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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 14, 2006

MEMORANDUM

SUBJECT: Review of "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair"

FROM: Charles Smith, Environmental Scientist/Risk Assessor
Reregistration Branch 2
Health Effects Division (7509C)

THRU: Alan Nielsen, Branch Senior Scientist
Reregistration Branch 2
Health Effects Division (7509C)

TO: Jaqueline Guerry, Chemical Review Manager
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

DP Barcode: 320041
PC Code: 109701
MRID Number: 465941-02

Attached is a review of the MRID 465941-02 "*Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair*" submitted by Bayer Health Care LLC. The purpose of the study was to measure imidacloprid and permethrin residues in the hair coat of beagle dogs after topical application of a spot-on test product containing 10% imidacloprid (w/v) and 50% permethrin (w/v).

The test substance was applied in four spots to the back of the dog (between the shoulder blades) at a dose of 0.1 ml/g body weight. Hair samples were collected from the sides of the dogs (in the front and back) on days 1, 4, 7, 14, 21, and 28 after application. Four dogs were sampled at each sampling interval; however, the same set of dogs was not sampled at each sampling interval (i.e.,

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four dogs were sampled on days 1 and 14, four dogs were sampled on days 4 and 21, and four dogs were sampled on days 7 and 28).

The average, standard deviation, and geometric mean of the residue in the dog hair was calculated for each sampling interval. Also a plot of the average and geometric mean of the residues versus time (days after treatment) was performed. The results of this study indicate that imidacloprid and permethrin residues spread from the application spot on the back of the dog to the sides of the dog. For the permethrin front and back residues and the imidacloprid front residues, the maximum average residue was observed 4 days after application. For imidacloprid back residues, the maximum average residue was observed 1 day after application. By the end of the study period, the imidacloprid and permethrin residues in the front and back of the dogs decreased to below the day 1 levels; however, the residue pattern showed significant residue increases and decreases throughout the study period. In general, the residues in the back of the dogs were lower than the residues in the front of the dogs.

The primary review was conducted by Versar, Inc. A secondary review was conducted by HED. A study protocol was not provided with the study and no applicable guidelines specific to this type of study were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study. Based on the information presented in the study, the following issues of concern were noted:

Based on the information presented in the study, the following issues of concern are noted:

- The study was conducted with only a single type of dog.
- Only four replicates were conducted at each interval and the same set of dogs was not sampled each interval.
- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.
- Could not adjust the reported residues for lb ai applied or the weight of the dog since residues were reported in terms of kg hair coat, and the total weight of the hair sample was not provided.
- The surface area of the skin from which the hair was collected was not provided.
- Field fortification samples were not collected.
- Detailed information regarding the analytical methodologies was not provided.
- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided.

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Versar inc.

MEMORANDUM

TO:	Bill Smith	cc:	110082.5000.001.01
FROM:	Karie Riley/Kelly McAloon/Sally McDonald		
DATE:	September 12, 2005		
SUBJECT:	Review of "Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair" (MRID 465941-02)		

This report reviews a study entitled "*Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair*" (MRID 465941-02). There are no applicable OPPT Guidelines established for this type of study. However, OPPTS Series 875 Part B, Guideline 875.2400 Dermal Exposure, Postapplication and Part C Guidelines were used to review this study. General issues of concern were also noted with the review.

Reviewers: Karie Riley/Kelly McAloon/Sally McDonald **Date:** September 12, 2005

STUDY TYPE: Residues in Dog Hair after Application of Spot-on Pesticide Formulation

TEST MATERIAL: The test substance was a spot-on formulation containing 10% (w/v) imidacloprid and 50% (w/v) permethrin as the active ingredients.

SYNONYMS: Imidacloprid: 1-((6-CHLORO-3-PYRIDINYL)METHYL)-N-NITRO-2-IMIDAZOLIDINIMINE

Permethrin: (3-PHENOXYPHENYL) METHYL-3-(2,2-DICHLOROETHENYL)-2,2-DIMETHYL-CYCLOPROPANE-CARBOXYLATE

CITATION:

Author:	S. Bischof and Dr. R. Krebber
Title:	*Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair*
Study Completion Date:	October 30, 2002
Testing Facility:	Bayer AG, BHC Animal Health Research and Development Animal Center D-51368 Leverkusen
Identifying Codes:	Project No. 1303; Study No. V 01-012; AHD Study No. 142.859 Bayer Report No. 75754 MRID 465941-02

SPONSOR: Bayer AG-
Research and Development
Parasiticides
51368 Leverkusen, Germany

EXECUTIVE SUMMARY:

This report reviews "*Pharmacokinetics of the Compound Preparation Permethrin 50%/Imidacloprid 10% Spot On in the Hair*" submitted by Bayer AG. The study measured imidacloprid and permethrin residues in the hair coat of beagle dogs after topical application of a spot-on test product containing 10% imidacloprid (w/v) and 50% permethrin (w/v). The test substance was applied in four spots to the back of the dog (between the shoulder blades) at a dose of 0.1 ml/g body weight. Hair samples were collected from the sides of the dogs (in the front and back) on days 1, 4, 7, 14, 21, and 28 after application. Four dogs were sampled at each sampling interval; however, the same set of dogs was not sampled at each sampling interval (i.e., four dogs were sampled on days 1 and 14, four dogs were sampled on days 4 and 21, and four dogs were sampled on days 7 and 28).

The study authors reported the concentration of imidacloprid and permethrin in the hair coat of each individual dog on each sampling day. Means for each sampling day were also reported. Versar verified the results provided in the Study Report.

