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

MAY 21, 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Revised Exposure Assessment for Application by Veterinarians/Pet Groomers of Frontline Spray Treatment and Frontline Spot Treatment (active ingredient: fipronil) on Dogs and Cats for Flea and Tick Control.

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THRU: Mark I. Dow, Ph.D., Section Head for Dana F. Rutherford
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DP Barcode: D219825, D222391, and D226161

Pesticide Chemical Code: 129121

EPA Reg. No.: 65331-1; 65331-EUP-E

PHED: No

I. INTRODUCTION
A. Purpose

The Risk Characterization and Analysis Branch (RCAB) has requested that the Occupational and Residential Exposure Branch (OREB) provide an additional exposure assessment for the application of two fipronil-containing products for use as a pet spray and a pet spot treatment for flea and tick control. This assessment assumes that the two above-mentioned products will be applied by veterinarians or pet groomers.

B. Background

The active ingredient in Frontline Spray Treatment and Frontline Spot Treatment is fipronil, the common name for 5-amino-1-(2,6-dichloro-4-(trifluoromethyl) phenyl)-4-[(1,R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-carbonitrile.

A previous OREB memorandum (DP Barcode: D219825/D222391; copy attached) dated April 23, 1996 to Richard Griffin of RCAB includes an exposure estimate for use of fipronil on dogs and cats for flea and tick control; this estimate assumed one time use by a consumer/pet owner.

II. DETAILED CONSIDERATIONS

The information in Table 1, below, is taken from the labels and labeling information provided by the registrant, Rhone Merieux, Inc.

Table 1. Information on Fipronil-Containing Spray and Spot Treatment

Parameter	Frontline Spray Treatment	Frontline Spot Treatment
Pests	Fleas and ticks	Fleas and ticks
Quantity of Active Ingredient w/w	0.29%	9.7%
Net Contents per Container	100 ml	0.67 ml
Intended Use	For dogs, puppies, cats, and kittens	For dogs and cats
Method of Application	Holding bottle upright, ruffle animal's coat with one hand while applying spray mist to the animal's back, sides stomach, legs, shoulders, and neck. For head and eye area, spray product on a gloved hand and rub into animal's hair. Apply until animal's hair is damp to thoroughly wet.	Inverting applicator over animal's back, part hair and apply entire recommended solution to the animal's skin in one spot between the shoulder blades.
Personal Protective Equipment required by label	Household latex gloves	None

Table 2. Assumptions for Exposure Assessments

Factors	Quantities per Label	
Maximum Application Rate for Frontline Spray Treatment	For cats*	1 ounce for "average size cat"
	For dogs*	2 ounces for 25 lb dog
Maximum Application Rate for Frontline Spot Treatment	For cats	0.5 ml for all sizes
	For dogs	0.67 ml for small dogs weighing between 5 & 10 kg
		1.34 ml for medium dogs weighing >10 and up to 20 kg
		2.68 ml for large dogs weighing >20 kg
Frequency of Application	For this exposure assessment, for use of these products by veterinarians or pet groomers, a frequency of 20 applications a day is assumed.	

*For kittens and puppies 8 weeks of age or older (per labeling).

Information on toxicity categories and a NOEL of 5.0 mg/kg/day for fipronil are derived from the Toxicology Endpoint Selection Document dated 1/27/95. In addition, a 4% dermal absorption factor for fipronil in these two formulations is assumed. This dermal absorption factor is based on a memorandum dated May 20, 1996 from R. Zendian, PhD, of the Science Analysis Branch to D. McCall of RCAB (see copy attached) Toxicity categories for the end-use product containing 0.25% active ingredient (Frontline Spray Treatment) are derived from a memorandum (DP Barcode: D202243; copy attached) dated June 7, 1994 from V. Dobozy, VMD, MPH, of TB II to R. Brennis and D. Waldo of Registration Division (PM 10) entitled: "Fipronil - Review of Acute Toxicity Studies to Support EUP for Domestic Animal Product (0.25% fipronil)."

TYPE OF TOXICITY	TOXICITY CATEGORY	
PRODUCT	**FIPRONIL (technical)**	**FRONTLINE SPRAY (0.25%)**
Acute oral	II	IV
Acute dermal	II	III
Acute inhalation	III	IV
Primary eye irritation	III	III
Primary dermal irritation	IV	IV Slight dermal irritation

III. CONCLUSIONS

Table 3, below, summarizes the OREB estimates for total exposure for applicators to fipronil, the active ingredient in Frontline Spray and Frontline Spot Treatments. These estimates are based on the assumptions outlined in Table 2, and, in the absence of exposure data, are based on acute exposure to the active ingredient in the volume of product recommended for 20 treatments of a large dog. Calculations used in estimating exposure are found in Attachment A.

Table 3. Exposure to Fipronil

End-use Product	Absorbed Daily Dose (per 20 treatments)	Margin of Exposure (MOE)
Frontline **Spray** Treatment Application of 100 ml (0.29% ai)	0.003 mg ai/kg bw/treatment	1,667
Frontline **Spot** Treatment Application of 2.68 ml (9.7% ai)	0.003 mg ai/kg bw/treatment	1,667

As there is no exposure data available to quantify the exposure to either the spray or spot treatment, the above exposure estimate assumes that the applicator is exposed to the entire quantity of active ingredient used in any given treatment (a dermal absorption factor of 4% is then applied). In the two scenarios evaluated by OREB, that is, in an instance where a large dog is treated with either the amount recommended on the label or an amount assumed appropriate for a large dog based on label directions (see Appendix A) the amounts of active ingredient per treatment that an applicator may be exposed to are very similar.

