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

Office of Prevention, Pesticides
and
Toxic Substances

August 30, 2000

MEMORANDUM

SUBJECT: Fipronil - Review of Registrant's Incident Analysis for Three Frontline® Products

DP Barcodes: D266554, D266556, D266557, D266850, D266851, D266852
Submissions: S580593, S580596, S580594, S581183, S581189, S581190
PC Code: 129121

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Virginia A Dobozy 8/30/00

THRU: Whang Phang, Ph.D., Branch Senior Scientist
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TO: Arnold Layne/Ann Sibold/PM 03
Registration Division (7505C)

Action Requested: 1) Reconsider recommendation for label warning against use of Frontline® products in rabbits; 2) Review incident analysis for three Frontline® products.

Recommendations: It is reiterated that a label warning against use on rabbits should be added to all Frontline® products, as recommended in the January 24, 2000 Memorandum. It is recommended that the registrant submit a yearly report for 2000 analyzing the incident data by breed, sex and age. It is also recommended that the registrant should submit details of the conditions of the deaths in the 2000 yearly report of the incident data, including product and amount applied, animal species, breed, sex, age, clinical signs, time between Frontline® treatment and initiation of clinical signs, treatment received and where (veterinarian, owner,etc.) and time between treatment and death. The bases for these recommendations are presented in the Discussion/Conclusions section at the end of this Memorandum.

Background

In a January 24, 2000 Memorandum (Virginia Dobozy to Arnold Layne/Ann Sibold), the domestic animal incident data for three fipronil flea and tick control products (Frontline® Spray, Frontline® Top Spot for Cats and Frontline® Top Spot for Dogs) submitted in letters dated April 15, 1998 and July 29, 1999 from Merial, Limited, were reviewed. HED recommended that details of all incidents of death (D-A) in the incident summary reports should be submitted to the Agency, including product and amount applied, animal species, breed, sex, age, clinical signs, time between Frontline® treatment and initiation of clinical signs, treatment received and where (veterinarian, owner, etc.) and time between treatment and death. In addition, it was recommended that, based on the consistency of reports of neurological signs and subsequent death in rabbits, the labels of all products be revised to warn against use on this species.

In a February 23, 2000 Memorandum (Virginia Dobozy to Arnold Layne/Ann Sibold), incident data in letters of December 16, 1998 and March 1, 1999 were reviewed. HED requested a more detailed categorization of the data for 1998 and 1999 by breed, age and sex as was done in the 1997 analysis for the three products. In addition, it was requested that the rate of adverse reactions should be calculated on a yearly basis, rather than since product inception. The rates should be expressed consistently, either as a function of the amount of product sold or per 100, 000 units.

Data Review

1) D266554, D266556 and D266557

a) *Minutes of the EPA/Merial Meeting, Suspected Adverse Incidents for Frontline® Products Pending Registration of Frontline® Plus Products, June 1, 2000*

At this meeting, the March 30, 2000 EPA letter which described the label warning against use in rabbits and requested the additional data and analyses was discussed. The registrant requested a reconsideration of the label warning against use on rabbits, based on data showing that the number of misuse incidents relative to the number of doses sold is insignificant and has been declining as the product has gotten established in the market. [See discussion under (b) below.] The registrant made a commitment to submit the analyses and data requested in the January 24 and February 23 Memoranda. EPA indicate that, after an evaluation of the 1998 and 1999 data, the registrant will be informed if a detailed categorization of incidents is required for the year 2000.[1]

b) Data on Adverse Reaction Incidence Rate in Rabbits per Unit Dose Sold (%)

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[1] Routinely, registrants are required to submit summaries of the number of adverse effects incidents by category of severity. More detailed analysis was required initially for Frontline® products due to their conditional registration. Since possible trends in misuse and higher rates of incidents in certain breeds of dogs were identified in earlier EPA reviews, a more detailed analysis and categorization was requested for 1998 and 1999.

Tables were submitted for Frontline® Spray, Frontline® Top-Spot (cat and dog products combined) and all Frontline® products combined by year (1997 through 1999) presenting the number of doses sold (in millions), number of reacting animals and incidence rate per unit dose sold (%) for the United States, Europe and Australia. The data are presented in Tables 1-3 below. It is noted that, in addition to the three rabbits, Frontline® Top Spot was also misused on a monkey in 1999.

