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MEMORANDUM

SUBJECT: Revisions for "Amendment to "Amitraz: Revised Residential Exposure Assessment for the Reregistration Eligibility Decision (11/19/2004, D310631)": (D318939)" DP Barcode: 310229, PC Code: 106201

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This document serves as a revision to the previous document, "Amendment to "Amitraz: Revised Residential Exposure Assessment for the Reregistration Eligibility Decision (D310631)": (D318939)." The purpose of this update is to adjust the risk assessment for decisions made concerning amitraz carcinogenic potential. The adult and toddler dermal and toddler incidental oral (hand-to-mouth) risk estimates from exposure to dogs treated with amitraz-impregnated pet collars, as presented in the previous document (D318939), remain the same and were included for consistency.

On October 31, 1990, the HED Peer Review Committee met to discuss and evaluate the weight-of-evidence (WOE) on amitraz for its carcinogenic potential. They concluded that it should be classified as a "*Group C, possible human carcinogen*", and that quantification should be based on low dose extrapolation (Q1*). On July 6, 2006, the HED Peer Review Committee re-evaluated this conclusion in light of the 2005 Cancer Guidelines and HED's 2003 interim guidance document (#G2003.02) for dose selection. Based on the Committee's re-evaluation and concurrence from the voting CARC members, it was recommended that amitraz be classified as a non-quantifiable

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"Suggestive Evidence of Carcinogenic Potential." Therefore, residential postapplication carcinogenic risk and adult estimated lifetime exposure to treated dogs as calculated in (D318939) were removed to reflect this decision. Again, all other parts of the risk assessment were not altered and are included for consistency.

In an effort to better characterize the risk associated with the use of the amitraz-impregnated pet collars, a lower weight/ai (2.4 g ai/ 27.5 g collar) pet collar was considered in addition to the heavier 3.8 g ai/ 42 g collar (maximum application rate) pet collar. Results for both collars are presented in this addendum.

Estimated risk for residential postapplication adult and toddler dermal and toddler incidental oral (hand-to-mouth) exposures to dogs treated with amitraz were reassessed using an oral human endpoint, dermal absorption factor from a rat study, and an alternate percent transferable active ingredient (TC) from pet collars. The Human Studies Review Board (HSRB), in the April 3-6, 2006 meetings, recommended HED use an oral endpoint selected from a single-dose human oral study combined with a single-dose oral metabolism study in humans. Based on these two studies, a NOAEL of 0.125 mg/kg/day was selected (highest dose tested). HED also used an 8% dermal absorption factor from a rat study to modify the NOAEL from an oral study for use in assessing dermal risk. The toxic effects of amitraz are not considered to be cumulative, that is, the effects do not cumulate over time. Exposures to amitraz of greater than 1 day in duration are considered to be a series of acute (1-day) exposures. Therefore, this endpoint has been used to estimate non-cancer risks associated regardless of duration.

An alternate percent transferable active ingredient (TC) from pet collars was required, as the previous study (*Boone, J.S.; Chambers J.E.; and Tyler, J.W., (2001), Exposure to Children and Adults to Transferable Residues Chlorpyrifos from Dogs Treated with Flea Control Collars*) used to assess postapplication adult and toddler dermal and toddler incidental oral (hand-to-mouth) exposures to dogs treated with amitraz, was determined to have ethical issues. A carbaryl pet collar study (*MRID 45792201 Emlay, D.; Rudolph, R. (1977) Determination of the Quantity of Carbaryl Removed by Petting Dogs Wearing 16% Carbaryl Dog Collars: Lab Project Number: TR-506. Unpublished study prepared by Zoecon Industries, Inc.)* was used in lieu of the former. It is judged to be of equivalent scientific value as the chlorpyrifos study, with no known ethical issues, and is, therefore, the best available study for the use pattern (i.e., pet collar exposure scenario). The carbaryl pet collar study has been determined to require review for its ethical conduct as well. EPA is currently preparing this ethics review in accordance with EPA Human Subjects Protections Rule, 40 CFR Part 26.

