United States Environmental Protection Agency (7508P)
Office of Prevention, Pesticides and Toxic Substances
July 2006

Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Amitraz

Approved By:

_____

Debra Edwards, Ph.D.
Director, Special Review and
Reregistration Division

_____

Date:

TABLE OF CONTENTS

I. Introduction

This is the Environmental Protection Agency's (hereafter referred to as EPA or the Agency) "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision for Amitraz." This document is also known as a Tolerance Reassessment Eligibility Decision, or TRED. EPA issued a Reregistration Eligibility Decision (RED) in 1995. This TRED reassesses the tolerances associated with amitraz, to ensure the pesticide meets the standards of FQPA.

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, requires the EPA to reassess all the pesticide tolerances that were in effect before the enactment of the FQPA by August 3, 2006. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and toddlers, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern, the tolerances are considered reassessed.

II. Background

Amitraz [N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide] is an insecticide/miticide, and was first registered in 1975. Currently, the U.S. technical registration Amitraz Insecticide 97% is held by Arysta Life Sciences. Amitraz formulations include emulsifiable and soluble concentrates.

There are registered uses on beef and dairy cattle, and hogs for tick, mite and lice management. The amitraz product with these uses is registered to Intervet, Inc., under the trade name Taktic® (EC 12.5%; EPA Reg No. 54382-3). Taktic® can be applied to cattle and swine via dip or low pressure hand wand. In addition, Taktic® may be used to treat the walls and surfaces of swine houses.

In addition, amitraz is used to treat ticks on dogs via amitraz-impregnated dog collars. Virbac currently holds the registrations for two dog collars: Preventic Tick Collar for Dogs and Puppies (2.4g amitraz; EPA Reg No. 2382-104) and Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (Preventic Plus) (3.8g amitraz; EPA Reg No. 2382-170). Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 includes a second active ingredient for flea control, pyriproxyfen.

III. Risk Summary

The Agency has completed the human health risk assessment of amitraz for purposes of issuing a TRED. These findings are presented in their entirety in the document *"Amitraz. Revised Human Health Risk Assessment for the Tolerance Reassessment Eligibility Decision (based on discussions of the Human Studies Review Board),"* dated July 26, 2006. For further details, refer to this assessment and other technical documents pertaining to the amitraz TRED in the amitraz docket (OPP-2004-0048) at www.regulations.gov.

Ecological and occupational assessments and risk management decisions for amitraz were presented in the 1995 RED. Therefore, no ecological or occupational assessment was conducted for the amitraz TRED. The RED and supporting documents are also accessible in the amitraz docket (OPP-2004-0048) at www.regulations.gov.

The Agency has evaluated the human health risks associated with all currently registered uses of amitraz and has determined that there is reasonable certainty that no harm to any population subgroup will result from aggregate non-occupational exposure to amitraz provided the registrant implements the mitigation measures identified in this document and the tolerance for residues in hops is revoked. Though some of the residential post-application scenarios currently exceed the Agency's Level of Concern (LOC), the mitigation measures outlined in this document address those risks.

A. Toxicity

The toxicological data and findings are presented fully in Section 3.3 of the document, *Amitraz. Revised Human Health Risk Assessment for the Tolerance Reassessment Eligibility Decision (based on discussions of the Human Studies Review Board)*, dated July 26, 2006.

The toxicological database for amitraz is incomplete, and there are several major data gaps relating to developmental, reproductive, and neurotoxic effects. As a result, submission of confirmatory data (a developmental study and a two-generation reproduction study) are required. However, sufficient toxicity data are available to assess human health risks, and potential susceptibility to children. Additionally, EPA has retained the 10X FQPA safety factor to account for database uncertainties.

Acute toxicity profile

On an acute basis, amitraz has moderate toxicity (Category II) by the dermal route, and it is slightly toxic (Category III) via the oral and inhalation routes of exposure. Further, it is not a skin or eye irritant, nor is it a skin sensitizer. Table 1 below illustrates the acute toxicity profile for amitraz.

