UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

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MEMORANDUM:

SUBJECT: Residential Exposure Assessment for the Tolerance Reassessment Eligibility
             Decision (**TRED**) Document For **Amitraz**

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        This document describes the residential exposure and risk assessment for the EPA
Registered insecticide amitraz.

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1.0   EXECUTIVE SUMMARY

1.1   Background and Purpose

EPA published a Registration Eligibility Document (RED) for amitraz in March, 1995. In the RED, EPA assessed occupational applicator exposure to amitraz for handlers and applicators as well as post-application occupational exposure resulting from agricultural uses registered for amitraz at that time including cotton and pears. Residential uses were not assessed for the RED.

This document addresses the exposures and risks associated with the residential uses of amitraz only. A regulatory review of residential exposure to amitraz [N-methylbis(2,4-xylyliminomethyl)amine] was conducted for this TRED because there is potential exposure to non-occupational (residential) handlers (applicators) during handling and application of pet collars which have been impregnated with the active ingredient amitraz to dogs for the prevention of canine ticks and fleas. There is also potential residential post-application exposure to amitraz for the duration of the use of the collar on the dog. Product labeling specifies only the use of these collars on dogs.

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered <u>and</u> (2) there is potential exposure to handlers (mixers, loaders, applicators) during use or to persons entering treated sites after application is complete. Amitraz toxicological endpoints were selected for short- and intermediate-term exposures, no chronic exposure scenarios are thought to exist for amitraz. In addition, amitraz is classified as a Group C possible human carcinogen and it has a Q_1*of 2.83 x 10^{-2}. Based on the potential for exposure, risk assessments are required for residential handlers and in particular for residential postapplication scenarios.

1.2   Summary of Use Patterns and Formulations and Target Pests

As of the date of this document, pesticide products containing amitraz are intended for both occupational (i.e., cattle dipping) and residential uses (i.e., dog collars). There are two Federally registered dog collar products impregnated with amitraz, manufactured in France for Virbac of Fort Worth, Texas; EPA Reg. Nos. 2382-104 and 2382-170. Each of these collars contain 9.0% amitraz as the active ingredient. EPA Reg. No. 2382-170 also contains 0.5% Pyripoxyfen as an active ingredient and each product label contains the language "For Veterinary Use Only". According to product labeling, the collars kill ticks, fleas and flea eggs on a dog for three months. For the purposes of this assessment, HED used EPA Reg. No. 2382-170* to estimate potential residential exposure to the insecticide amitraz via it's use in impregnated pet collars on domestic dogs for the prevention of fleas and ticks.

Amitraz is registered insecticide; for residential purposes the targeted pests are ticks and fleas on dogs.

1.3   Registered Use Sites, and Frequency

Amitraz is registered as an insecticide/miticide for the control of ticks, mange mites, lice on domestic livestock such as dairy and beef cattle and swine. For the purposes of this document, HED is concerned with use of amitraz on dog collars for the control of fleas and ticks on the dog. According to the labeling associated with this product, the collars prevent ticks for 3 months, therefore, the collars can be applied 4 times per year.

1.4   Hazard Identification

The March 17th, 2004 report of the Hazard Identification Assessment Review Committee (HIARC) for amitraz identified toxicological endpoints of concern for amitraz. All calculations completed in this document are based on the most current toxicity information available for amitraz. Endpoints used to complete this assessment are summarized in Table 2.
For short and intermediate term dermal and inhalation exposure, a NOAEL of 0.25 mg/kg/day with a LOAEL of 1.0 mg/kg/day, from a chronic oral study based on CNS depression during the first two days of dosing was selected. A dermal absorption factor of 8.0% is applied for dermal exposure for route to route extrapolation.

The HIARC determined that a Margin Of Exposure (MOE) of 1000, based on an uncertainty factor of 100X for traditional inter and intra species variation and an additional 10X for lack of acceptable developmental and reproductive data is adequate for residential exposures.

