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DRAFT

MEMORANDUM

TO: Jeff Evans

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FROM: Hai-Ming Chou H.M. Chou

DATE: May 1, 1998

SUBJECT: Review of the Exposure Study - Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment (MRID # 444333-02)

An Exposure Study - Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment (MRID # 444333-02) was submitted in support of the registration requirements for the pesticide Frontline® formulated as Frontline® Spray Treatment. The requirements for this study were specified by the U.S. Environmental Protection Agency under Subdivision U of the Pesticide Assessment Guidelines (U.S. EPA, 1996).

The following information could be used to identify the Study:

Title:	Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment
Sponsor:	Merial Limited (formerly Rhone Merieux, Inc.) 115 Transtech Drive Athens, Georgia 30601 USA
Performing Laboratory:	ABC Laboratories, California 32380 Avenue 10 Madera, California 93638
Analytical Laboratory	Merial Limited (formerly Rhone Merieux, Inc.) 2116-8th Avenue South Fort Dodge, Iowa 50501
Authors:	Nicholas J. Meo Celeste M. Gonzalez, C.V.T. Thomas C. Mester, Ph.D.
Report Dates:	November 12, 1997
Identifying Codes:	MRID # 444333-02

EXECUTIVE SUMMARY

Frontline® is a new pesticide used to control fleas and ticks on dogs and cats. This study examined dermal and inhalation exposure of commercial pet groomers to fipronil, the active ingredient of Frontline®, during spray treatment of the pesticide on dogs in an indoor commercial dog grooming shop in Savannah, Georgia.

A liquid formulation, known as Frontline® Spray Treatment, was packaged in 250 mL ready-to-use trigger spray pump bottles containing 0.25 percent of the active ingredient (ai), fipronil (w/v; equivalent to 2.5 mg/mL). Field data were collected from July 16 to July 21, 1997. Sixteen groomers/treatment applicators (replicates) were included in the study. Each replicate applied treatments to eight dogs of varying weight, size, and hair length within a typical working day.

Dermal exposure was quantified using: (1) 100 percent cotton, pre-washed, one-piece, whole-body suits (dosimeter units), (2) 100 percent "pallbearers" gloves worn underneath the PPE latex gloves, and (3) facial swabs. A total of 11 dermal samples were collected for each replicate.

Inhalation exposure was measured using a personal air pump (SKC Air Check® Sampler, model 224-43XR) connected with a cassette containing fiber filter with a 1 µm pore size and a cellulose support pad followed by a Chromosorb 102 vapor collection tube. The air flow rate was approximately 1.5 liters per minute, and was pre- and post-calibrated.

The product was applied at the rate of two pumps per pound of dog body weight, the maximum label rate. The amount of ai applied per replicate ranged from 859 mg to 2,959 mg (mean = 1,773 mg), and the sampling time per replicate ranged from 38 to 72 minutes (mean = 56 minutes).

A method validation study on sampling media using GC analysis was conducted to determine laboratory recoveries (method accuracy), method precision, limit of quantification (LOQ), and limit of detection (LOD). Field recovery data were also collected; however, storage stability results were not reported.

Field recoveries ranged from 81.6 percent to 105.8 percent. The average laboratory recoveries (method accuracy) based on the method validation study ranged from 72.9 percent to 106 percent with the lower 95 percent confidence limit greater than 70 percent. Method precision, measured as the percent relative standard deviation of the mean laboratory recoveries (RSD), ranged from 2.12 percent to 10.35 percent. Limit of detection was determined as 0.192 ng/mL, and limit of quantification (LOQ) based was determined as 0.576 ng/mL.

In summary, most of the requirements contained in Subdivision U of the Pesticide Assessment Guidelines (U.S. EPA, 1996) were met. Sixteen replicates were performed, but they are represent one site, instead of three. Typical working practices including number of pets

treated per day, application methods, and durations should be further defined to interpret the exposure results.