Table 1. Acute Toxicity Profile of Amitraz Technical

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	00041539	LD_{50}: 531 mg/kg (M) 515 mg/kg (F)	III
870.1200 Acute dermal toxicity	00040862	LD_{50}: > 200 mg/kg	II
870.1300 Acute inhalation toxicity	00029963	LC_{50}: 2.4 mg/L	III
870.2400 Acute eye irritation	00040861	Non-irritating	IV

Table 1. Acute Toxicity Profile of Amitraz Technical			
Guideline No./ Study Type	**MRID No.**	**Results**	**Toxicity Category**
870.2500 Acute dermal irritation	00040862	Non-irritating	IV
870.2600 Skin sensitization	00029965	Not a sensitizer under conditions of study	N/A

Evidence of neurotoxicity

Based on available human and animal studies, humans are the most sensitive of any species tested, followed by the dog. Multiple species display evidence of neurotoxicity following exposure to amitraz. In the single dose human metabolism study, neurotoxic effects such as dry mouth, drowsiness, decreased temperature, and bradycardia were seen and persisted for up to 12 hours at the LOAEL of 0.25 mg/kg/day.

In both the subchronic and chronic oral studies in dogs, signs of central nervous system (CNS) depression were observed along with a decrease in pulse rate and hypothermia noted in the subchronic study. In both the subchronic and chronic oral studies and in the 21-day inhalation study in the rat, irritability, nervousness and/or excitability were observed. In the rabbit developmental toxicity study, clinical signs that were considered to be related to treatment included languor and polypnea. Sedation was also observed in rabbits in the repeated dose dermal study. The toxicological effects observed are significant; the clinical signs of neurotoxicity occur across species, sexes, and routes of administration.

Endpoint selection

In April 2006, the Human Studies Review Board (HSRB) reviewed the amitraz human single dose oral and human single dose metabolism studies. The HSRB found these studies to be scientifically and ethically sound, and concluded that "the results from the single oral dose study are informed by the human metabolism study, such that the single oral dose study is appropriate for developing a point of departure for acute dietary risk […]." An oral No Observable Adverse Effects Level (NOAEL) of 0.125 mg/kg/day (highest dose tested) was selected from the human oral study. A Lowest Observable Adverse Effects Level (LOAEL) of 0.25 mg/kg/day was selected from the human single oral dose metabolism study based on central nervous system (CNS) effects. The NOAEL was used to assess amitraz dietary risk and incidental oral, and dermal risk to toddlers exposed to a dog wearing an amitraz-impregnated collar.

An amitraz human dermal toxicity study was rejected by the HSRB because no effect or biological response was observed at any dose tested. As a result, EPA used the human oral study and an 8% dermal absorption factor (from a rat study, MRID: 42133501) to determine dermal risk from residential post-application exposure to the dog collar. Another human study, *Determination of the Quantity of Carbaryl Removed by Petting Dogs Wearing 16% Carbaryl Dog Collars* (MRID 45792201), was used to calculate percent transferable residues for the dog collars.

In the absence of an amitraz-specific study, the carbaryl study is considered the most appropriate study for the percent transferable residues of amitraz.

Rationale for using the acute human endpoint to assess all exposure durations

The CNS effects of amitraz do not appear to be cumulative, i.e., do not accumulate with increased duration. In the 90-day repeat dose dog study, the CNS effects appear early on (within 3 hours of dosing), rapidly end, and recur daily after dosing throughout the study. In the chronic (2-year) dog study, the CNS effects are seen following a single dose on the first 2 days of the study, with transient hypothermia detected in only one female throughout the rest of the study, indicative of some potential adaptation occurring at lower doses over longer periods of testing. The NOAEL and LOAEL for the 90-day and chronic dog studies are the same, also indicating that the CNS effects are not cumulative, but are a response to each daily dose that is likely reversible if exposure were to stop. Additionally, the single dose (acute) studies across several species show an onset of CNS effects within a few hours and recovery within a few hours to several days. For other effects, such as body weight changes and the tumors in the mouse study, those effects are likely to be cumulative. However, those effects occur at higher dose levels than the CNS depression. The human endpoint (0.125 mg/kg/day) will be protective of other longer term systemic effects as it is a lower dose level than the dose levels where these other systemic effects such as body weight change occur.

The effects of amitraz exposure appear early on, reverse rapidly, and recur after each daily dose, with some adaptation occurring after repeated daily doses. The human metabolism study showed neurotoxic effects shortly after dosing, which disappeared within 12 hours. Although the metabolism study was limited to two subjects, both human subjects exposed experienced clear CNS effects that were consistent with the animal data. This endpoint from the human oral and metabolism studies (CNS effects at 0.25 mg/kg; NOAEL of 0.125 mg/kg) is appropriate for assessing acute risks from exposures to amitraz. Because of the reversibility of the CNS effects, exposures of all durations can be regarded as a series of repeating one-day (acute) exposures. Therefore, the human oral endpoint is appropriate for assessing exposures to amitraz regardless of exposure duration.