Versar calculated an average, standard deviation, and geometric mean of the residue in the dog hair for each sampling interval. Versar also plotted the average and geometric mean of the residues versus time (days after treatment). The results of this study indicate that imidacloprid and permethrin residues spread from the application spot on the back of the dog to the sides of the dog. For the permethrin front and back residues and the imidacloprid

front residues, the maximum average residue was observed 4 days after application. For imidacloprid back residues, the maximum average residue was observed 1 day after application. By the end of the study period, the imidacloprid and permethrin residues in the front and back of the dogs decreased to below the day 1 levels; however, the residue pattern showed significant residue increases and decreases throughout the study period. In general, the residues in the back of the dogs were lower than the residues in the front of the dogs.

For imidacloprid front residues, the average residue at day 1 was 48.1 mg/kg hair coat and increased significantly to 1,381 mg/kg hair coat at day 4. The residues then decreased back down to 46.9 mg/kg hair coat at day 7 and then ranged between 1.20 and 7.98 mg/kg hair coat until the end of the study period. The standard deviation was greater than the average residue at days 4, 7, and 28. For imidacloprid back residues, the average residue at day 1 was 43.8 mg/kg hair coat. The back residues declined to 4.75 on day 7, then increased slightly to 17.5 mg/kg hair coat on day 14, and declined to 0.98 mg/kg hair coat by day 28. The standard deviation was greater than the average at day 14 and day 28.

For permethrin front residues, the average residue at day 1 was 246 mg/kg hair coat and increased significantly to 18,070 mg/kg hair coat at day 4. The residues then decreased to 274 mg/kg hair coat at day 28. The standard deviation was greater than the average at days 4, 7, and 28. For permethrin back residues, the average residue at day 1 was 144 mg/kg hair coat. The residues increased to a maximum of 268 mg/kg hair coat on day 4 and then ranges between 75 and 239 mg/kg hair coat until the end of the study.

Versar did not perform a regression analysis for the following reasons:

- The samples were not collected from the spot of application.
- The residue pattern did not show a steady increase or decrease.
- There were an inadequate number of replicates at each sampling interval (only 4).
- The same set of dogs was not sampled at each sampling interval.
- The individual residues were highly variable at each sampling interval as shown by the large standard deviations.

A study protocol was not provided with the study and no applicable guidelines specific to this type of study were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study. Based on the information presented in the study, the following issues of concern were noted:

Based on the information presented in the study, the following issues of concern are noted:

- The study was conducted with only a single type of dog.
- Only four replicates were conducted at each interval and the same set of dogs was not sampled each interval.
- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.
- Versar could not adjust the reported residues for lb ai applied or the weight of the dog since residues were reported in terms of kg hair coat, and the total weight of the hair sample was not provided.
- The surface area of the skin from which the hair was collected was not provided.
- Field fortification samples were not collected.
- Detailed information regarding the analytical methodologies was not provided.

- Versar could not distinguish between the method validation recoveries conducted prior to the start of the analysis and the concurrent recoveries conducted during analysis. Method validation and concurrent recovery results were reported in the same table of the Study Report.

- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided.

- The application rate was not specified on the product label; however, according to "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs" (MRID 465941-01), the amount which can be applied to a large dog is 4 ml. In the study, a dog received 0.1 ml/kg body weight. The largest dog in this study, 13.6 kg (30 lb), received 1.36 ml test substance.

COMPLIANCE:
Signed and dated GLP, Data Confidentiality, and Quality Assurance statements were provided. The study sponsor waived claims of confidentiality within the scope of FIFRA Section 10(d)(1)(A), (B), or (C). The Study Report indicated that the study was not necessarily conducted according to the requirements of EPA Good Laboratory Practice Standards (40 CFR Part 160), but was conducted according to OECD Principles of Good Laboratory Practices.

GUIDELINE OR PROTOCOL FOLLOWED: A study protocol was not provided with the study report. OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study.

I. MATERIALS AND METHODS

A. Materials:

1. Test Material:

Formulation:	A spot-on formulation containing a nominal 10% (w/v) imidacloprid and 50% (w/v) permethrin
Lot/Batch # formulation:	1303/27-3
Formulation guarantee:	According to the certificate of analysis, the product contains 10.1 g imidacloprid/100 ml and 49.3 g permethrin /100 ml.
Purity:	The reference substances had purities of 99.7% for imidacloprid, 96.1% for permethrin, 98.2% for chloroacetylenic permethrin (internal standard), and 10 mg/ml in acetonitrile for imidacloprid-pyridine-5-d-methylene-d2, 13C (internal standard)
CAS #(s):	Imidacloprid: 105827-78-9 Permethrin: 52645-53-1

2. Relevance of Test Material to Proposed Formulation(s):

The test substance is a solution of imidacloprid and permethrin designed for spot-on application animals, which is the same as the product K9 Advantix™ (the product name was obtained from "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs", MRID 465941-01).

B. Study Design:

1. Test Animal/Site Description:

Number and Type of Animals:	Twelve adult female beagle dogs were used. These dogs were bred and reared at Harlan Winkelmann in Germany and at Marshall Farms in the USA. The dogs were identified through ear tattooing. The dogs had not been treated with imidacloprid or permethrin for at least 8 weeks prior to the study.
Weight of Animals:	The dogs were weighed on days -1, 0, 14 and 28 after application. On day 0, the dogs weighed between 6.7 and 13.6 kg (14.8 and 30 lbs). The weights stayed constant through out the study.
Animal Assignment:	Four dogs were tested on each day. The same dogs were tested on days 1 and 14, 4 and 21, and 7 and 28.
Housing:	Testing was conducted at Bayer Health Care facilities. No further housing information was provided, except that the boxes were cleaned once a day.
Environmental Conditions:	Room temperature and relative humidity were measured by thermohygrograph over 4 days. The room temperature ranged from 19 to 22 °C and the humidity ranged from 40 to 65%, except during the daily cleaning sessions in which the humidity reached 90%. Artificial lighting was provided for 12 hours from 6 am to 6 pm.
Diet:	Dogs were fed once daily following the manufacturer's recommendations with a commercially available dog food "V3234-000 sniff Hd-H, 10MM," Sniff Spezialdiaten GmbH D 59494 Soest. Drinking water was provided *ad libitum*.
Clinical Observations:	Special clinical observations were performed on days -1, 0 and 1, 14 and 28 after treatment. Each animal was examined concerning general health status, oral mucous membrane, skin and hair coat, respiratory tract, cardiovascular system, alimentary tract, urinary tract, locomotor system, and central nervous system. General health status, food intake, and characteristics of feces were observed daily throughout the study by using a scoring system.