Study Background

Frontline® is a new pesticide used to control fleas and ticks on dogs and cats. This study examined dermal and inhalation exposure of commercial pet groomers to fipronil, the active ingredient of Frontline®, during spray treatment of the pesticide on dogs.

Test Site

An indoor commercial dog grooming shop in Savannah, Georgia, was used as the test site. A 21 ft. X 11 ft. room in the shop was used for dog treatment, and additional rooms in the shop were used for the field fortification study (surgical preparation room), grooming, and bathing dogs (see Figure 1 & 2 in this review's Appendix for layout). Ventilation in the treatment area was via a central air conditioning system with two ceiling-mounted outflow registers, one producing a flow of 200 cubic feet per minute (cfm), and the other 50 cfm. The treatment room did not have an air return register. A different central air conditioning system was used for the fortification room (for field recovery study) with two ceiling-mounted outflow registers, one producing a flow of 50 cubic feet per minute (cfm), and the other 100 cfm. There was no air return register in the fortification room. Three grooming tables (measuring 48" X 25" X 36 3/4", 48" X 24" X 34 3/4", and 36" X 24" X 30 1/2" for length, width, and height) were used in the study with each one used only once each day (except for the day with four replicates).

Materials, Application, and Sampling

A liquid formulation, known as Frontline® Spray Treatment, was used in the study. It was packaged in 250 mL ready-to-use trigger spray pump bottles containing contained 0.25 percent of the active ingredient (ai), fipronil (w/v; equivalent to 2.5 mg/mL). Field data were collected from July 16 to July 21, 1997. Sixteen human subjects (replicates) were included in the study in the role of pet groomer/treatment applicator. Each replicate applied treatments to eight dogs of varying weight, size, and hair length within a typical working day.

Dermal exposure was quantified using: (1) 100 percent cotton, pre-washed, one-piece, whole-body suits (dosimeter units), (2) 100 percent "pallbearers" gloves worn underneath the PPE latex gloves, and (3) facial swabs. The dosimeters were worn under normal work clothing (see Clothing below). The facial swabs were used for quantifying the exposure of the neck and face of each groomer. They consisted of ethanol-soaked 4" X 4" cotton gauze squares and were applied three times over the face and neck of each groomer; with a new gauze square each time. A total of 11 dermal samples were collected for each replicate.

Inhalation exposure was measured using a personal air pump (SKC Air Check® Sampler, model 224-43XR) attached to the test subject's belt. The pump was connected with a cassette containing fiber filter with a 1 µm pore size and a cellulose support pad followed by a Chromosorb 102 vapor collection tube. The vapor collection tube contained a large section,

intended to absorb all vapors, and a small section used for vapor break-throughs. A piece of tygon tubing (0.5 inch) was used to connect the cassette and the vapor collection tube. The closed-cassette was attached to the lapel of the test subject's smock near the breathing zone and directed downward, mimicking the nasal passage (see photos in Appendix 6 of the Study Report). The air flow rate was approximately 1.5 liters per minute, and was pre- and post-calibrated.

Treatment Information

The application rate was two pumps per pound of dog body weight; the maximum label rate. The maximum label rate equates to 7.5 mg of ai per pound of dog weight. The actual average application rate across eight dogs within a replicate ranged from 4.8 to 8.6 mg of ai per pound of dog weight (see p. 37 to p. 43; see Comments below for discussion of variability). A concentration of 2.5 mg fipronil/mL product, and a specific activity of 0.852 g product/mL product were used for calculation (see Appendix). The amount of ai applied per replicate ranged from 859 mg to 2,959 mg (mean = 1,773 mg). The sampling time per replicate ranged from 38 to 72 minutes (mean = 56 minutes). The equipment used for spraying the product was a 250 mL polyethylene dispenser equipped with a trigger pump and a bell spray nozzle. Each spray pump delivered approximately 1.5 mL of product per full trigger pump depression.