Carcinogenicity

Amitraz is classified as "Suggestive Evidence of Carcinogenicity" based on the 2005 Office of Pesticide Programs cancer guidelines. No quantification is required.

Previously, amitraz had been classified as a Group C, possible human carcinogen with a Q* of 2.83 X 10^{-2} mg/kg/day (memo entitled *Peer Review of Amitraz*, dated January 3, 1991), based on significant dose-related positive trends in hepatocellular adenomas, carcinomas, and in combined adenomas and/or carcinomas in female mice. The Health Effects Division (HED) Cancer Assessment Review Committee (CARC) recently completed a re-evaluation of amitraz (memo entitled *Re-evaluation of the Carcinogenicity of Amitraz*, dated July 6, 2006), in light of the 2005 Cancer Guidelines and HED's 2003 interim guidance document (# G2003.02) for dose selection. Based on this re-evaluation, the CARC recommended that amitraz be classified as a non-quantifiable "Suggestive Evidence of Carcinogenicity" for the reasons stated below:

- There are no tumor responses in the rat (acceptable study with adequate dosing).

- The only tumor responses in the mouse are found at the highest dose tested (400 ppm). This dose would likely be considered excessive by today's criteria based on body weight changes as reported in the 1991 CARC report.

- The tumor responses found in the mouse were liver and lung, which are common tumors in the mouse.

- Amitraz is not mutagenic, however, it forms a mutagenic (*in vitro* evidence only) and carcinogenic metabolite, 2,4 dimethylaniline. The tumor response for 2,4 dimethylaniline is different from amitraz in that neither liver nor lung tumors are observed.

- Structural activity relations (SAR): Amitraz is structurally similar to chlordimeform, another formamidine pesticide, which has been reported to be carcinogenic in mice (e.g. hemangioendotheliomas in both sexes).

Although potential carcinogenicity cannot be totally dismissed because of the mutagenic/carcinogenic metabolite, the tumor data for amitraz are not very compelling for the reasons stated above. Thus, the Agency is regulating this chemical on the basis of an acute endpoint which is considered protective for all effects, regardless of exposure duration.

FQPA Safety Factor considerations

The FFDCA as amended by FQPA, directs the Agency to use an additional tenfold (10X) safety factor to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and toddlers.

Although a 2-generation reproduction study and two rabbit developmental toxicity studies are available, none is acceptable for regulatory purposes, due to deficiencies in either the study design and/or the studies themselves. Evidence for increased pre- and/or post-natal susceptibility to amitraz could not be definitively determined from these studies. However, there is no evidence (quantitative or qualitative) to suggest increased susceptibility following pre-natal exposure to rats. Although susceptibility could not be ascertained in rabbits, the results of the two unacceptable studies show that developmental effects occurred at doses higher than the doses that caused maternal toxicity.

A 10X FQPA safety factor for database uncertainty is required because of a lack of acceptable rabbit developmental toxicity and two-generation reproduction studies. This additional 10-fold uncertainty factor is considered protective of all population subgroups including infants and toddlers. For all exposure scenarios, a 10X uncertainty factor for intraspecies variation and a 10X FQPA safety factor for database uncertainty (total UF of 100)

were used. A 10X uncertainty factor for interspecies variation is not needed because the endpoint used to assess risk for all exposure scenarios was taken from a human oral study.

Table 2. Summary of Toxicological Dose and Endpoints for Risk Assessment		
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Study and Toxicological Effects**
Acute Dietary (General population including infants and toddlers)	NOAEL = 0.125 mg/kg/day **Acute RfD** = 0.0125 mg/kg **Acute PAD** = 0.00125 mg/kg **Uncertainty Factor (UF) =** 100[1]	2 combined human studies (a single oral dose and a single oral dose metabolism) MRID: 43283101 and 00160964 LOAEL = 0.25 mg/kg/day based on dry mouth, drowsiness, decreased temperature, decreased blood pressure and decreased heart rate.
Incidental Oral	NOAEL= 0.125 mg/kg/day **Residential** MOE = 100[1]	2 combined human studies (a single oral dose and a single oral dose metabolism) MRID: 43283101 and 00160964 LOAEL = 0.25 mg/kg/day (effects listed above)
Dermal	Oral NOAEL = 0.125 mg/kg/day Dermal Absorption Rate 8% MRID: 42133501 **Residential** MOE = 100[1]	2 combined human studies (a single oral dose and a single oral dose metabolism) MRID: 43283101 and 00160964 LOAEL = 0.25 mg/kg/day (effects listed above)
Inhalation	Oral NOAEL = 0.125 mg/kg/day Inhalation Absorption Rate = 100%) **Residential** MOE =100[1]	2 combined human studies (a single oral dose and a single oral dose metabolism) MRID: 43283101 and 00160964 LOAEL = 0.25 mg/kg/day (effects listed above)
Cancer (oral, dermal, inhalation)	Suggestive evidence of carcinogenicity	Forms a mutagenic (*in vitro* evidence only) and carcinogenic metabolite, 2,4 dimethylaniline.