2. Surface(s) Monitored:

Types of Surface(s):	Dog haircoats
Areas treated:	Dogs were treated with the test formulation by administering the formulation to the skin on the back (between the scapulae) of the dog.
Other products used:	No

3. Physical State of Formulation as Applied: Liquid (spot-on formulation)

4. Application Rates and Regimes:

Application Equipment:	The test material was applied with a syringe.
Application Regime:	On day 0, each animal was treated once. While the dog was standing, the test item was applied on the dog's back between the scapulae. The hair coat was

separated in this region until the skin became visible. Using a syringe, the calculated volume of test item was poured on the dog's skin.

Application rate(s): Each dog received a dose of 0.10 ml/kg body weight (10 mg/kg body weight for imidacloprid and 50 mg/kg body weight for permethrin). The dogs received between 0.67 and 1.36 ml of test product. An application rate was not specified on the product labels; however, according to MRID 465941-01, the amount which can be applied to a large dog is 4 ml. Table 1 identifies the application rate information for each dog.

Table 1. Application Rate Information

Dog No.	Body weight of animal (kg)	Volume of test item (ml)	Amount of imidacloprid applied (mg)[a]	Amount of permethrin applied (mg)[b]	Application rate of product (ml product/kg)[c]	Application rate for imidacloprid (mg ai/kg)[d]	Application rate for permethrin (mg ai/kg)[e]
6506	9	0.9	91	444	0.10	10.1	493
1728	9.4	0.94	95	463	0.10	10.1	493
751	13.6	1.36	137	670	0.10	10.1	493
4317	10.4	1.04	105	513	0.10	10.1	493
4015	7.5	0.75	76	370	0.10	10.1	493
4791	8.9	0.89	90	439	0.10	10.1	493
996	8	0.8	81	394	0.10	10.1	493
5844	6.7	0.67	68	330	0.10	10.1	493
1974	7.5	0.75	76	370	0.10	10.1	493
4911	8.7	0.87	88	429	0.10	10.1	493
4252	9.2	0.92	93	454	0.10	10.1	493
1228	10.5	1.05	106	518	0.10	10.1	493

a Amount of imidacloprid applied (mg) = Content of imidacloprid (10.1 g/100 mL) * volume of test item (mL) * 1000 mg/g

b Amount of permethrin applied (mg) = Content of permethrin (49.3 g/100 mL) * volume of test item (mL) * 1000 mg/g

c Application rate of product (mL product/kg) = Volume of test item (mL) / Body weight of animal (kg)

d Application rate for imidacloprid (mg ai/kg) = Amount of imidacloprid applied (mg) / Body weight of animal (kg)

e Application rate for permethrin (mg ai/kg) = Amount of permethrin applied (mg) / Body weight of animal (kg)

C. Sampling:

Surface Areas Sampled: The surface area of the skin from which the hair sample was collected was not provided. The total weight of the sample was also not provided.

Number of sampling intervals: There were six sampling intervals after the application, including days 1, 4, 7, 14, 21 and 28 after application. Samples were also collected from all dogs 1 day prior to the application.

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Replicates per sampling interval: Four dogs were sampled at each interval. The same dogs were sampled on each of two sampling days (on days 1 and 14, 4 and 21, or 7 and 28 after application).

Method and Equipment: The hair was clipped. The specific clipping equipment used was not mentioned in the Study Report.

Sampling Procedure: The hair coat samples were collected by clipping two defined areas on the sides of the animals. At each interval, samples were collected from the left front and back or from the right front and back. No area was sampled twice on the same dog. The samples were placed in white plastic receptacles. The workers washed their hands prior to handling the dogs and changed outer clothes if the clothes were worn in other rooms where dogs were housed.

D. Sample Handling and Storage:
The samples were stored at -18°C or below until delivery to the analytical laboratory on January 25, 2002. At the laboratory, they were stored at -18°C or below until analysis.

II. ANALYTICAL METHODOLOGIES

A. Extraction method: The residues of imidacloprid and permethrin were extracted simultaneously by shaking with acetonitrile and subsequent treatment in an ultrasonic bath.

B. Detection methods: Imidacloprid residues were determined according to the method 00674/M001 (MR-108/01) without further purification of the extract by HPLC with detection by tandem mass spectrometry. An internal standard was used.

Permethrin residues were determined according to the method 00740/M001 (MR-41/02) without further purification of the extract by gas chromatography with mass spectrometric detection. An internal standard was used.

C. Method Validation: According to the Study Report, "for verification of the methods, a validation was carried out when starting the analytical part as well as concurrent recoveries were conducted during analyses." The results of the validation and concurrent recoveries conducted are shown in Table 2 for imidacloprid and in Table 3 for permethrin. The overall recoveries were 99% with relative standard deviation of 2.8% for imidacloprid and 106% with a relative standard deviation of 6.3% for permethrin.

The limit of quantitation was reported as 0.25 mg/kg for imidacloprid and 2.5 mg/kg for permethrin.

Table 2. Method Validation and Concurrent Recoveries Conducted During Analysis for Imidacloprid

Fortification Level (mg/kg)	Recovery values (%)	Average (%)	Standard Deviation (%)
0.5	97, 101, 97, 99, 96	98	2.0
62	100, 98, 99, 99, 101	99	1.1
1000	97, 103, 106	102	4.6
Overall		99	2.8

Table 3. Method Validation and Concurrent Recoveries Conducted During Analysis for Permethrin			
Fortification Level (mg/kg)	Recovery values (%)	Average (%)	Standard Deviation (%)
2.5	103, 112, 104, 104, 115,	108	5.1
82	104, 101, 106, 104, 97	102	3.4
1,000	102, 94, 100	99	4.2
10,000	113, 112, 118	114	2.8
Overall		106	6.3

Instrument performance and calibration: Instrument performance and calibration data were not provided.