Toddler dermal and incidental oral (hand-to-mouth) risk estimates were combined. HED's level of concern (LOC) for amitraz dermal and incidental oral (hand-to-mouth) exposures is 100 (i.e., a margin of exposure (MOE) less than 100 exceeds HED's level of concern) for residential scenarios.

While 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 potentially affect more sensitive residents including infants and children.

Therefore this document focuses on residential post-application exposures only, and does not address residential handlers.

Residential postapplication adult dermal exposure for the maximum application rate (3.8 g ai/ 43 g collar) pet collar resulted in an estimated MOE greater than 100 and, therefore, is not of concern to HED. Toddler combined dermal and incidental oral (hand-to-mouth) resulted in an estimated MOE less than 100 and, therefore, is of concern to HED.

Residential postapplication adult dermal exposure for the lower application rate collar (2.4 g ai) resulted in an estimated MOE greater than 100 and the toddler combined dermal and incidental oral (hand-to-mouth) is approximately 100 and are, therefore, not of concern to HED.

These risk estimates reflect conservative assumptions regarding contact factors for estimating exposure, the best available toxicity data from human and animal studies, and residue data from a surrogate chemical. Furthermore, these risk estimates may be refined with chemical-specific residue data on amitraz; specifically, a study which refines the percent transferable active ingredient.

Revised Residential Postapplication Exposure and Risk Estimates

HED uses the term postapplication to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide. Amitraz can be used to control fleas and ticks on dogs with impregnated pet collars. There is potential for dermal exposure to adults and toddlers and incidental oral exposure to toddlers following contact with a treated dog.

Data and Assumptions for Residential Postapplication Exposure Scenarios

The series of 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 "HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 19, 1997)." The value for transferable active ingredient in the pet collar is derived from MRID 457922-01.

General assumptions and factors used in the risk calculations include:

- 3 year old toddlers are expected to weigh 15 kilograms (representing an average weight from years one to six), and adults are expected to weigh 70 kg;

- for risk assessments, HED always considers the maximum application rates allowed by labels in its risk assessments in order to be able to consider what is legally possible based on the label; however, for the purposes of this risk assessment, two application rates/ ai's will be considered based upon the two active collar sizes (2.4 g ai/ 27.5 g collar and 3.8 g ai/ 43 g collar);

- the dermal absorption factor is 8 % as determined by HED;
- HED default for the surface area of a child hug is 1875 cm^2, an adult hug is 5625 cm^2;
- HED default for the treated surface area of a dog (30 lbs) is 5986 cm^2;
- saliva extraction efficiency is 50 percent meaning that every time the hand goes in the mouth approximately half of the residues on the hand are removed;
- exposure durations are expected to be 2 hours (hand-to-mouth scenario only);

The algorithms used for residential postapplication dermal and incidental oral (hand-to-mouth) pet exposure scenarios are presented below, with a summary of the estimated exposures and risks presented in Tables 1 through 4.

Adult and toddler exposure from dermal activity (hug) to treated companion animal (flea collar):

The following demonstrates the method used to calculate dermal exposures that are attributable to an adult and toddler touching a treated dog.

Where:

AA (mg ai/ dog/ day) = W (gm ai/ collar) x CF / CL (days)

AA = Available Active Ingredient (mg ai/dog/ day)

W = Weight of Active Ingredient (Amitraz) in Collar (2.4, 3.8 g ai/collar)

CF = Conversion Factor (1000 mg/g)

CL = Collar Active Lifetime (90 days)

TR (mg/cm^2) = AA (mg ai/dog/day) x TC (%) / SA_{dog} (cm^2)

TR = Transferable Residue (mg/cm^2)

AA = Available Active Ingredient (26.7, 42.2 mg ai/dog/day)

TC = Transferable Active Ingredient from Collar (2.6% or 0.026) as referenced from Carbaryl pet collar study (MRID 457922-01)

SA_{dog} = Treated Dog Surface Area (5986 cm^2)