[1] UF of 100 (10x for intraspecies variations and 10x FQPA Safety Factor for database uncertainty).

B. Dietary Risks from Food and Drinking Water

For a complete discussion of dietary risk, see Section 4.2 of the *Amitraz. Revised Human Health Risk Assessment for the Tolerance Reassessment Eligibility Decision (based on the discussions of the Human Studies Review Board),* dated July 26, 2006.

Dietary risk assessment incorporates both exposure to and toxicity of a given pesticide. Dietary risk is expressed as a percentage of a level of concern. The level of concern is the dose predicted to result in no unreasonable adverse health effects to any human population subgroup, including sensitive members of such population subgroups. This level of concern is referred to as the population adjusted dose (PAD), and reflects the Reference Dose, acute or chronic, adjusted to account for the FQPA safety factor (i.e., RfD/FQPA safety factor). In the case of amitraz the FQPA safety factor is 10X. A risk estimate that is less then 100% of the acute PAD (aPAD) does not exceed the Agency's level of concern.

Acute dietary risk (food only)

A probabilistic acute dietary risk assessment was conducted using DEEM-FCID™ (Version 1.30), which uses food consumption data from the United States Department of Agriculture's (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Anticipated residue values were based on data from animal metabolism (livestock dermal treatment) studies provided by the registrant and percent crop treated information from EPA. Food items included in the assessment were meat, milk, and related products (from the cattle and swine uses), hops and related products (import tolerance), and cottonseed products (import tolerance).

The acute PAD (aPAD) is the highest predicted dose to which a person could be exposed on any given day with no adverse health effects expected. Acute dietary risks from food are presented in Table 3 and are above the Agency's level of concern for the U.S. general population (502% of the aPAD) and the most highly exposed population subgroup adults 20-49 years old, (582% of the aPAD).

Table 3. Summary of Acute Dietary (Food Only) Exposure and Risk Estimates

Population Subgroup	99.9th Percentile	
	Exposure	% aPAD
U.S. Population:	0.006269	502
All infants:	0.00009	7
Children 1-2 yrs:	0.000349	28

Table 3. Summary of Acute Dietary (Food Only) Exposure and Risk Estimates		
Population Subgroup	**99.9th Percentile**	
	Exposure	**% aPAD**
Children 3-5 yrs:	0.000264	21
Children 6-12 yrs:	0.000137	11
Youth 13-19 yrs:	0.00509	407
Females 13-49 yrs:	0.004523	362
Adults 20-49 yrs:	0.00728	582
Adults 50+ yrs:	0.003788	303

Chronic dietary risk (food only)

A chronic dietary assessment was not performed because repeated exposures to amitraz may be considered a series of one-day (acute) exposures. The acute exposure assessment is therefore protective of chronic dietary exposure, as well as any repeat dietary exposures, regardless of duration.

Acute and chronic dietary risk (water only)

EPA initially calculated estimated environmental concentrations (EECs) for amitraz based on the swine use (see *Amitraz: Drinking Water Assessment for Tolerance Reassessment Eligibility Decision,* dated February, 11 2004 and *Revised Amitraz Drinking Water Assessment for Tolerance Reassessment Eligibility Decision (TRED),* dated May 1, 2004). However, EPA has since determined that cattle and swine are seldom treated outdoors. Since the only other use of amitraz is in impregnated dog collars, amitraz is not expected to enter water-bodies through currently registered uses. As a result, the Agency has determined that use of amitraz will not result in drinking water exposure, and a drinking water assessment is not needed.