Sample Storage and Handling

After sampling, the facial swabs were placed into pre-labeled glass jars and capped with Teflon®-lined lids. The removed cotton gloves, and air sampling units (cassettes, and Chromosorb tube units) were packaged into pre-labeled Kapak bags and then heat-sealed. Dosimeter suits were sectioned into parts to represent forearms, upper arms, chests, backs, and lower bodies before they were packaged into Kapak bags and heat-sealed. All samples were stored and shipped frozen to the laboratory for analysis.

QA/QC

Gas chromatography (GC) with electron capture detectors was used for analyzing fipronil levels (see Appendix for models and columns used). A method validation study on sampling media using GC analysis was conducted to determine laboratory recoveries (method accuracy), method precision, limit of quantification (LOQ), and limit of detection (LOD). Laboratory recovery data were collected for the following matrices and fortification levels:

Matrix	Fortification levels (µg fipronil)
Gauze pads (facial swabs)	1.1, 11, 1100
Dosimeter (Union) suit (12 gram)	0.440, 4.40, 440
Paired gloves	0.440, 4.40, 440
Single gloves	0.440, 4.40, 440
Type AE glass fiber plus cellulose support pad	0.11, 1.1, 110, 1100
Chromosorb 102	0.11, 1.1, 110

A total of seven replications were collected and analyzed at each fortification level for each matrix. Blank samples were also collected as controls. The percent relative standard deviation (percent RSD) of the average percent laboratory recoveries at each fortification level for each matrix was used to evaluate the precision of the analytical method. Calibration curves were generated using the linear regression analysis.

In addition, a method verification study for each matrix were performed by analyzing freshly fortified samples and untreated controls in conjunction with field samples (extracted and analyzed on the same day).

Triplicate field recovery samples (weathered samples) were collected on July 22, 1997 for each of the sampling matrices (whole body dosimeters, cotton gloves, facial swabs, and glass fiber filters) at each of the following fortification levels: (1) 0.439, 4.39, and 439.2 µg/mL for cotton gloves and dosimeters, and (2) 1.09, 10.9, and 1,098.0 µg/mL for glass fiber filters and facial wipes. After being fortified, these "weathered" samples were either left exposed at ambient temperature or with air pumps turned on (fiber filters) for approximately two hours. Additional triplicate travel samples (unweathered) fortified at one concentration for each matrix were stored in the freezer without being weathered. Duplicate field control samples for each matrix were collected with approximately the same exposure period as the field recovery samples (weathered). All the field recovery samples (including controls) were handled the same manner as the field samples. At the end of the fortifications, duplicate samples from each of the fortification solutions were also collected to obtain recovery results (see "Comments" below).

No storage stability results were reported. However, as noted by the authors, a storage stability study using analytical standards is ongoing, and the results will be issued as a report amendment.

Clothing/Protective Clothing

The work clothing, worn over the whole-body dosimeter suit, consisted of the following: (1) short-sleeved cotton shirts; (2) long cotton pants; (3) long-sleeved, ribbed cuff smock of 65

percent polyester/35 percent cotton worn over short-sleeved cotton shirts; and (4) socks and shoes covering the entire foot. In addition, undergarments, made from either cotton and/or synthetic materials, were worn underneath the dosimeter suit.

As per label directions, all groomers wore household latex gloves as PPE.

Data Summary

The exposures of applicators' faces and necks to fipronil, determined by analyzing cotton gauze pads (facial swabs) collected from each of the sixteen replicates, ranged from 0.00087 to 0.018 µg ai/cm^2 (mean = 0.0074 µg ai/cm^2). Fipronil residues on gloves (pair) ranged from 0.0033 µg ai/cm^2 to 0.14 µg ai/cm^2 (mean = 0.031 µg ai/cm^2). Total fipronil residues found on dosimeter suits ranged from 0.028 µg ai/cm^2 to 2.2 µg ai/cm^2 (mean = 0.76 µg ai/cm^2). These results were summarized on p. 31 of the Study Report. A relatively large portion of exposure was found on forearms (mean = 0.6568 µg ai/cm^2), upper arms (mean = 0.06799 µg ai/cm^2), and gloves (mean = 0.031270 µg ai/cm^2), as shown on p. 705 of the Study Report. Total fipronil residues on the glass fiber filters, cellulose support pads, and vapor collection tubes (combined) ranged from 0.0011 µg/L to 0.034 µg/L (mean = 0.012 µg/L), as shown on p. 707 of the study report. These results were reported on page 687 to page 708 of the Study Report.