E. Quality Control:

Lab Recovery: According to the Study Report, concurrent fortification samples were conducted during the analysis, along with method validation samples. The results are reported in Tables 2 and 3 above.

Field Fortification: Field fortification recoveries were not conducted as a part of this study.

Control Samples: According to the Study Report, residues of imidacloprid or permethrin were not found above the LOQ in any of the control samples. Control samples were collected from each dog prior to the treatment.

Storage Stability: Information regarding storage stability of the samples was not provided

III. RESULTS

A. Observations:

The daily observation of general health, food intake, and quality of feces was normal. No deviations from the physiological health status were observed during the post treatment clinical exams. The body weight remained constant throughout the study.

B. Dog Hair Residues:

The study authors reported the concentration of imidacloprid and permethrin in the hair coat of each individual dog on each sampling day. Means for each sampling day were also reported. Versar verified the results provided in the Study Report.

Versar calculated an average, standard deviation, and geometric mean of the residue in the dog hair for each sampling interval. When residues were <LOQ, Versar used ½ LOQ in the calculations. The results are shown in Table 4 for imidacloprid and Table 5 for permethrin.

For imidacloprid front residues, the average residue at day 1 was 48.1 mg/kg hair coat and increased significantly to 1,381 mg/kg hair coat at day 4. The residues then decreased back down to 46.9 mg/kg hair coat at day 7 and then ranged between 1.20 and 7.98 mg/kg hair coat until the end of the study period. The standard deviation was greater

than the average residue at days 4, 7, and 28. Figures 1a and 3a depict the average and geometric mean of the imidacloprid residues on the front of the dog, respectively. For imidacloprid back residues, the average residue at day 1 was 43.8 mg/kg hair coat. The back residues declined to 4.7 on day 7, then increased slightly to 17.5 mg/kg hair coat on day 14, and declined to 0.98 mg/kg hair coat by day 28. The standard deviation was greater than the average at day 14 and day 28. Figures 1b and 3b depict the average and geometric mean of the imidacloprid residues on the front of the dog, respectively.

For permethrin front residues, the average residue at day 1 was 246 mg/kg hair coat and increased significantly to 18,070 mg/kg hair coat at day 4. The residues then decreased to 274 mg/kg hair coat at day 28. The standard deviation was greater than the average at days 4, 7, and 28. Figures 2a and 4a depict the average and geometric mean of the permethrin residues on the front of the dog, respectively. For permethrin back residues, the average residue at day 1 was 144 mg/kg hair coat. The residues increased to a maximum of 268 mg/kg hair coat on day 4 and then ranges between 75 and 239 mg/kg hair coat until the end of the study. Figures 2b and 4b depict the average and geometric mean of the permethrin residues on the back of the dog, respectively.

Versar did not perform a regression analysis for the following reasons:

- The samples were not collected from the spot of application.
- The residue pattern did not show steady increase or decrease in residues.
- There were an inadequate number of replicates at each sampling interval (only 4).
- The same set of dogs was not sampled at each sampling interval.
- The individual residues were highly variable at each sampling interval.

VI. CONCLUSION

The results of this study indicate that imidacloprid and permethrin residues spread from the application spot on the back of the dog to the sides of the dog. For the permethrin front and back residues and the imidacloprid front residues, the maximum average residue was observed 4 days after application. For imidacloprid back residues, the maximum average residue was observed 1 day after application. By the end of the study period, the imidacloprid and permethrin residues in the front and back of the dogs decreased to below the day 1 levels, however, the residue pattern showed significant residue increases and decreases throughout the study period. In general, the residues in the back of the dogs were lower than the residues in the front of the dogs.

LIMITATIONS OF THE STUDY:

A study protocol was not provided with the study and no applicable guidelines were available to assess the accuracy and validity of the methods utilized. However, OPPTS Series 875 Part B, Guideline 875.2400: Dermal Exposure, Postapplication and Part C Guidelines were used to review this study. Based on the information presented in the study, the following issues of concern are noted:

- The study was conducted with only a single type of dog.
- Only four replicates were conducted at each interval and the same set of dogs was not sampled each interval.
- The individual residues were highly variable at each sampling interval, as indicated by large standard deviations.
- Versar could not adjust the reported residues for lb ai applied or the weight of the dog since residues were reported in terms of kg hair coat, and the total weight of the hair sample was not provided.
- The surface area of the skin from which the hair was collected was not provided.
- Field fortification samples were not collected.

- Detailed information regarding the analytical methodologies was not provided.

- Versar could not distinguish between the method validation recoveries conducted prior to the start of the analysis and the concurrent recoveries conducted during analysis. Method validation and concurrent recovery results were reported in the same table of the Study Report.

- The storage conditions of the samples prior to receipt at the analytical laboratory were not provided. Additionally, information regarding the storage stability of the samples was not provided.

- The application rate was not specified on the product label; however, according to "Assessment of Residential Exposure to Permethrin during and following Spot-on Application of K9 Advantix™ to Dogs" (MRID 46594 1-01), the amount which can be applied to a large dog is 4 ml. In the study, a dog received 0.1 ml/kg body weight. The largest dog in this study, 13.6 kg (30 lb), received 1.36 ml test substance.