C. Residential Handler Risks

For a complete discussion of the residential and post-application residential assumptions for modeling, and risks refer to the *"Revisions for 'Amendment to Amitraz: Revised Residential Exposure Assessment for the Reregistration Eligibility Decision,'" dated July 27, 2006.*

Although the Agency considers the residential handler scenario as having some potential exposure (i.e., an owner placing a treated pet collar on their dog), the most significant exposure of concern is for post-application scenarios as these exposures are of longer duration and may be significant for toddlers. Therefore, the primary residential exposure scenarios assessed for amitraz are post-application from the dog collar uses: dermal exposures of adults, and dermal and incidental oral exposures of toddlers. The dermal exposures result from hugging or petting a dog.

The post-application residential assessment is protective of the handler scenario; therefore, the handler scenario was not quantitatively assessed.

D. Residential Post-Application Risks

The term post-application describes exposures of individuals to pesticide residues that occur as a result of being in an environment that has been previously treated with a pesticide. Amitraz is registered to control ticks on dogs with impregnated pet collars. There is potential for dermal (adults and toddlers) and incidental oral (toddlers) exposures following daily contact with a treated dog. The dog collar is labeled to be effective for 90 days.

Risks based on neurotoxic effects were estimated for post-application dermal exposures of adults, and dermal and incidental oral exposures of toddlers. The Agency assessed post-application exposures of adults and toddlers to the Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1, maximum rate collar (3.8 g ai), and the Preventic Tick Collar for Dogs and Puppies, lower rate collar (2.4 g ai).

The assumptions and exposure factors which serve as the basis for estimating the dermal and incidental oral (hand-to-mouth) exposures from pet collars are derived from the memo, "*HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments*, dated December 19, 1997. The value for transferable active ingredient in the pet collar is derived from the study, "*Determination of the Quantity of Carbaryl Removed by Petting Dogs Wearing 16% Carbaryl Dog Collars"* (MRID 45792201). In the absence of an amitraz-specific study, the carbaryl study is considered the most appropriate study for the percent transferable residues of amitraz.

General assumptions and factors used in the residential post-application risk calculations include:

- exposure duration of 90 days (collar active lifetime)
- for the purposes of this risk assessment, two application rates were considered based on the two currently registered dog collars (2.4 g ai/ 27.5 g collar and 3.8 g ai/ 43 g collar);
- the dermal absorption factor is 8%;
- the treated surface area of a dog (30 lbs) is 5986 cm^2;
- transferable active ingredient from collar is assumed to be 2.6% (0.026), based on the carbaryl dog collar study.

MOE = NOAEL (mg/kg/day) / ADD (mg/kg/day), where

MOE = Margin of Exposure

NOAEL = No Observed Adverse Effect Level (0.125 mg/kg/day)

ADD = Average Daily Dose (0.00015, 0.000244 mg/kg/day)

Risk estimates for both sizes of collars are presented below in Tables 4a, 4b, 5a, and 5b.

Table 4a. Residential Post-Application Risk Estimates for the Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (3.8 g ai)

Resident	Exposure Scenario	ADD (mg/kg/day)	MOE
Toddler	Dermal (Pet Hug)	0.0018	**68**
Toddler	Oral (Hand-to-Mouth)	0.00024	511
Adult	Dermal (Pet Hug)	0.0012	106

Table 4b. Combined Residential Post-application Risk Estimates for Toddler Exposure to the Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (3.8 g ai)

Resident	Exposure Scenario	Combined MOE
Toddler	Dermal (Pet Hug) and Oral (Hand-to-Mouth)	**60**

Table 5a. Residential Post-application Risk Estimates for the Preventic Tick Collar for Dogs and Puppies (2.4 g ai) Collar

Resident	Exposure Scenario	ADD (mg/kg/day)	MOE
Toddler	Dermal (Pet Hug)	0.0012	108
Toddler	Oral (Hand-to-Mouth)	0.00015	833
Adult	Dermal (Pet Hug)	0.00077	167

Table 5b. Combined Residential Post-application Risk Estimates for Toddler Exposure to the Preventic Tick Collar for Dogs and Puppies (2.4 g ai) Collar

Resident	Exposure Scenario	Combined MOE
Toddler	Dermal (Pet Hug) and Oral (Hand-to-Mouth)	**97**

The Agency's LOC for amitraz dermal, and incidental oral (hand-to-mouth) exposures is 100 (i.e. an MOE less than 100 indicates a risk which exceeds the Agency's LOC) for residential scenarios. For the maximum rate collar, Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (3.8 g ai), adult dermal exposures resulted in an MOE of 106, which does not exceed the LOC. Toddler dermal exposure resulted in an MOE of 68, which exceeds the Agency's LOC. Toddler

incidental oral (hand-to-mouth) exposure resulted in an MOE of 511. *Combined* toddler dermal and oral exposures resulted in an MOE of 60, which also exceeds the Agency's LOC.