Field recoveries for the sampling matrices (dosimeter suits, cotton gloves, gauze pads, and glass fiber filters plus support pads) ranged from 81.6 percent to 105.9 percent (see p. 698 and 700). Analysis of the field fortification solutions indicated recoveries ranging from 95.08 percent to 108.5 percent (see p. 710 - p. 712 of the Study Report).

Average recoveries based on the method verification study ranged from 94.87 percent to 109.4 percent indicating an acceptable method performance was maintained (see p. 670, and p. 687 - p. 708 of the Study Report).

The average laboratory recoveries (method accuracy) based on the method validation study ranged from 72.9 percent to 106 percent (refer to p. 360 - p. 371 of the Study Report) with the lower 95 percent confidence limit greater than 70 percent. Method precision, measured as the percent relative standard deviation of the mean laboratory recoveries (RSD), ranged from 2.12 percent to 10.35 percent. Limit of detection based on a minimum of signal to noise ratio of 3 was determined as 0.192 ng/mL, and limit of quantification (LOQ) based on a minimum of signal to noise ratio of 10 was determined as 0.576 ng/mL. LOQs for different matrices and their calculations were attached in Appendix of this review.

Review Summary

Compliance with sections 230-236 of Subdivision U of the Pesticide Assessment Guidelines (U.S. EPA, 1996) is critical for determining whether a study is acceptable to the Agency. The itemized list below is based on the "Checklist for Applicator Monitoring Data" and summarizes the major points of Subdivision U:

- *Typical end use product of the active ingredient tested.* This criterion was met as a commercial product was used in the study.

- *End use product handled and applied using recommended equipment, application rates, and typical work practices.* This criterion was met as the equipment used in this study, ready-to-use spray pump bottles, was in conformity with the application method on the label. The application rate also conformed with the label instruction. However, typical work practices should be more clearly defined.

- *For outdoor exposure monitoring at least five replicates at each of at least three sites for each job function with the exception of pilots should be monitored. Pilots should have at least three replications at each of at least three sites.* This criterion is not applicable to this study.

- *For indoor exposure monitoring at least five replicates at each of at least three sites for each job function must be monitored.* This criterion was not met as only one test site was included in this study (16 replicates).

- *Monitoring period is sufficient to collect measurable residues, but not excessive so that residue loss occurs.* The criterion was met as the monitoring time ranged from 38 to 72 minutes (mean = 56 minutes).

- *Dermal and/or inhalation exposure must be monitored by validated methodologies. Biological monitoring is consistent with and supported by pharmacokinetic data accepted by the Agency.* This criterion was met as the method validation study was conducted with an acceptable precision and accuracy (refer to "Data Summary" above). No biological monitoring was conducted in this study.

- *Quantity of active ingredient handled and duration of monitoring period reported for each replicate.* This criterion was met (refer to "Treatment Information" above).

- *Clothing worn by each study participant and location of dosimeters reported.* This criterion was met (refer to "Clothing/Protective Clothing" and "Materials, Application, and Sampling" above).

- *Quantitative level of detection is at least 1 ug/cm^2.* This criterion was met (refer to Appendix of this review). LOQs for dermal and inhalation media are shown in Tables 12 and 13 of the Appendix.

