) and after removal of strips (Days 43, 44, 45, 46, 48, 52 and 57 or 1, 2, 3, 4, 6, 10 and 15 DPT). Honey samples were analysed from only six of the eight treated hives (i.e. four with the honey supers and two without the honey supers) for residues of amitraz equivalents (i.e. amitraz + BTS 27271 + BTS 27919 analysed as total 2,4-dimethylaniline (or BTS 24868)) at each sampling interval. Residues of amitraz equivalents reached a maximum on Day 44 (i.e. 2 DPT) and generally decreased until the end of the sampling period on Day 57 (15 DPT).

Commodity	**Total Rate**	**Sampling Time (days)**	**Residue Levels (ppb)**					
			n	**Min.**	**Max.**	**Median**	**Mean**	**SD**
Honey (1993 trials)	2 Apivar strips per hive for 42 days	21	4	< 10	< 10	10	10	0
		42	4	< 10	< 10	10	10	0
		45	4	< 10	< 10	10	10	0
		49	4	< 10	< 10	10	10	0
Honey (1998 trials)		21	6	26	138	91	87	40
		42	6	67	117	75	81	19
		43	6	58	297	150	147	87
		44	6	72	471	142	225	180
		45	6	64	441	91	148	146
		46	6	61	186	89	103	44
		48	6	40	321	84	115	103
		52	6	59	229	84	102	64
		57	6	45	139	69	75	35

FIELD TRIALS ON HONEY (NEW ZEALAND TRIALS)	PMRA # 1937893-1937894; 2213016 ≡ 2213001

Two beehives were treated in New Zealand during the fall of 2001 at one-fold the use pattern for Apivar Strips (i.e. two strips per hive). The Apivar Strips were placed inside the hives (i.e. brood chambers) for 42 consecutive days. After removal of Apivar Strips, one honey super was placed on top of each hive for 142 days after which the honey supers were removed. Honey was collected from the honey supers 44 days later and analysed at the laboratory approximately 130 days later (or approximately 174 days after removal of honey supers from hives). Conditions of storage of honey supers were not reported. Honey samples were kept cool at 4°C until analysis. Residues of amitraz equivalents (i.e. amitraz + BTS 27271 + BTS 27919 analysed as total 2,4-dimethylaniline (or BTS 24868)) in honey were all less than LOQ (< 0.03 ppm) except for one sample which had measurable residues at 0.05 ppm. However, due to the known instability of amitraz residues at 25°C and 60% relative humidity in honey, there are concerns that residues of amitraz equivalents in the honey samples may have dissipated with time (i.e. approximately 174 days from removal of honey supers from hives to analysis of honey in the laboratory). In light of all these major limitations, this study was not considered further in establishing the MRL.

Commodity	Total Rate	Sampling Time (days)	Residue Levels (ppm)					
			n	Min.	Max.	Median	Mean	SD
Honey	2 Apivar strips per hive for 42 days	142	11	< 0.03	0.05	0.03	0.03	0.006

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops (pear, lemon)**	Amitraz and all the metabolites containing the 2,4-dimethylaniline moiety (N-(2,4-dimethylphenyl)-N′-methyl formamidine (BTS 27271) + N-(2,4-dimethylphenyl)formamide (BTS 27919)), expressed as amitraz equivalents
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops (pear, lemon)**	Amitraz and all the metabolites containing the 2,4-dimethylaniline moiety (N-(2,4-dimethylphenyl)-N′-methyl formamidine (BTS 27271) + N-(2,4-dimethylphenyl)formamide (BTS 27919)), expressed as amitraz equivalents
METABOLIC PROFILE IN DIVERSE CROPS	The metabolic profile is similar in pear and lemon.
ANIMAL STUDIES (Not assessed in the context of this submission)	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	N,N-bis(2,4-xylyliminomethyl)methylamine, including the metabolite N-(2,4-dimethylphenyl)-N'-methyl formamidine
RESIDUE DEFINITION FOR RISK ASSESSMENT	N,N-bis(2,4-xylyliminomethyl)methylamine, including the metabolite N-(2,4-dimethylphenyl)-N'-methyl formamidine
METABOLIC PROFILE IN ANIMALS	The metabolic profile was determined in cattle.
FAT SOLUBLE RESIDUE	Yes

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary risk **ADI = 0.00025 mg/kg bw**	**All infants < 1 year**	2.1	N/A
	Children 1–2 years	4.3	N/A
	Children 3–5 years	3.7	N/A
	Children 6–12 years	2.4	N/A
	Youth 13–19 years	1.6	N/A
	Adults 20–49 years	1.4	N/A
	Adults 50+ years	1.2	N/A
	Females 13–49 years old	1.2	N/A
	Total population	1.7	N/A
Refined acute dietary exposure analysis, 95th percentile **ARfD = 0.00025 mg/kg bw**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
	All infants < 1 year	19.14	N/A
	Children 1–2 years	25.42	N/A
	Children 3–5 years	21.63	N/A
	Children 6–12 years	14.29	N/A
	Youth 13–19 years	9.43	N/A
	Adults 20–49 years	9.27	N/A
	Adults 50+ years	7.85	N/A
	Females 13–49 years old	8.15	N/A
	Total population	11.82	N/A

Table 5 Nitrile Protective Properties – EPA Chemical Resistance Chart

Category of Liquid Pesticide Listed on Label	Type of Personal Protective Material							
	Barrier Laminate	Rubber [a]				Polyethylene	Polyvinyl Chloride [a]	Viton [a]
		Neoprene	Butyl	Nitrile	Natural			
A	high	high	high	high	high	high	high	high
B	high	slight	high	slight	none	slight	slight	slight
C	high	high	high	high	moderate	moderate	high	high
D	high	moderate	high	moderate	none	none	none	slight
E	high	high	slight	high	slight	none	moderate	high
F	high	moderate	high	high	slight	none	slight	high
G	high	slight	slight	slight	none	none	none	high
H	high	slight	slight	slight	none	none	none	high

[a] Recommendation based on personal protective equipment (PPE) at least 14mm or greater in thickness.