Table 1: Suspected Adverse Incidents in Rabbits Reported for Frontline® Spray(1997-1999)[a]

Country	No. of Doses Sold (in millions)[b]			No. of Reacting Animals			Incidence Rate per Unit Dose Sold (%)		
	1997	1998	1999	1997	1998	1999	1997	1998	1999
USA	1.66	1.45	1.04	1	0	5	0.00006	0.00	0.0005
Europe	10.2	9.8	10.3	57	47	9	0.0006	0.0005	0.00009
Australia	0.5	0.33	0.26	1	5	3	0.0002	0.0015	0.0012
Total	12.4	11.6	11.6	59	52	17	0.00048	0.00045	0.00015

a Extracted from Unnumbered table in June 5, 2000 letter from Merial, Limited
b A single dose refers to 100 ml of Frontline® Spray

Table 2: Suspected Adverse Incidents in Rabbits Reported for Frontline® Top-Spot (Cats and Dogs) (1997-1999)[a]

Country	No. of Doses Sold (in millions)[b]			No. of Reacting Animals			Incidence Rate per Unit Dose Sold (%)		
	1997	1998	1999	1997	1998	1999	1997	1998	1999
USA	22.5	37.7	36.3	27	7	3	0.00012	0.00002	0.00001
Europe	8.6	16.0	26.4	5	10	8	0.00006	0.00006	0.00003
Australia	1.1	2.7	4.1	6	6	1	0.00055	0.00022	0.00002
Total	32.2	56.4	66.8	38	23	12	0.00012	0.00004	0.00002

a Extracted from Unnumbered table in June 5, 2000 letter from Merial, Limited
b A single dose refers to an individual Frontline® Top Spot Pipette

Table 3: Suspected Adverse Incidents in Rabbits Reported All Frontline® Products (1997-1999)[a]

Country	No. of Doses Sold (in millions)			No. of Reacting Animals			Incidence Rate per Unit Dose Sold (%)		
	1997	1998	1999	1997	1998	1999	1997	1998	1999
USA	24.2	39.2	37.3	28	7	8	0.00012	0.00002	0.00002
Europe	18.8	25.8	36.7	62	57	17	0.00033	0.00022	0.00005
Australia	1.6	3.03	4.36	7	11	4	0.00044	0.00036	0.00001
Total	44.6	68.0	78.4	96	75	29	0.00022	0.00011	0.00004

a Extracted from Unnumbered table in June 5, 2000 letter from Merial, Limited

2) D266850, D266851, D266852

Adverse Reaction Incidence Rates

This submission contains an analysis of the 1998 and 1999 domestic animal incident data for each of the three Frontline® products by breed, age and sex. Additional details on the incidents resulting in death were also provided, as well as yearly rates of suspected adverse incidents (as a function of the number of units sold in the U.S. during the calendar year). Table 4 provides the rates for 1998 through 1999. Previous calculations of incidence rates were based on the amount sold from product launch until December 31, 1996 and December 23, 1997. Those rates are in the April 29, 1998 Memorandum (Virginia Dobozy to Susan Lewis/Ann Sibold). The rates since product introduction are low and fairly consistent from year to year. However, they are probably higher than calculated by the registrant for several reasons. First, incidents of adverse reactions are under-reported. Second, as stated in the April 29, 1998 Memorandum, the use of "doses sold" overestimates the amount of product actually used and thus decreases the rate.

Table 4: Adverse Reaction Incidence Rates (number of reacting animals/number of doses sold) Frontline® Products (1998-1999)[a]

	Year					
Product	1998			1999		
	No. of Doses Sold*	No. of Reacting Animals	Incidence Rate (%)	No. of Doses Sold*	No. of Reacting Animals	Incidence Rate (%)
Frontline® Spray	1,456,237	30	0.002	1,038,922	35	0.00336
Frontline® Top Spot for Cats	8,915,625	149	0.0016	8,432,052	198	0.00235
Frontline® Top Spot for Dogs	28,772,535	363	0.00126	27,922,770	294	0.00105

a Extracted from unnumbered tables in June 12, 2000 letter from Merial, Limited

* A single dose refers to 100 ml bottle for Frontline® Spray or an individual pipette for Frontline® Top-Spot

Analysis by Sex, Breed and Age

The analyses of the incident data by sex, breed and age were reviewed. There doesn't appear to be any sex or age predilection for adverse effects. For cats, the breed most frequently affected with the spray and spot-on products is the domestic shorthair, which is the most popular breed. The breeds of dogs with the highest incidence rates with Frontline® Top Spot for Dogs for each year are presented in Table 5. The data show that the Laborador and Golden Retriever and the German Shepherd dog are the breeds with the highest incidence rates. This is understandable as they are popular breeds and thus, more dogs are treated with the product. There were only 7 incidents with Frontline® Spray so any evaluation of breed predilection is meaningless.