For the lower rate collar, Preventic Tick Collar for Dogs and Puppies (2.4 g ai), adult dermal exposures resulted in an MOE of 167, which does not exceed the LOC. Toddler dermal and incidental oral (hand-to-mouth) exposures resulted in MOEs of 108 and 833, respectively. *Combined* toddler dermal and oral exposures resulted in an MOE of 97.

E. Aggregate Risk

The aggregate risk assessment generally does not combine high-end (acute) dietary and residential exposures. In general, aggregate assessments combine average (chronic) dietary exposures with high-end residential exposures. However, a chronic dietary assessment was not performed since the acute dietary assessment is protective of any chronic exposures. In addition, in the case of amitraz, since residential exposure from the dog collar could not be characterized as high-end, residential exposures have been combined with acute (high-end) dietary exposures to calculate aggregate risk. Based on this approach, the resulting aggregate risk estimates are considered to be protective, and may overestimate risk.

For adults, acute dietary risks alone exceed the level of concern, up to a maximum of 582% of the aPAD for adults 20 to 49 years old. This dietary risk is driven by the contribution of hops; although hops is not a currently registered use, the technical registrant has proposed to maintain an import tolerance. Aggregating this dietary exposure with exposure from the dog collars would only further exceed the LOC.

For toddlers (and all population subgroups under the age of 13), acute dietary risks alone are below the Agency's LOC, with the most exposed subgroup (children 1-2) at 28% of the aPAD. However, post-application risk estimates to toddlers exceed the Agency's LOC, with a combined MOE from dermal and incidental oral exposures of 60 for the high rate, Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (3.8 g ai) collar. For the lower rate, Preventic Tick Collar for Dogs and Puppies (2.4 g ai) collar, the combined MOE is 97. If acute dietary exposure is added to post-application exposure, risk to toddlers further exceeds the level of concern, with an aggregate MOE of 76 (acute food plus dermal plus incidental oral risks).

F. Incidents

The following databases have been consulted for the poisoning incident data on the active ingredient amitraz: OPP Incident Data System, 1993-2000; Poison Control Centers, 1993-1998; California Data, 1982 - 2001; National Pesticide Information Center (NPIPC); NIOSH SENSOR.

From 1982 to 2001 there were 45 incidents reported. Symptoms from product handling (technical product or dog collar) included skin rashes, eye irritation, oral irritation, coughing, nausea, headache, sore throat and sweating. In one case of accidental ingestion, an eighteen month old child went into a coma with respiratory pauses. It was reported that the child recovered quickly. It appears that amitraz has been responsible for mainly minor effects, primarily involving skin or oral irritation.

On the list of the top 200 chemicals for which NPIC received calls from 1984-1991 inclusively, amitraz was ranked 194th with 11 incidents in humans reported and 9 in animals (mostly pets).

Among the seven states reporting over a period of 5 years (NIOSH SENSOR data), there were 4,221 reported cases of pesticide illness. Only one of these cases was related to amitraz. In 1999 in Texas, a 70 year old man ingested a couple of mouthfuls of amitraz by mistake. The primary symptom was esophageal burning which was considered to be moderately severe.

IV. Regulatory Determination

EPA has determined that after the measures outlined below are implemented, risk from exposure to amitraz fits within its own "risk cup." In other words, EPA is able to conclude that the tolerances for amitraz meet the FQPA safety standards. In reaching this determination, the Agency has considered the available information on the potential sensitivity of infants and toddlers, as well as chronic and acute food exposure. Results of this aggregate assessment indicate that the human health risks from these exposures are within acceptable levels provided that the mitigation measures described in this document are implemented. Consequently, the import tolerance for hops will be revoked, and the registrant has agreed to voluntarily cancel the heavier weight (3.8 g ai) collar as well as amend the lower weight (2.4 g ai) label to market two sizes of dog collars (an 18 inch collar with 1.8 g ai, and a 25 inch collar with 2.5 g ai) depending on the weight of the dog.

A. FQPA Assessment Supporting Tolerance Reassessment Decision

The Agency will propose that the current tolerance expression for amitraz be changed by removing the reference to certain metabolites. The tolerance expression should specify that the terminal residues of concern for enforcement purposes are amitraz and its metabolites containing the 2,4-dimethylaniline moiety.