High: Highly chemical resistant. Clean or replace PPE at end of each day's work period. Rinse off pesticides at rest breaks.
Moderate: Moderately resistant to chemicals. Clean or replace PPE within an hour of contact.
Slight: Slightly chemical resistant. Clean or replace PPE within 10 minutes of contact.
None: No chemical resistance. Do not wear this type of material as PPE when contact is possible.

Nitrile is recognized as providing at least some protection against all categories of liquid pesticides. The protective barrier of nitrile has been proven to be particularly effective against penetration by pesticides in dried form. The chemical resistance of the above materials is in reference to liquid formulations, all of the chemical resistant materials in Table 6 are considered sufficient protection against dried forms of pesticides. Since the degree of effectiveness of the protective material is governed by the composition of the end use product, the USEPA category of the pesticide (A-H) is considered confidential proprietary information. As such, the determination of the most appropriate glove material required is carried out by the registrant.

Similarly, the PMRA can only recommend that the PPE should be chemical resistant gloves, with the onus on the registrant to determine the specific material most appropriate for the end use product and use scenario. In the instance of Apivar, the registrant has submitted a study which, although limited, does suggest that:

- amitraz is transferred to the hands/gloves during handling of the strips
- latex gloves provide less protection against amitraz penetration than nitrile, and therefore exposure may be reduced by the use of nitrile gloves

The existing literature indicates that nitrile is an acceptable example of material that provides effective protection against exposure to pesticides in dried form. Given the nature of the material of nitrile gloves, it is reasonable to conclude that beekeepers who wear nitrile gloves while handling Apivar Strips should minimize their exposure to amitraz. It is therefore recommended that the labels for Apivar should require the use of chemical resistant gloves, with nitrile listed as an appropriate example.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

There is no tolerance established in the US (40 CFR Part 180) in/on honey. Codex has established MRLs on some crops and commodities (Codex MRLs).

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Honey	0.1	0.2	Not Established
Honeycomb	Not Established	9	Not Established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
1647186	1999, AMZ-ATY-1 AgrEvo Canada Inc. Amitraz Technical Daco 2 Chemistry Applicants Name & Office Manufacturers Name & Office, Summary, Description of Starting Materials, etc. , DACO: 2.1,2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.1,2.13.2,2.13.3,2.13.4,
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1936871	1987, Amitraz: Physical and Chemical Characteristics - Colour, Physical State and Odour, DACO: 2.14.1,2.14.2,2.14.3 CBI
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1936873	1987, The Determination of the Density of Amitraz Technical, DACO: 2.14.6 CBI
1936874	1991, BTS 27919 (R000230): Determination of the pKa, DACO: 2.14.7 CBI
1936875	1989, Amitraz: Solubility in Organic Solvents at 25C, DACO: 2.14.8 CBI
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1936877	1987, Determination of the Vapour Pressure of Amitraz, DACO: 2.14.9 CBI
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1936880	1990, Amitraz: Determination of the Partition Coefficient Between n-Octanol and Water at 25, DACO: 2.14.11 CBI
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1937849	2009, Product Properties - Group A, DACO: 3.2.1,3.2.2,3.3.1,3.4.1 CBI
1937852	2009, Product Properties - Group B, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13, 3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9
2003696	2010, Response to clarification, DACO: 3.2.2 CBI
2003697	2010, Response to clarification, DACO: 3.4.1 CBI

2003811 2010, Validation Method, DACO: 3.4.1 CBI

2.0 Human and Animal Health

PMRA Document Number	Reference
2213006 ≡ 2212992	Apivar Safety in the Target Species (bees) and Residues in Bee Products - Appendix 6, DACO: 7.2.1,7.4.1
2213007≡ 2212994	Apivar Safety in the Target Species (bees) and Residues in Bee Products - Appendix 7, DACO: 7.2.1,7.4.1
2213009 ≡ 2212995	1993, Apivar Safety in the Target Species (bees) and Residues in Bee Products - Appendix 8, DACO: 7.2.1,7.4.1
2213011 ≡ 2212996*	1998, Maximal Residue Limits of Amitraz in Honey Consolidated Response to the List of Questions. EMEA/MRL/007/96-FINAL, DACO: 7.4.1
2216754	1998, Maximal Residue Limits of Amitraz in Honey Consolidated Response to the List of Questions. EMEA/MRL/007/96-FINAL, DACO: 7.4.1
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2213014 ≡ 2212999	Interim Laboratory Residue Report Amitraz in honey samples, DACO: 7.4.1
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1937886	1993, Apivar Safety in the Target Species (bees) and Residues in Bee Products, DACO: 7.2.1,7.4.1
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1937891	1998, Maximal Residue Limits of Amitraz in Honey Consolidated Response to the List of Questions, DACO: 7.4.1
1937893	2002, Amitraz Residues in honey and bees wax HortReseach Client Report No. 2003/119, Contract No. 17756; Project Number: 2532, DACO: 7.4.1
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* Incomplete report. Full report submitted under PMRA # 2216754.

3.0 Value

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2057784 Apivar Registration File – Existing Clinical Data, DACO: 10.2.3.4, 10.3, 10.3.2

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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Purdue, 2003. Pesticides and Personal Protective Equipment Selection, Use and Care. Purdue Pesticide Programs, Purdue University Cooperative Extension Service, West Lafayette, IN, 47907. March, 2003. PPP-38.

ii) Unpublished Information

1.0 Human and Animal Health

PMRA No.	Reference
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