On October 31, 1990, the Cancer Peer Review Committee classified Amitraz as a Group C - possible human carcinogen, and recommended that, for the purpose of risk characterization, a low dose extrapolation model be applied to the experimental animal tumor data for quantification of human risk (Q_1^*). A Q1* based upon female rat liver (carcinoma and/or adenoma) tumor rates was generated using mg/kg b.w.$^{2/3}$'s/day cross species scaling factor. The revised unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Amitraz based upon female mouse liver combined adenoma and carcinoma tumor rates is 2.83×10^{-2} in human equivalents (converted from animals to humans by use of the $3/4$'s scaling factor - Tox_Risk program, Version 5.31, K. Crump, 2000). The dose levels used from the 107-week dietary study were 0, 25, 100, and 400 ppm of Amitraz.

1.5   Residential Exposure & Risk Estimates

Although HED considers the residential handler scenario as having potential exposure risk, the most significant exposure of concern is for post-application scenarios as these exposures are of longer duration and potentially affect more sensitive residents including infants and children. Therefore this document primarily focuses on residential post-application exposures only, and does not address residential handlers.

All post-application scenarios resulted in MOEs which exceed HED's level of concern. Post-application dermal exposure estimates for toddlers indicate MOEs of 22. Incidental oral post-application exposure to toddlers from amitraz (via hand to mouth), from such activities hugging the dog has an MOE of 65. For adults, dermal post-application exposure estimates for amitraz via such an activity of the hugging the dog indicate MOEs of 32.

Post-application cancer risk estimates for adults range from 2.8^{-5} to 5.6^{-5}, and exceed HED's level of concern

1.4.1 Acute Toxicity Categories

Table 1. represents the acute toxicity categories outlined in the hazard identification document for amitraz.

Table 1. Acute Toxicity of Amitraz				
Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	00041539	LD_{50}: 531 mg/kg (M) 515 mg/kg (F)	III
81-2	Acute Dermal	00040862	LD_{50}: > 200 mg/kg	II
81-3	Acute Inhalation	00029963	LC_{50}: 2.4 mg/L	III
81-4	Primary Eye Irritation	00040861	Non-irritating	IV
81-5	Primary Skin Irritation	00040862	Non-irritating	IV
81-6	Dermal Sensitization - G. Pigs	00029965	Not a sensitizer under conditions of study	N/A

1.4.2 Toxicological Endpoints

The March 17, 2004 report of the Hazard Identification Assessment Review Committee (HIARC) identified toxicological endpoints of concern for amitraz. All calculations completed in this document are based on the most current toxicity information available for amitraz. Endpoints used to complete this assessment are presented below in Table 2.

Table 2. Summary of Toxicological Dose and Endpoints for Amitraz			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General population including infants and children)	NOAEL = 0.25 mg/kg/day UF = 1000 **Acute RfD =** 0.00025 mg/kg/day	FQPA SF = 1 aPAD = acute RfD FQPA SF = 0.00025 mg/kg/day	Chronic oral study in the dog (capsule)_ LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Chronic Dietary (All populations)	NOAEL= 0.25 mg/kg/day UF = 1000 **Chronic RfD =** 0.00025 mg/kg/day	FQPA SF = 1 **cPAD =** chronic RfD FQPA SF = 0.00025 mg/kg/day	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Short- and Intermediate - Term Incidental Oral (1-30 days and 1-6 months)	NOAEL= 0.25 mg/kg/day	**Residential** LOC for MOE = 1000 **Occupational** = NA	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Dermal (All Durations)	Oral study NOAEL= 0.25 mg/kg/day (dermal absorption rate 8%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Inhalation (All Durations)	Oral study NOAEL= 0.25 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 100	Chronic oral study in the dog (capsule) LOAEL = 1.0 mg/kg/day based on CNS depression during the first two days of dosing.
Cancer (oral, dermal, inhalation)	$Q_1^* = 2.83 \times 10^{-2}$	N/A	Combined hepatocellular adenomas and carcinomas in female mice.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

2.0 Incident Reports

Animal incident reports for currently registered amitraz products from 1992 through 2003 were reviewed. In general, there have been few reports of amitraz toxicity in recent years.

The most notable incidents were reports of dogs pulling a tick collar off another dog and ingesting the collar. This has resulted in serious toxicity including bradycardia and depression, resulting in emergency veterinary care. Yohimbine is a specific antidote for amitraz toxicity in dogs.