Adequate residue data have been submitted to reassess the established tolerances for the following commodities: cattle, fat; cattle, meat byproducts; cattle, meat; hog, fat; hog, kidney; hog, liver; hog, meat byproducts; hog, meat; hop, dried cones; milk; and milk, fat. The available data indicate that the established tolerances for the meat, fat and meat byproducts of cattle, and hog liver and kidney, and milk fat may be reduced. The tolerances for hog fat, hog meat byproducts (except liver and kidney), hog meat, and milk are reassessed at the same level.

Arysta Life Sciences has requested to retain an import tolerance for cotton, undelinted seed. However, Arysta must submit information about the use pattern in foreign countries, and residue data from those countries to support the import tolerance.

In addition, the following tolerances for animal commodities will be maintained due to amitraz use on cattle and swine: cattle fat, cattle meat byproducts, cattle meat, hog fat, hog kidney, hog liver, hog meat byproducts, hog meat, milk, and milk fat.

All registered uses of amitraz in beehives have been cancelled, along with the voluntary cancellation of amitraz use on cotton and pears in the U.S (5/3/06). Therefore, the established U.S. (Section 3) tolerances for the following commodities should be revoked: honey; honeycomb; and pear. Certain tolerances were based on cotton as a livestock feed item; however there will no longer be any dietary exposure of livestock to amitraz through feed. Therefore, the established tolerances for the following animal commodities should be revoked: egg; goat, fat; goat, meat byproducts; goat, meat; poultry fat/meat; poultry meat byproducts; sheep, fat; sheep, meat byproducts; and sheep, meat. The tolerance for hops will also be proposed for revocation, based on dietary risk.

Codex Harmonization

Several maximum residue limits (MRLs) for amitraz have been established by Codex in various commodities. The Codex MRLs are currently expressed as the sum of amitraz and N-(2,4-dimethylphenyl)-N'-methylformamidine calculated as N-(2,4-dimethylphenyl)-N'-methylformamidine.

The Codex tolerance expression is somewhat different from the U.S. tolerance expression. The Codex expression is the sum of amitraz plus metabolite BTS-27271, calculated as BTS-27271. The U.S. expression is the sum of amitraz and its metabolites BTS-27271 and BTS-27919, both calculated as the parent compound. The enforcement methods for amitraz tolerances in the U.S. (Methods I and II of PAM Vol. II) consist of hydrolysis of all metabolites containing the 2,4-DMA moiety to 2,4-DMA and determination using gas chromatography with electron capture detection. The enforcement method under the Codex system involves treatment of the RAC with acidic methanol to convert the parent compound to metabolite BTS-27271, followed by extraction, cleanup, and determination of BTS-27271 using gas liquid chromatography with flame ionization detection. Presently, compatibility between the Codex MRL and U.S. tolerance cannot be achieved due to the differences between the tolerance definitions and analytical enforcement methods.

The current U.S. tolerances and Codex MRLs are identical in magnitude for cattle and pig meat. However, the reassessed tolerances in the U.S. are lower than Codex MRLs with the exception of milk which are the same. There are several Codex MRLs for which there are no U.S. tolerances. Refer to Table 6 below for detail on the tolerance reassessment.

Table 6. Tolerance Reassessment Summary for Amitraz

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comments/ Correct Commodity Definition
Tolerances under 180.287 (a)			
Cattle, fat	0.1	0.04	
Cattle, meat byproducts	0.3	0.2	

Table 6. Tolerance Reassessment Summary for Amitraz			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comments/ Correct Commodity Definition
Cattle, meat	0.05	0.02	
Cotton, undelinted seed	1	1	The registrant has cancelled use of amitraz on cotton in the US. The tolerance should be retained for imported cottonseed. The following footnote should be added to the tolerance listing for cottonseed: "No U.S. registrations as of 5/3/06."
Egg	0.01	Revoke	Amitraz use on cotton (feed item) has been cancelled; there is no need for poultry commodity tolerances.
Goat, fat	0	Revoke	Amtiraz use on cotton (feed item) has been cancelled; there is no need for goat commodity tolerances.
Goat, meat byproducts	0		
Goat, meat	0		
Hog, fat	0.1	0.1	
Hog, kidney	0.2	0.1	
Hog, liver	0.2	0.1	
Hog, meat byproducts	0.3	0.3	Hog, meat byproducts, except kidney and liver
Hog, meat	0.05	0.05	
Honey	1	Revoke	There are no longer any registered uses of amitraz in beehives.
Honeycomb	6	Revoke	
Hop, dried cones	60	Revoke	The existing tolerance for hops will be proposed for revocation based on dietary risk.
Milk	0.03	0.03	
Milk, fat	0.3	0.2	