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Name:
Evaluator
Occupational Exposure Assessment Section

Date

Name:
Peer Reviewer
Occupational Exposure Assessment Section

Date

Name:
Head,
Occupational Exposure Assessment Section

Date

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FRONT						
6506	56.4	NS	NS	8.8	NS	NS
1728	27	NS	NS	14.3	NS	NS
751	38.2	NS	NS	7.1	NS	NS
4317	70.9	NS	NS	1.73	NS	NS
4015	NS	1,333	NS	NS	0.75	NS
4791	NS	3,980	NS	NS	1.06	NS
996	NS	76.9	NS	NS	2.35	NS
5844	NS	134	NS	NS	0.63	NS
1974	NS	NS	20.8	NS	NS	24.5
4911	NS	NS	129	NS	NS	0.57
4252	NS	NS	17.8	NS	NS	1.28
1228	NS	NS	19.8	NS	NS	1.77
Average (Front only)	48.1	1,381	46.9	7.98	1.20	7.03
Standard Deviation (Front only)	19.4	1,826	54.8	5.18	0.789	11.7
Geometric Mean (Front only)	45.1	483.5	31.2	6.27	1.04	2.37
BACK						
6506	13.1	NS	NS	2.19	NS	NS
1728	27.2	NS	NS	5.95	NS	NS
751	105	NS	NS	57.1	NS	NS
4317	30	NS	NS	4.67	NS	NS
4015	NS	16.9	NS	NS	0.53	NS
4791	NS	17.3	NS	NS	0.34	NS
996	NS	30.5	NS	NS	0.7	NS
5844	NS	4.9	NS	NS	0.52	NS
1974	NS	NS	2.21	NS	NS	0.64
4911	NS	NS	2.71	NS	NS	<LOQ[c]
4252	NS	NS	6.23	NS	NS	<LOQ[c]

1228	NS	NS	7.83	NS	NS	2.77
Average (Back only)	43.8	17.4	4.75	17.5	0.523	0.978
Standard Deviation (Back only)	41.4	10.5	2.73	26.5	0.147	1.21
Geometric Mean (Back only)	32.5	14.5	4.13	7.68	0.506	0.577
Overall Average (Back and Front)	46.0	699	25.8	12.7	0.860	4.00
Overall Standard Deviation (Back and Front)	30.1	1400	42.4	18.4	0.638	8.33
Overall Geometric Mean (Back and Front)	38.3	83.6	11.4	6.94	0.726	1.17

a. Residues collected from left side of dog
b. Residues collected from right side of dog
c. Imidacloprid LOQ = 0.5 mg/kg dog hair. Half the LOQ was used in the calculations when residues were <LOQ.

NS= No sample collected from dog

FRONT						
6506	409	NS	NS	267	NS	NS
1728	164	NS	NS	143	NS	NS
751	86.5	NS	NS	199	NS	NS
4317	326	NS	NS	73	NS	NS
4015	NS	12,647	NS	NS	24.9	NS
4791	NS	54,881	NS	NS	81.9	NS
996	NS	932	NS	NS	443	NS
5844	NS	3,820	NS	NS	197	NS
1974	NS	NS	371	NS	NS	739
4911	NS	NS	11,629	NS	NS	36.2
4252	NS	NS	382	NS	NS	156

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1228	NS	NS	414	NS	NS	163
Average (Front only)	246	18,070	3,199	171	187	274
Standard Deviation (Front only)	147	25,042	5,620	82.4	185	316
Geometric Mean (Front only)	209	7,051	909	153	116	161
BACK						
6506	105	NS	NS	103	NS	NS
1728	94.5	NS	NS	155	NS	NS
751	245	NS	NS	492	NS	NS
4317	130	NS	NS	206	NS	NS
4015	NS	152	NS	NS	35.2	NS
4791	NS	162	NS	NS	34.7	NS
996	NS	556	NS	NS	121	NS
5844	NS	202	NS	NS	109	NS
1974	NS	NS	48.5	NS	NS	97.2
4911	NS	NS	112	NS	NS	43.8
4252	NS	NS	157	NS	NS	95.1
1228	NS	NS	176	NS	NS	236
Average (Back only)	144	268	123	239	75.0	118
Standard Deviation (Back only)	69.2	193	56.7	173	46.5	82.4
Geometric Mean (Back only)	133	229	111	201	63.4	98.9
Overall Average (Back and Front)	195	9,169	1,661	205	131	196
Overall Standard Deviation (Back and Front)	120	18,955	4,030	131	139	229
Overall Geometric Mean (Back and Front)	167	1,272	317	175	85.5	126

a. Residues collected from left side of dog
b. Residues collected from right side of dog
Permethrin LOQ = 2.5 mg/kg dog hair.
NS= No sample collected from dog