There were fewer reports for toxicity in dogs while wearing tick collars, including weakness, ataxia, vomiting, or seizures. These reports were unverified.

There were 3 reports of abortions or stillbirths in pigs from 1992 - 1996. These reports were unverified. There were several reports of misuse of cattle/pig formulation on horses or dogs resulting in death.

A review of human incident data is pending and is not available at this time.

3.0   Residential Exposure and Risk Estimates

One applicator/handler scenario and three post-application scenarios were identified and used as a basis for HED's residential exposure estimates. Intermediate-term dermal and oral MOEs were calculated for this assessment. The scenarios identified and examined in this TRED:

- Adult residential handler (applicator), the person unwraps the collar and places it on the dog - dermal.

- Toddler - dermal (post-application)

- Toddler - incidental oral (post-application)

-Adult - dermal (post-application)

A target MOE of 1000 is considered adequate for Intermediate-term residential exposure via dermal routes.

In this TRED HED estimated dermal postapplication cancer risks for adults. (Cancer risk estimates $< 1 \times 10^{-6}$ are not of concern.)

Although HED considers the residential handler scenario as having potential exposure risk, the most significant exposure of concern is for post-application scenarios as these exposures are of longer duration and potentially affect more sensitive residents including infants and children.   Therefore this document primarily focuses on residential post-application exposures only, and does not address residential handlers.

3.1   Residential Exposures

As stated above, HED considers post-application exposure to residents, including children, to be the primary concern of potential exposure to amitraz via this registered use. Residents (adults and children) can be exposed to amitraz via it's use in a dog collar. Once the collar is applied the amitraz residues potentially are spread throughout the surface area of the dog exposing residents to these residues by dermal contact with the treated dog. Therefore, HED assessed residential post-application exposure to amitraz via it's presence in the collar on the dog and thereby potentially spreading throughout the fur of the dog. Identifying toddlers as the most sensitive of potentially exposed residential populations, HED conducted two assessments based on likely activities for a toddler: hugging the dog, and incidental oral ingestion through hand-to-mouth actions after hugging the dog.   An additional assessment for adults, based on hugging the dog was also conducted.

Since the vapor pressure for amitraz = 3.4 x 10^{-4} Pa at 25 °C, and as such is considered moderate, HED feels that there is potential inhalation exposure as a certain amount of off-gassing is expected to occur. However, HED did not address inhalation exposures as the dermal exposures exceeded HED's levels of concern and data concerning inhalation exposures via pet collars was not available.

3.2   Residential Exposure & Risk Estimates: Post-application (non-cancer)

HED considered the postapplication exposure in the residential environment to amitraz from the use of amitraz treated dog collars. For this home use scenario, residential risks attributable to non-dietary ingestion and dermal exposure were assessed for toddlers and adults after contact with treated pets based on the guidance provided in the *SOPs for Residential Exposure Assessment* (U.S. EPA, 1997, 1999)[1], and also *Exposure to Children and Adults to Transferable Chlorpyrifos Residues from Dogs Treated with Flea Control Collars (Boone, J.s. et al. 2001)*[2]. *Boone, J. et al.* also served as a source of surrogate data for transferrable pesticide residues from dog fur. To this date, HED has received no chemical specific data concerning this use pattern from the amitraz registrant(s).

The **dermal** contact scenario is based on the use of the transferable residue data normalized by the sampling area and by the amount of active ingredient in the collar (in units of μg/cm2/gram ai). A linear relationship between the active ingredient and the residues is assumed. The transferable residues are then extrapolated to the surface area of a "hug" (i.e., 1875 cm2 - toddlers). No data are available to determine the frequency of "hugs". However, the

transferability of the residues from the 5 minute vigorous petting routine in the study is a reasonable surrogate for the transferability of a days worth of "hugs" of a dog by a child.