Table 6. Tolerance Reassessment Summary for Amitraz			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comments/ Correct Commodity Definition
Pear	3	Revoke	The registrant has cancelled the use of amitraz on pears.
Poultry, fat/meat	0.01	Revoke	Amitraz use on cotton (feed item) has been cancelled; there is no need for poultry commodity tolerances.
Poultry, meat byproducts	0.05	Revoke	
Sheep, fat	0	Revoke	Amitraz use on cotton (feed item) has been cancelled; there is no need for sheep commodity tolerances.
Sheep, meat byproducts	0	Revoke	
Sheep, meat	0	Revoke	

B. Cumulative Risk

FQPA requires that EPA consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency considers other substances because low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect, as would a higher level of exposure to any of the substances individually. Risks summarized in this document are those that result only from the use of amitraz. The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to amitraz and any other substances. In addition, amitraz does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U.S. Therefore, for the purposes of tolerance reassessment, EPA has not assumed that amitraz shares a common mechanism of toxicity with other compounds.

C. Endocrine Disruptor Effects

EPA is required under the FFDCA as amended by FQPA, to develop a screening program to determine whether certain substances "may have an effect in humans that is similar to endocrine effects." In the available toxicity studies on amitraz, there was no estrogen or androgen mediated toxicity. When additional appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disruption Screening Program (EDSP) have been developed, amitraz may be subjected to further screening and/or testing to better characterize potential effects related to endocrine disruption.

D. Risk Mitigation

The tolerance for hops will be proposed for revocation, based on dietary risks to youth and adults. This will reduce the dietary risk to the general population to 5.1% of the aPAD. In addition, risks to the most highly exposed population subgroup (children 1-2 years old) will be 28% of the aPAD.

Virbac has requested voluntary cancellation for the heavier weight, Amitraz-Pyriproxyfen Flea and Tick Collar for Dogs #1 (3.8 g ai, EPA Reg. No: 1238-170).

The lower weight, Preventic Tick Collar for Dogs and Puppies (2.4 g ai) collar (EPA Reg. No: 2382-104) shall be amended, contingent upon the following mitigation measures listed below.

Virbac has agreed to produce two different dog collars depending upon the weight of the dog: an eighteen inch collar (1.8 g ai) for dogs weighing less than 60 pounds, and a twenty-five inch collar (2.5 g ai) for dogs 60 pounds and above. As a result of Virbac marketing the two dog collars, the aggregate toddler MOE for the eighteen inch collar is 95, and the aggregate toddler MOE for the twenty-five inch collar is 101. Virbac has submitted a letter committing to amend the Preventic Tick Collar for Dogs and Puppies label (EPA Reg. No. 2382-104) to reflect these changes.

The Agency considers the aggregate MOE of 95 sufficiently protective of potential risks to toddlers due to several conservative inputs to the risk estimate. This MOE was calculated using an oral toxicity study with an 8% dermal absorption factor from a rat study (for route-to-route extrapolation) to assess dermal risk. The Agency prefers to use toxicological endpoints from route specific, dermal studies for dermal risk assessments because they provide more appropriate estimates of risk associated with dermal exposures. The use of a non-route specific endpoint along with the dermal absorption factor may be considered conservative. Furthermore, the aggregate assessment combined the (high-end) acute dietary exposure with the residential post-application exposure.

E. Data Requirements

<u>Toxicology</u>

870.3700: Prenatal developmental toxicity study in rabbits.

870.3800: A two-generation reproduction study which should be modified to include the following:

-Due to the concern for the lack of stability of the test material in the diet, treatment should be via oral (gavage) administration.

-The potential for neurotoxicity in the developing fetuses should be evaluated according to the OPPTS Guideline 870.6300.

-The potential for neurotoxicity in adults should be evaluated according to the OPPTS Guideline 870.6200.

Product Chemistry

All pertinent product chemistry data requirements are satisfied for the only registered technical product, the 97% T, except that data are required concerning the UV/visible absorption of the PAI (OPPTS 830.7050). Provided that the registrant submits the required data for the amitraz technical product, and either certifies that the suppliers of beginning materials and the manufacturing process have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, the Agency has no objections to the reregistration of amitraz with respect to product chemistry data requirements.

Residue Chemistry

The registered uses on cotton and pears have been cancelled. Consequently, there are no residue chemistry deficiencies.