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Table 5: Top 10 Canine Breeds with the Highest Incidence Rates of Adverse Reactions with Frontline® Top Spot for Dogs in 1998 and 1999[a]

	Year	
Number	1998	1999
1	Laborador Retriever (12.1)	Laborador Retriever (11.9)
2	Golden Retriever (6.6)	German Shepherd Dog (5.4)
3	German Shepherd Dog (5.8)	Golden Retriever (4.8)
4	Mixed Breed (3.9)	Sheltie (4.1)
5	Yorkshire Terrier (3.9)	Bichon Frise (4.1)
6	Cocker Spaniel (3.3)	Unknown Breed (3.7)
7	Terrier (2.8)	Chihuahua (2.7)[b]
8	Rottweiler (2.5)[b]	Cocker Spaniel (2.7)[b]
9	Sheltie (2.5)[b]	Schnauzer Miniature (2.7)[b]
10	Bichon Frise (2.5)[b]	Shih Tzu (2.7)[b]

a Extracted from unnumbered tables in June 12, 2000 letter from Merial, Limited; rates (%) are in parentheses.
b Arbitrarily assigned number; rate is the same for other breeds.

Deaths

The detailed information on the deaths which occurred after exposure to either of the three Frontline products was reviewed. Conditions associated with the deaths, which may help determine if the product was responsible for the fatality, can be divided into several possible categories as follows.

1) Concomitant medical conditions or treatment - suggests that other causes besides Frontline exposure may be responsible for the death.

2) Misuse (use in species not on the label or use on dogs and cats younger than the minimum age on the label) - could account for the death.

3) Possible exposure to other pesticides - complicates the determination of causality.

4) Time between application of the Frontline product and adverse reaction may help determine causality. If adverse reactions occur after the application of Frontline products, it is expected they would be observed acutely. An arbitrary cut-off of one day was used by the reviewer when evaluating the data. Reactions within one day increase suspicion of causality, whereas reactions that

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occurred after one day decrease suspicion of causality.

5) There were insufficient details in some incident reports to assign causality.

The data on deaths in 1998 and 1999 were reviewed and categorized using the above categories, as presented in Table 6. Many of the deaths were explained by other causes, including concomitant medical conditions or treatments, misuse, exposure to other pesticides or unexpected time between application and adverse reaction. However, there are some, especially with the Top Spot products, which appear to occur relatively acutely in reportedly healthy animals. Many of the clinical signs prior to death are neurological in nature, which is consistent with the known mechanism of toxicity of fipronil. Therefore, exposure to Frontline® products as a cause of these deaths cannot be ruled out.

Table 6: Categorization of Conditions Associated with Deaths After Frontline Exposure[a]

	1998			1999		
	Dogs	Cats	Other	Dogs	Cats	Other
Frontline Spray						
Concomitant Medical Conditions/Treatments	1	1			3	
Misuse		2[b]				1[c]
Other Pesticides		2				
Reaction < 24 hrs after application	1	1		1		
Limited Information				1		
Frontline Top Spot for Cats						
Concomitant Medical Conditions/Treatments		4			5	
Misuse			1[d]		1[e]	2[f]
Reaction >24 hrs after application		2			4	
Reaction < 24 hrs after application		4			5	
Limited Information		1				
Frontline Top Spot for Dogs						
Concomitant Medical Conditions/Treatments	5			3		
Misuse			2[g]		2[h]	
Reaction >24 hrs after application	1					
Reaction < 24 hrs after application	3			6		
Limited Information	1					

a Categorization by reviewer based on data in unnumbered tables of June 12, 2000 letter from Merial. Limited

b Used in two 6-week old kittens; c Rabbit - seizures prior to death;

d Rabbit - seizure 1 week after application of product, increased ALT, BUN, glucose and phosphorus

e Used on nursing kittens; f Rabbits - both had seizures prior to death; g Rabbits - both had seizures prior to death; h Dog product used on two cats