No defensible rationale is available to determine an "area" weighted mean of the residues from the neck with collar, neck without collar, and back. Therefore, to avoid unnecessary postulating on percentage of each area of the dog hugged, a simplistic use of proportions (i.e., thirds) of the three monitored areas of the dog has been selected. That is, residues measured on the neck of the dog with collar, without collar, and the back of the dog from 1 to 168 days after treatment (DAT) were weighted by 1/3 each, summed and averaged. The initial 4 - hour measurement was not included in the time-weighted average (TWA). The surrogate value to be used as the dermal TWA transferable residue of amitraz is 0.29 μg/cm2/gram ai (or 0.29 μg/cm2/gram ai x 1875 cm2 hug = 540 μg/gram ai). This represents a unit daily exposure for an intermediate to chronic duration.

The traditional estimates of **hand-to-mouth** exposure are based on estimates of residues on a child's hand, the frequency of which the hand goes in the mouth, and the duration the child is in contact with the treated surface. While duration estimates are available for a child playing outside (e.g., on lawn), no estimates of contact time are available for pets. Therefore, it is recommended for the pet collar scenario that the oral hand-to-mouth route be based on the amount of residue transferred from the neck with the collar (highest of the three areas monitored). The residues available from the 5 minute vigorous petting routine is believed to be a conservative estimate of the amount of residue available for ingestion for a day. It is believed to be a conservative estimate because it represents 7.5 seconds of petting *prior to each of 40 hand-to-mouth events* (i.e., (5 minutes sampling x 60 seconds/minute) / (2 hours per day x 20 hand-to-mouth events per hour)). The two hour duration is arbitrary, only presented as a point of reference. Furthermore, the biological monitoring data, even though inconclusive for regulatory decisions, do not indicate any dose levels higher than that estimated by the residue method. However, more research is needed in this area of pet collar exposure.

Labels for the impregnated collars states efficacy for three months, therefore, the maximum application to the dog would be four times/year. The net weight of the collar is 42g with 9.0% amitraz yields 3.8 g active ingredient (ai) in the collar (EPA Reg. No. 2382-170*).

A series of assumptions and exposure factors served as the basis for completing intermediate-term homeowner non-cancer, post-application risk assessments. Each assumption is detailed below:

– The average body weight of an adult used in all assessments is 70 kg. For toddler assessments, 15 kg weight was used as directed by SOPs for Residential Exposure Assessment.

– The amount of available pesticide on the dog's fur as a result of wearing the treated collar on a Time Weighted Average (TWA) = 0.29 ug/cm^2 /g ai as a transferable unit of residue.[2]

- In calculating potential post-application dermal exposure for such dog related activities as hugging, HED used the following surface areas (the dermal contact area) of a hug to a dog: toddler = 1875 cm^2; adults = 5625 cm^2.[1]

Thus the equation for Estimated Absorbed Dermal Dose (EADD) exposure postapplication for residents becomes:

EADD = Transferable residue x fraction transferred x application rate x dermal absorption/ body weight.

Thus for toddlers:

- EADD (mg/kg/day) = (0.29 ug/cm^2 /g ai) x 0.001 mg/ug x 1875 cm^2 x (3.8 g ai Amitraz pet collar) x Dermal Absorption(DA*)/ 15 kg.

And, the equation for Estimated Absorbed Dermal Dose (EADD) exposure postapplication for adults becomes:

- EADD (mg/kg/day) = (0.29 ug/cm^2 /g ai) x 0.001 mg/ug x 5625 cm^2 x (3.8 g ai Amitraz pet collar) x Dermal Absorption(DA*)/ 70 kg.

Toddler Hand-to-Mouth exposure from Residential Exposures Assessment SOPs was calculated as follows:

Dose (mg/kg/day) = (Dog's neck with collar of 1.5 ug/cm^2 /gram ai x 3.8 gm ai Amitraz/collar x 0.001mg/ug x 0.5 saliva extraction efficiency x 20 cm^2 palmar surface area of fingers into mouth)*/15 kg body weight.