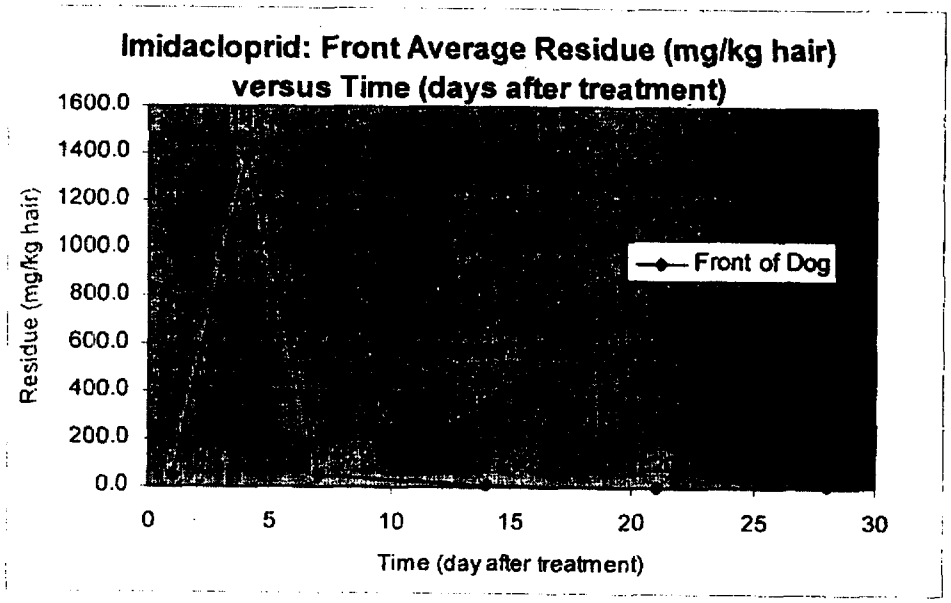

Figure 1a. Average Front Residues for Imidacloprid

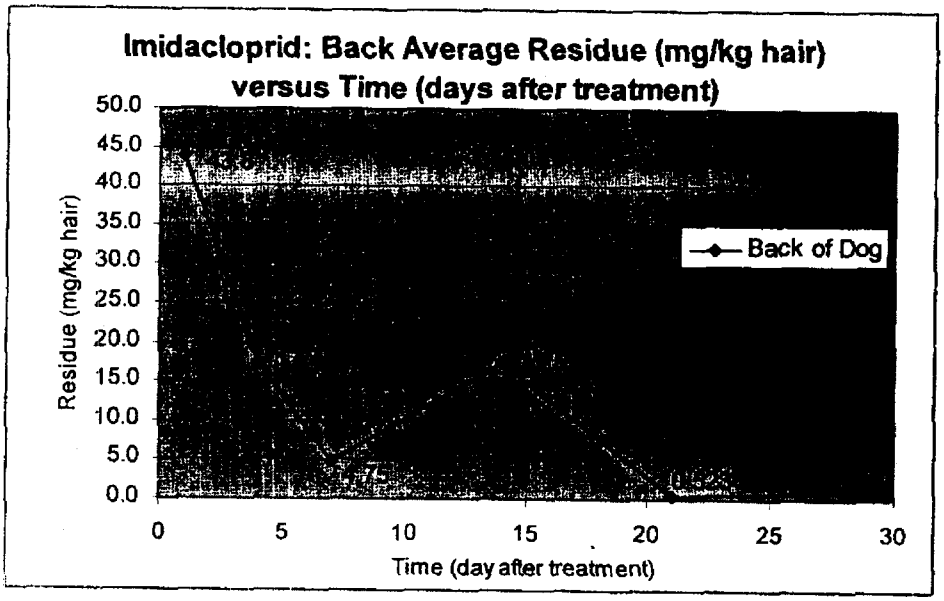

Figure 1b. Average Back Residues for Imidacloprid

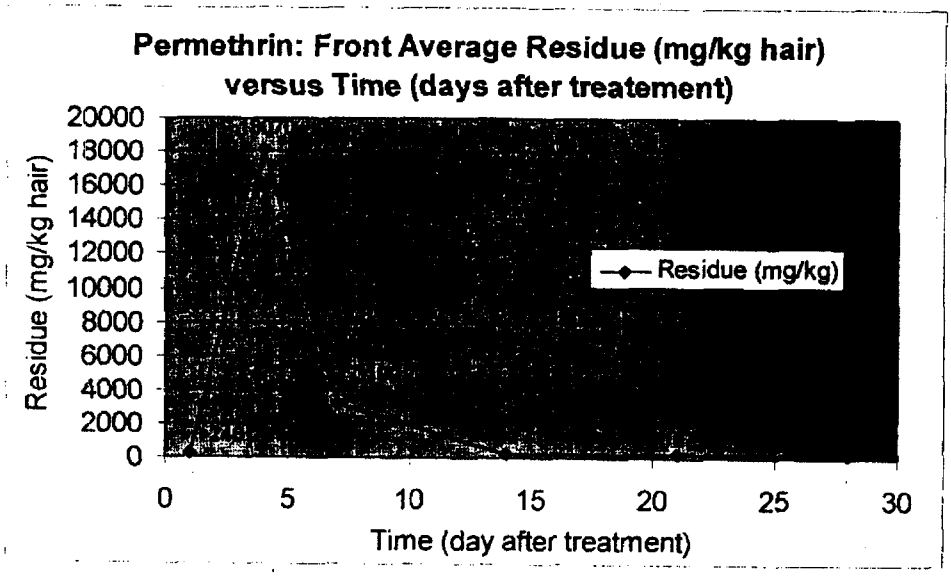

Figure 2a. Average Front Residues for Permethrin

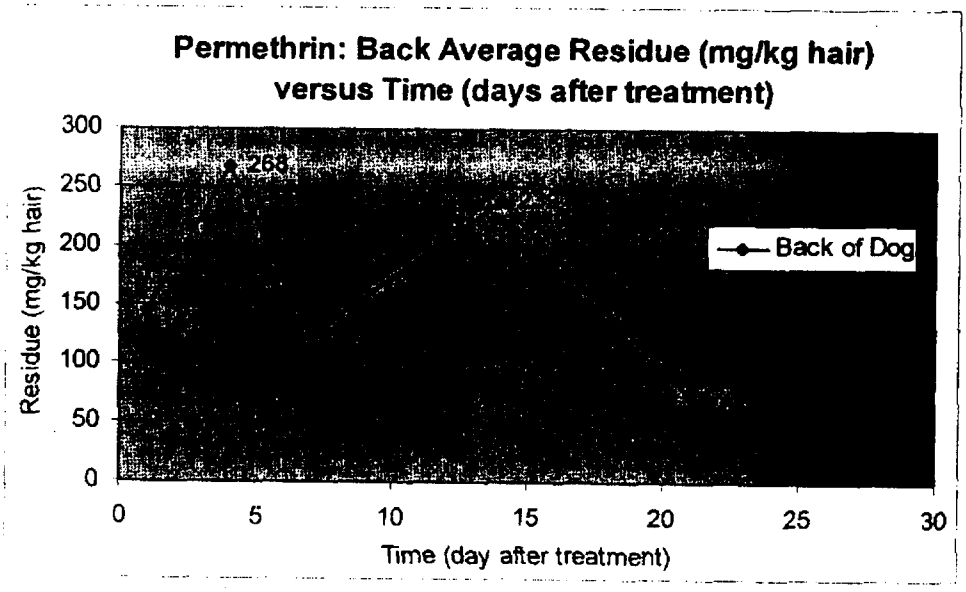

Figure 2b. Average Back Residues for Permethrin

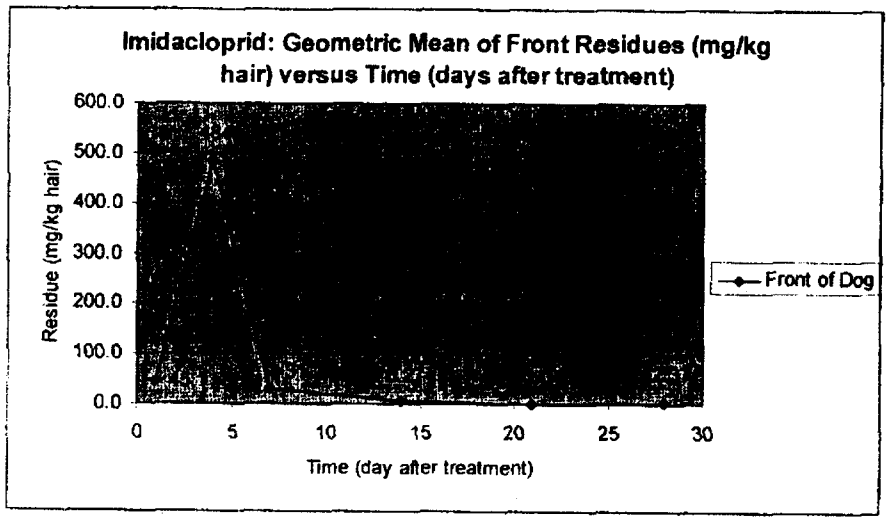

Figure 3a. Geometric Mean of Front Residues for Imidacloprid

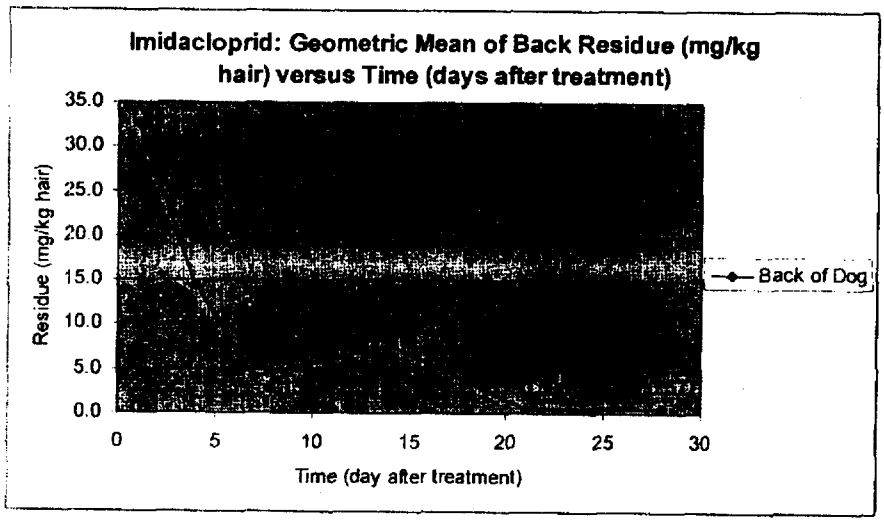

Figure 3b. Geometric Mean of Back Residues for Imidacloprid

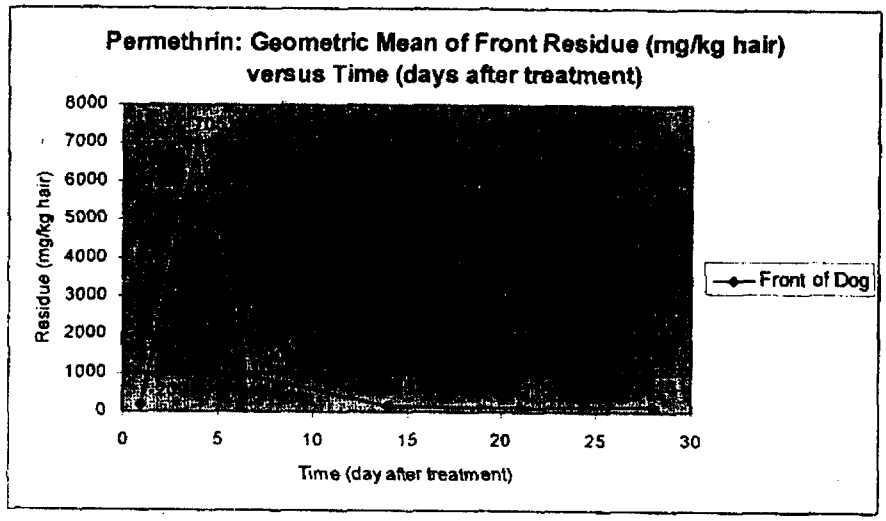

Figure 4a. Geometric Mean of Front Residues for Permethrin

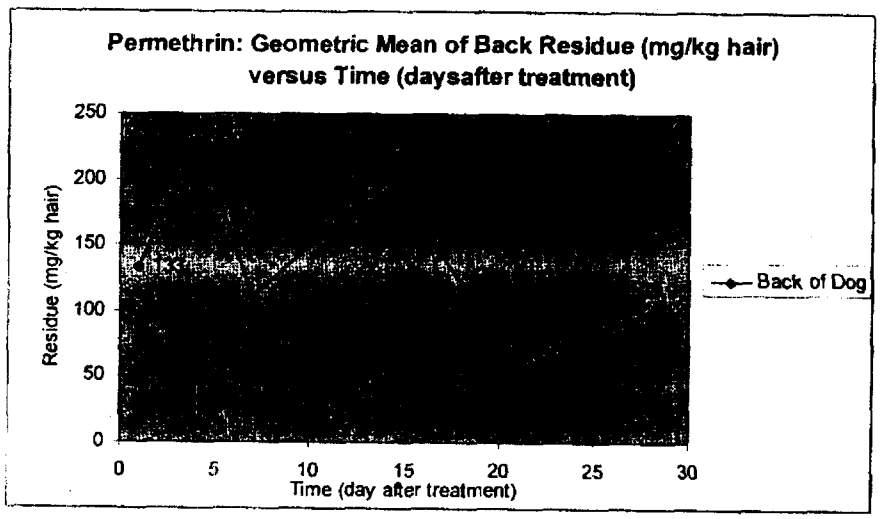

Figure 4b. Geometric Mean of Back Residues for Permethrin

APPENDIX A

Compliance Checklist for *"Stroking Test in Dogs After Topical Application Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On"*

DRAFT
COMPLIANCE CHECKLIST
GUIDELINE 875.2400
DERMAL EXPOSURE MONITORING
POSTAPPLICATION

1. *The test substance must be the typical end use product of the active ingredient.* This criterion was met.

2. *The production of metabolites, breakdown products, or the presence of contaminants of potential toxicologic concern, should be considered on a case-by-case basis.* It is unclear if this criterion was met. There was no mention of metabolites, breakdown products or other contaminants.

3. *Applications should occur at the time of season that the end-use product is normally applied to achieve intended pest control.* This criterion does not apply to this study.

4. *Initiating testing immediately before a precipitation event should be avoided.* This criterion does not apply to this study.

5. *The end use product should be applied by the application method recommended for the crop. Information that verifies that the application equipment (e.g., sprayer) was properly calibrated should be included.* This criterion was met. However, the test formulation was applied to an animal rather than a field crop. No calibration of equipment was required.

6. *The application rate used in the study should be provided and should be the maximum rate specified on the label. However, monitoring following application at a typical application rate is more appropriate in certain cases.* The application rate (volume of product) was not specified on the product label; however, according to MRID 465941-01, the amount which can be applied to a large dog is 4 ml. In this study, each dog received a dose of 0.10 ml/kg body weight.