Discussion/Conclusions

Rabbit Warning

As discussed in the January 24, 2000 Memorandum and at the June 1, 2000 meeting with the registrant, the major reasons for recommending a label warning against use of the Frontline® products in rabbits are the consistency and severity of the adverse reactions, i.e., seizures followed by death in the many cases. The toxicity of fipronil in rabbits has also been recognized by veterinarians. At a toxicology meeting sponsored by the University of Illinois, a veterinarian from the ASPCA's National Animal Poison Control Center stated that fipronil, used off-label, has been reported anecdotally to cause seizures in rabbits, but that no studies have been done to confirm this.[2] A veterinarian with the San Diego Chapter of the House Rabbit Society has repeatedly reported that the spot-on Frontline® products are toxic to rabbits.[3] The registrant argues that the rate of reactions in rabbits is low and has been declining. The submitted data demonstrate that the incidence rates (per unit dose sold) of adverse reactions in rabbits are low. However, they are probably higher than calculated for several reasons. First, incidents of adverse reactions are under-reported. Second, as stated in the April 29, 1998 Memorandum, the use of "doses sold" overestimates the amount of product actually used and thus decreases the rate. In addition, the rates were not calculated for the Top Spot products individually but rather the dog and cat products were combined. Table 4 demonstrates that far more Top Spot for Dogs is sold than Top Spot for Cats. By combining the data, there is the possibility that higher incidence rates with the cat product are diluted by the disproportionate amount of dog product sold.

It is reiterated that a label warning against use on rabbits should be added to all Frontline® products, as recommended in the January 24, 2000 Memorandum.

Adverse Reactions in Dogs/Cats

The incidence rates for the three Frontline® products are low and fairly consistent from year to year since product introduction. However, as stated above, the rates are probably higher due to under-reporting and the use of "doses sold" in the calculations.There doesn't appear to be an age or sex predilection for adverse reactions. Regarding breed, for cats, the breed most frequently affected with the spray and spot-on products is the domestic shorthair, which is the most popular breed. The breeds of dogs with the highest incidence rates with Frontline® Top Spot for Dogs are the Laborador and Golden Retriever and the German Shepherd dog. This is understandable as they are popular breeds and thus, more dogs are treated with the product. There were only 7 incidents in 1998 with Frontline® Spray so any evaluation of breed predilection is meaningless. In 1999, there were 23

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[2]Talk presented by Dr. Tina Wismer on Novel Insecticides and Insect Growth Regulators, Small Animal Toxicology Short Course, "Emerging Problems in Toxicology", University of Illinois, Urbana. IL. May 5, 2000.

[3]Recommendation from Dr. Jeffrey Jenkins on House Rabbit Society Web site: www.rabbit.org/chapters/san-diego/health/vet-talk/frontline.html

incidents with the spray product which were fairly equally distributed across breeds. In previous reviews of the Frontline® incident data, the incidence rate of adverse reactions (5.3%) in the Bichon Frise, a relatively unpopular breed, was raised as a concern. In the April 2, 1998 Memorandum analyzing the 1997 data, it was noted that this breed may be especially sensitive to dermal irritation with Top Spot for Dogs. With the 1998 and 1999 data, the incidence rates in this breed are 2.5% and 4.1%, respectively. The rate has declined somewhat but is still of concern and should be followed.

It is recommended that the registrant submit a yearly report for 2000 analyzing the incident data by breed, sex and age. The monitoring of incidence rates is considered especially important to assure that there is no increased breed sensitivity to Frontline® products.

Deaths

Many of the deaths which occurred after application of Frontline® products may be explained by other causes, including concomitant medical conditions/treatments, misuse, exposure to other pesticides or unexpected time between application and the adverse reaction. However, there are some, especially with the Top Spot products, which appear to occur relatively acutely in reportedly healthy animals. Many of the clinical signs prior to death are neurological in nature, which is consistent with the known mechanism of toxicity of fipronil. Therefore, exposure to Frontline® products as the cause of these deaths cannot be ruled out.

It is recommended that the registrant should submit details of the conditions of the deaths in the 2000 yearly report of the incident data, including product and amount applied, animal species, breed, sex, age, clinical signs, time between Frontline® treatment and initiation of clinical signs, treatment received and where (veterinarian, owner,etc.) and time between treatment and death. This information is important in monitoring the cause of death in Frontline®-exposed animals.

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