- *Storage of samples consistent with storage stability data.* This criterion was not met since storage stability results were not reported. However, as noted by the authors, a storage stability study using analytical standards is ongoing, and the results will be issued as a report amendment. The length of time the field samples were stored may have been up to three months (collected on July 16 to 21, 1997, and analyzed in September and October, 1997).

- *Efficiency of extraction in laboratory provided as mean plus or minus one standard deviation. Lower 95 percent confidence limit is not less than 70 percent based on a minimum of seven replications per fortification level or prior Agency approval of extraction methodology provided.* The criterion was met. Recovery data were provided as mean plus or minus one standard deviation and every one of the lower 95 percent confidence limit values was greater than 70 percent (refer to "QA/QC" above).

- *At least one field fortification sample per worker per monitoring period per fortification level for each matrix. At least one field blank per worker per monitoring period for each matrix.* The criterion was not met. Triplicate field recovery samples (weathered samples) were collected for each of the sampling matrices (whole body dosimeters, cotton gloves, facial swabs, and glass fiber filters) at three different levels (see "QA/QC" above). Thus, only nine samples were collected for each matrix while a total of sixteen replicates were included in the study. Only two field blank samples for each matrix were collected.

Comments

Additional notes and data gaps critical to the scientific validity of the study, not addressed above, are presented below. The following issues were identified:

- The reported results were not corrected for recoveries.

- As noted by the authors, "the degree of exposure due to the act of spraying the dog can not be separated from the exposure due to restraining the animal, or lifting and carrying the dog to the grooming facility cage or kennels..... a large portion of the residues detected on the forearms, upper arms and chest may be due to the transport of a series of wet dogs".

- Typical working practices including number of pets treated per day, application methods, and durations should be further defined. As noted by the authors, the study design specifying eight dogs to be treated consecutively in each replicate did not mimic actual procedures. In addition, groomers in the study were not allowed to change outer clothing. In actual practice, the groomer would have the option of changing outer clothing as needed.

- As per label rate, two pumps per pound of dog weight was recommended. However, squeezing the pumps would cause variability in the amount of ai applied.

- As per label attached, 0.29 percent (w/w) of ai is contained in the product. However, 0.25 percent (w/v) was used in the study for calculations.

- The sampling times reported for each replicate included the intervals between treatments of dogs (eight dogs were treated for each sample replicate). The actual treating times were less than the reported sampling times.

- Field recovery samples were exposed for approximately two hours; however, the length of time for which the actual field samples were exposed was not provided.

- Field recovery data were collected in a different room from the treatment room used for the field study. However, the air temperature and relative humidity of these two rooms were similar during the time the studies were conducted.

- The following discrepancy was found in the Study Report; on p. 25, field recovery data on glass fiber filters were collected at 1.09, 10.9, and 1,098.0 µg/mL; however, on p. 671, the results were reported at 0.109, 1.09, and 109.8 µg/mL.

- At the end of the fortifications, duplicate samples from each of the fortification solutions were also collected to obtain recovery results. However, dates of extraction and analysis of these samples were not reported.

- Several protocol amendments were noted and there were several minor exceptions to GLP compliance, but the authors stated there was no effect on the integrity of the study.

In summary, most of the requirements contained in Subdivision U of the Pesticide Assessment Guidelines (U.S. EPA, 1996) were met. Sixteen replicates were performed, but they all represented one site, instead of three. Typical working practices including number of pets treated per day, application methods, and durations should be further defined to interpret the exposure results.

APPENDIX

The following items were attached in the Appendix:

- Summary of exposure and residues on dermal and inhalation matrices
- Field calculations
- Test site layout
- Product label
- GC specifications, and columns used
- LOQ and LOD summaries and calculations

Page _____ is not included in this copy.

Pages 12 through 22 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

__X__ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

_____ Proprietary information pertaining to the chemical composition of an inert ingredient provided by the source of the ingredient.

_____ Attorney-Client Privilege.

_____ Claimed Confidential by submitter upon submission to the Agency.

_____ Internal Deliberative Information.

* The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.