7. *If multiple applications are made, the minimum allowable interval between applications should be used.* This criterion does not apply to this study. The test material was only applied once.

8. *A sufficient number of replicates should be generated to address the exposure issues associated with each population of interest. In general, the study should include minimum of 15 replicates per activity, distributed as follows: 5 replicates (i.e., individuals) on each of 3 monitoring periods (i.e., "n" days after application).* This criterion was not met. There were only four replicates on each of six monitoring periods.

9. *The monitoring period should be of sufficient duration to result in reasonable detectability on dosimeters. Monitoring should be conducted before residues have dissipated beyond the limit of quantification. Baseline samples should be collected before the exposure activity commences.* These criteria were met. Background samples were collected from each dog prior to application and analyzed. These residues were <LOQ.

10. *Activities monitored must be clearly defined and representative of typical practice.* This criterion does not apply to this study.

11. *Passive dosimetry studies must be carried out concurrently with transferable residue studies.* This criterion does not apply to this study.

12. *The selected sites and seasonal timing of monitoring must be appropriate to the activity.* This criterion does not apply to this study.

13. *Studies should be conducted under different geographic/climatologic sites.* This criterion does not apply to this study.

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14. *The sampling techniques (e.g., patches, whole-body dosimeters, hand rinse, gloves, fluorescent tracer) should be appropriate to the activities being monitored. The construction materials and location (i.e., inside or outside clothing) of monitoring devices and numbers (e.g., patches) should be appropriate to the use scenario. Hand rinse solutions must be appropriate to the pesticide being evaluated (i.e., selection of aqueous surfactants vs. isopropanol or other solutions, based on the physical chemical properties of the pesticide being evaluated.* This criterion was met.