However, use of the spray treatment according to label directions may cause a higher rate of exposure to the applicator, as the animal's coat is sprayed until damp or thoroughly wet, with the applicator instructed to ruffle the animal's coat with one hand during application. Also, for application of the spray treatment to the head and eye area, the label directs the applicator to spray product on a gloved hand and rub it into the animal's hair. The spray method of application (with ruffling of the hair), applying the product to a gloved hand and rubbing it on the animal, as well as the possibility of the animal shaking and causing droplets of the product to shower the applicant, all increase the likelihood of applicator exposure to the active ingredient. The spot method of application may have a reduced exposure to the active ingredient for the applicator, although evidence to confirm this is lacking.

Both Frontline Spray Treatment and Frontline Spot Treatment can be reapplied at 30 day intervals. The active ingredient in these products, fipronil, is

identified in the attached Toxicity Endpoint Selection Document to be a slight dermal irritant, additionally, the acute dermal toxicity category for fipronil (technical) is II. The toxicity category for Frontline Spray for primary dermal irritation is a IV, but it is noted to be a slight dermal irritant. The label for Frontline Spray Treatment requires that "groomers or other persons applying the product frequently must wear household latex gloves." It is recommended that these requirements also appear on the Frontline Spot Treatment label. This recommendation is also included in a recent memorandum (DP Barcode: D221800/D222392; copy attached) issued April 3, 1996 from V. Dobozy, VMD, MPH, TBII, to R. Keigwin and A. Sibold of Registration Division (PM Team 10) entitled: " Fipronil Pet Products - Review of Domestic Animal Safety Studies with Spot-on Formulation and Use Information with Spray Formulation." Further, it is recommended that, for both Frontline Spray Treatment and Frontline Spot Treatment, the directions for use clearly indicate the requirement for use of chemical-resistant gloves (i.e., household latex gloves or waterproof gloves) prior to the directions for opening and applying the product and throughout the directions for use in instances in which contact with the product is likely (e.g., "...while wearing waterproof gloves, ruffle the animal's coat with one hand while applying spray mist to the animal's back, sides, stomach, legs, shoulders, and neck...").

The OREB exposure assessment contained in this review is directed at the likely use of the spray and spot treatment products by pet groomers or veterinarians who may apply the products to numerous pets during the course of a day or in any specified period of time. While OREB has no data to use to estimate this exposure quantitatively, a worst-case scenario assuming 20 applications of a quantity of either the Frontline Spray or Spot Treatment recommended for use on a large dog is used for OREB's exposure assessment. It is noted, however, that the estimates in this review, while based on 20 treatments, represent only one day's exposure. Veterinarians and pet groomers may apply these products for multiple days per week over periods of months. A groomer may treat 20 large dogs per day, 260 days per year.

Attachments (4)
cc: C. Lang, OREB
Correspondence File
Chemical File, 129121 (Fipronil)

APPENDIX A. CALCULATIONS

ESTIMATES OF EXPOSURE AND MARGINS OF EXPOSURE (MOEs)

Applicators

Method of Application - Frontline Spray Treatment

The following exposure assessment represents the absorbed daily dose (ADD) of fipronil contained in one container of Frontline Spray Treatment and assumes that in treating a large dog the entire contents of a container might be used with subsequent exposure to the applicator of 100 ml of end- use product. Two additional assumptions are that the product, used by veterinarians or pet groomers, may be applied as many as 20 times per day; and that dermal absorption is 4%.

0.0029 mg ai/ml X 100 ml/container = 0.29 mg ai/treatment X 20 treatments/day
= 5.8 mg ai/day X 4% dermal absorption
= 0.232 mg ai/day absorbed, divided by 70 kg bw
= 0.003 mg ai/kg bw/treatment

Margin of exposure (MOE) = NOEL divided by the Absorbed Daily Dose
= 5 mg ai/kg/day divided by 0.003 mg ai/kg bw/treatment
= 1,667

Method of Application - Frontline Spot Treatment

The following exposure assessment represents the ADD of fipronil contained in one container of Frontline Spot Treatment and assumes that 2.68 ml might be used to treat a large dog (>20 kg) per label instructions, and that the applicator would be exposed to that amount of the end-use product. Additionally, this estimate is based on the use of the product 20 times per day, by veterinarians or pet groomers, and dermal absorption is assumed to be 4%.

0.097 mg ai/ml X 2.68 ml/treatment = 0.26 mg ai/treatment X 20 treatments/day
= 5.2 mg ai/day X 4% dermal absorption
= 0.208 mg ai/day absorbed, divided by 70 kg bw
= 0.003 mg ai/kg bw/treatment

Margin of exposure (MOE) = NOEL divided by the Absorbed Daily Dose
= 5 mg ai/kg/day divided by 0.003 mg ai/kg bw/treatment
= 1,667