ADD (mg/kg/day) = TR (mg/cm^2) x SA_{hug} (cm^2) x DA (%) / BW (kg)

ADD = Average Daily Dose (mg/kg/day)

TR = Transferable Residue (0.000116, 0.000183 mg/cm^2)

SA_{hug} = Surface Area of Dermal "Hug" (1875 cm^2 toddler, 5625 cm^2 adult)

DA = Dermal Absorption (8 % or 0.08)

BW = Body Weight (15 kg toddler, 70 kg adult)

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

MOE = Margin of Exposure

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

ADD = Average Daily Dose (0.00116, 0.00183 (toddler) and 0.00075, 0.00118 (adult) mg/kg/day)

Toddler exposure from incidental oral (hand-to-mouth) activity to treated companion animal (pet collar):

The following demonstrates the method used to calculate incidental oral (hand-to-mouth) exposures that are attributable to a child touching a treated dog and exhibiting mouthing behavior.

Where:

AA (mg ai/ dog/ day) = W (gm ai/ collar) x CF / CL (days)

AA = Available Active (mg ai/dog/ day)

W = Weight of Active Ingredient (Amitraz) in Collar (2.4, 3.8 g ai/collar)

CF = Conversion Factor (1000 mg/g)

CL = Collar Active Lifetime (90 days)

TR (mg/cm^2) = AA (mg ai/dog/day) x TC (%) / SA_{dog} (cm^2)

TR = Transferable Residue (mg/cm^2)

AA = Available Active (26.7, 42.2 mg ai/dog/day)

TC = Transferable Active Ingredient from Collar (2.6% or 0.026) as referenced from Carbaryl pet collar study (MRID 457922-01)

SA_{dog} = Treated Dog Surface Area (5986 cm^2)

ADD (mg/kg/day) = TR (mg/cm^2) x SA_{hand} (cm^2) x HTM (events/ hr) x ED (hr/ day) x SF (%)/ BW (kg)

ADD = Average Daily Dose (mg/kg/day)

TR = Transferable Residue (0.000116, 0.000183 mg/cm^2)

SA_{hand} = Palmar Surface Area of Toddler Hand (20 cm^2)

HTM = Toddler Hand-to-Mouth Frequency (1 event/ hr)

ED = Exposure Duration (2 hrs/day)

SF = Saliva Extraction Factor (50 % or 0.50)

BW = Body Weight of Todder (15 kg)

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

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)

Table 1. Residential Postapplication Risk Estimates (3.8 g ai/ collar)

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 2. Combined (Dermal and Oral) Residential Postapplication Toddler Risk Estimates (3.8 g ai/ collar)

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

Table 3. Residential Postapplication Risk Estimates (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)	0.00075	167

Table 4. Combined (Dermal and Oral) Residential Postapplication Toddler Risk Estimates (2.4 g ai/ collar)		
Resident	***Exposure Scenario***	**Combined MOE**
Toddler	Dermal (Pet Hug) and Oral (Hand-to-Mouth)	97

Summary of Residential Postapplication Risk Concerns

Residential postapplication adult dermal exposure for the maximum application rate (3.8 g ai/ 43 g collar) pet collar results in an estimated MOE greater than 100 and, therefore, is not of concern to HED. Toddler combined dermal and incidental oral (hand-to-mouth) results in an estimated MOE less than 100 and, therefore, is of concern to HED.

Residential postapplication adult dermal exposure for the lower weight/application rate (2.4 g ai/ 27.5 g collar) pet collar resulted in an estimated MOE greater than 100 and the MOE for the toddler combined dermal and incidental oral (hand-to-mouth) is approximately 100, therefore, these risk estimates are not of concern to HED.

These risk estimates reflect conservative assumptions regarding contact factors for estimating exposure, the most appropriate toxicity data from human and animal studies, and residue data from a surrogate chemical. Furthermore, these risk estimates may be refined with chemical-specific residue data on amitraz; specifically, a study which refines the percent dislodgeable active ingredient from pet fur.

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