> *Where: *Neck with collar of 1.5 μg/cm2/gram ai = (TWA 340 μg neck with collar/88 cm2 child's palm) / 2.54 gram ai in chlorpyrifos test collar. [child's palm surface area is 350 cm2 for both hands; therefore, 175 cm2 represents one hand and 88 cm2 represents the palm of one hand]. Using the child's hand assumes that the sampling area of the dog (258 cm2) would yield the same amount of transferable residue regardless if the hand used to pet the dog was an adult's hand (as monitored in the study) or a smaller hand of a child.*

MOE = NOAEL (0.25 mg/kg/day)/Estimated Absorbed Daily Dose (EADD)

*Dermal Absorption = 8.0%.

Table 3. represents the calculated residential MOEs for various activities as related to amitraz treated dog collars.

Table 3.   Residential Post-Application Intermediate-Term Risk Estimates

Resident	Dog Related Activity	EADD * (mg/kg/day)	MOE

Toddler	hugging	0.011	22
Toddler	hand to mouth	0.0038	65
Adult	hugging	0.007	35

* EADD = Estimated Absorbed Dermal Dose

MOE = NOAEL (0.25 mg/kg/day)/Estimated Absorbed Dermal Dose

3.3   Residential Carcinogenic Risk Estimates: Post-Application

To assess carcinogenic risk for amitraz exposure through the examined use, HED selected hugging the animal as the most likely or common vector of concern for the potential exposure over the course of a lifetime. HED therefore used the same Estimated Absorbed Dermal Dose (EADD) described above in the non-cancer risk estimates and extrapolated over a 70 year lifetime, using high and low end lifetime expectations for the dog (10 and 20 years) and employing the following assumptions:

−   The dog will wear the treated collar throughout it's lifetime (estimated for 10 and 20 years).

−   A dog owner will hug his or her dog once a day over the lifetime of the dog.

−   As in the case of post-application non-cancer estimates, the Time Weighted Average (TWA) of available pesticide on the dog's fur is constant.

Hence, the equation for carcinogenic risk estimate over a lifetime for the examined use, utilizing Q_1* method becomes:

-    LADD (Lifetime Average Daily Dose) = (EADD) x (number hugs/year) x (number of years of pet ownership/ 70 year lifetime).

−   Carcinogenic Risk = (LADD) x (Q_1*), where Q_1* = 2.83 x 10E-2 (mg/kg/day E-1) (Memorandum February 11, 2004).

The following table represents the numerical risk estimation for carcinogenic residential handler risk associated with application of pet collars impregnated with amitraz.

Table 4 : Residential Post-Application Carcinogenic Risk Assessment Over a Lifetime

Estimated Lifetime of Treated Dog	Estimated Absorbed Daily Dose[a] (mg/kg/day)	Amortization	LADD[b] (mg/kg/day)	Carcinogenic Risk[c] (mg/kg/day)

		# of Days Exposed /Year	Years of lifetime (70 yrs)		
10 years	0.007	365	10/70	0. 001	2.8 e^{-5}
20 years	0.007	365	20/70	0.002	5.6 e^{-5}

a.   Estimated Absorbed Daily Dermal Dose is from Table 3.

b.   LADD (lifetime average daily dose) = (absorbed dermal dose) x (number of days exposed/ 365days) x (number of years of pet ownership/70 year lifetime)

c.   Carcinogenic Risk = (LADD)*(Q_1^*), where the Q_1^*, is 2.83 x 10E-2 $(mg/kg/day)^{-1}$

References

1. U.S. EPA (1999) Overview of Issues Related to The Standard Operating Procedures For Residential Exposure Assessment, Health Effects Division of the Office of Pesticide Programs [Presented to the FIFRA SAP in September 1999]

U.S. EPA (1997) Standard Operating Procedures for Residential Exposure Assessment, Health Effects Division of the Office of Pesticide Programs

2. Boone, J.S.: Chambers, J.E.; and Tyler, J.W., (2001), Transferable Residues From Dog Fur and Plasma Cholinesterase Inhibition in Dogs Treated with a Flea Control Dip Containing Chlorpyrifos, Environmental Health Perspectives, Volume 109, Number 11, November 2001.

Boone, J.S.: Chambers, J.E.; and Tyler, J.W., (2001) Exposure to Children and Adults to Transferrable Residues Chlorpyrifos from Dogs Treated with Flea Control Collars, Presented at International Society of Exposure Analysis Meeting, 2001.

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