15. *Sufficient control samples should be collected.* This criterion was met. A control sample was collected from each dog prior to the application event.

16. *Samples should be stored in a manner that will minimize deterioration and loss of analytes between collection and analyses. Information of storage stability should be provided.* This criterion was partially met. The samples were stored frozen at the analytical laboratory; however, the storage conditions prior to receipt at the laboratory were not provided. Additionally, information regarding storage stability was not provided.

17. *Validated analytical methods of sufficient sensitivity are needed. Information on method efficiency (residue recovery) and limit of quantification (LOQ) should be provided.* These criteria were partially met. LOQ values for both permethrin and imidacloprid were provided; however, Versar could not distinguish between the recovery values of the method validation study conducted prior to the start of the analysis and the concurrent analysis study conducted during analysis. Method validation and concurrent recovery results were reported in the same table of the Study Report.

18. *Information on recovery samples must be included in the study report. A complete set of field recoveries should consist of at least one blank control sample and three or more each of a low-level and high-level fortification. These fortifications should be in the range of anticipated residue levels in the field study.* These criteria were not met. Field fortification samples were not utilized as a part of this study.

19. *Raw residue data must be corrected if appropriate recovery values are less than 90 percent.* Samples were not corrected for recoveries. There were no field fortification samples collected and results for laboratory fortification samples were not reported.

20. *Soil residues should be reported as mg or µg of pesticide active ingredient per body part sampled, if generated using the whole-body dosimetry techniques and on a surface area basis if the data were generated using the patch techniques (i.e., normalized on patch sample surface area; µg/cm^2 or mg/cm^2). Distributional data should be reported, to the extent possible.* This criterion was met.

13544

R125656

Chemical: Permethrin

PC Code:
109701

HED File Code: 14000 Risk Reviews
Memo Date: 3/14/2006
File ID: 00000000
Accession #: 412-06-0193

HED Records Reference Center
7/18/2006