

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING DOG PRODUCT
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Registration #: 65331-3

Registrant: Merial Limited

Subregistrant(s): Not Applicable

Product Name(s): Frontline Top Spot for Dogs

Active Ingredient: Fipronil (9.7 %), PC Code: 129121, CAS # 120068-37-3

Species: dog (the label states under DIRECTIONS FOR USE: "USE ON DOGS ONLY. DO NOT USE ON RABBITS. DO NOT USE ON OTHER ANIMALS.")

Sales Method: Veterinary and Retail

Weight Ranges:	Application Method (application tubes can contain 0.67, 1.34, 2.68 or 4.02 mL). Place applicator tip at the skin level between the shoulder blades. Squeeze applicator, applying entire contents in a single spot on the animal's skin. Avoid superficial application to the animal's hair.
≤ 22 pounds	Apply 0.67 mL.
23 - 44 pounds	Apply 1.34 mL.
45 - 88 pounds	Apply 2.68 mL.
89 - 132 pounds	Apply 4.02 mL.

Age: For Dogs & Puppies 8 weeks or older and up to 22 lbs. For Dogs 23-44 lbs, 45-88 lbs, 89-132 lbs.

Primary Reviewer: Melba Morrow **Signature:** *Melba Morrow* **Date:** 3/12/2010
Secondary Reviewer: Byron T. Backus **Signature:** *Byron T. Backus* **Date:** 3/12/2010

Product sold in retail stores.

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for Registration # 65331-3 containing Fipronil (9.7 %). The product is a topical spot-on pesticide for dogs and puppies 8 weeks of age and older, with monthly applications to control fleas, ticks, and chewing lice. The label says for use on dogs only, not for use on rabbits or other animals.

Background: The data were submitted in response to an Agency request to all registrants for enhanced reporting of incidents involving topical pet insecticides applied monthly. The Agency request for more data was made at a meeting on May 5, 2009 between EPA, registrants, Canada's Pest Management Regulatory Agency, and other stakeholders. The data are intended to better characterize incidents received in aggregate incident summaries submitted by registrants which do not describe details regarding the incidents.

The incidents have not been verified and may have causes other than exposure to the pesticide, may be associated with an underlying medical condition, or may be due to misuse of the product (such as overdose, applying on too young an animal, or applying on a different species). The total number of reported incidents may be influenced by many external factors, such as negative publicity on web sites and ease or difficulty in reporting due to information presented on the product label which may vary between registrants.

This report includes only incidents for which a registration number was available. The total number of affected animals may differ between the tables in this report because incidents with multiple animals were sometimes not counted when it was difficult to tell which animal the description applied, or because age, weight, breed, or route of exposure were not always reported. Data were reported differently by the different registrants and simplifying assumptions were sometimes made and in other cases ambiguous data were not considered.

The intent of this report was not just to report the total number of incidents, but to describe the nature of the incidents and to identify any susceptible subpopulations or use patterns which may predispose to toxicity so that mitigation could be implemented if appropriate. The focus of this report is on dermal exposure for which there was no indication of misuse. However, the consequences of misuse or for oral exposure by grooming are also reported.

Conclusions: A total of 255 (241 dermal, 6 oral and 8 unspecified route) incidents in dogs were evaluated for severity. Most were classified as minor (175 incidents or 68% of all incidents). There were 67 (26%) moderate incidents, 7 (3%) major incidents and 6 (<2%) deaths. (See Appendix for description of major, moderate and minor categories).

There were 19 incidents in cats, of which 11 (58%) were classified as minor, 7 (37%) as moderate, and 1 (5%) major. There were no deaths in cats.

For dermal exposure in dogs, there were 164 incidents (101 minor, 55 moderate, 5 major and 3 deaths) in which age was reported. There were 44 incidents (27%), including 1 death, that occurred in animals of less than 1 year of age. The one death was in a puppy 6-9 months of age. There were 6 incidents (1 moderate, 5 minor) in puppies of less than 3 months of age, but there were no reported incidents involving puppies of less than 8 weeks of age. The other two deaths for which age was reported occurred in dogs 5-7 years of age.

There were only 12 incidents (or 7% of a total of 165) in which the dog weight was less than the product weight range.

Approximately 45% (75/165) of the incidents occurred in dogs weighing less than 21 pounds. However, 38 of these incidents involved dogs weighing 11-21 pounds, and this may simply reflect the popularity of smaller dogs. There was no indication that adverse effects occurred more frequently in one gender.

Breeds (mixed or specific) were reported for 241 incidents. Mixed breed dogs were involved in 56 incidents (19 involving small dogs <10 kg; 9 for medium dogs 10-20 kg; 11 for large dogs

>20 kg; and 17 unknown). Among purebreds, Labrador Retrievers (23 incidents), Yorkshire Terriers (13 incidents) and Golden Retrievers (11 incidents) were the three top breeds in incidents, consistent with their rankings of 1, 2 and 3 in annual registrations with the American Kennel Club (AKC).

However, Maltese, Shih Tzu and Pugs were each involved in 8 incidents, and so were overrepresented with respect to their AKC rankings (20th, 15th and 10th, respectively). Conversely, beagles (used in the companion animal safety studies to register this product) were tied for 14th with 4 incidents despite an AKC ranking of 5.

For those incidents in which gender was reported, males and females were about equally represented.

The majority of the reactions in dogs involved (1) systemic, (2) application site, skin and appendages, (3) digestive, (4) application site, (5) neurological and (6) behavioral disorders. Consistent with reactions at the application site, the most common clinical signs were pruritus, dermatitis, sores, erythema and irritation. Alopecia and application site hair change were also noted. Other commonly reported clinical signs were lethargy (and similar observations) and emesis, which might be from ingestion. Clinical signs and symptoms reported after ingestion of fipronil by humans include nausea, vomiting and headache.

SEVERITY. (See Appendix for description of major, moderate, minor categories)

Tables 1-4 provide information on the severity of the reported incidents in dogs. A total of 255 incidents by all exposure routes were reported for dogs, with 6 incidents (2%) involving death and another 7 incidents (3%) being classified as of major severity. All deaths and incidents of major severity were associated with dermal administration of the product, and although there were 6 reported incidents from oral exposure, all were reported as being minor.

Table 1 (Reg # 65331-3).**Severity: Dermal, Oral and Unspecified Routes of Exposure in Dogs, 2008.**

Severity*	# of Incidents	Per Cent
Death	6	2
Major	7	3
Moderate	67	26
Minor	175	68
TOTAL	255	

* See appendix for explanation of severity categories

Table 2 (Reg # 65331-3). Severity: Dermal Exposure in Dogs*, 2008

Severity**	# of Incidents	Per Cent
Death	6	2%
Major	7	3%
Moderate	66	27%
Minor	162	67%
TOTAL	241	

*Animals that had both oral and dermal exposures were not included in this table

** See appendix for explanation of severity categories

Table 3 (Reg # 65331-3). Severity: Oral Exposure in Dogs*, 2008

Severity**	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	0	
Minor	6	100%
TOTAL	6	

*Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

Table 4 (Reg # 65331-3). Severity: Unspecified Exposure Route in Dogs, 2008.

Severity*	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	1	13
Minor	7	88
TOTAL	8	

* See appendix for explanation of severity categories

Cat exposed to dog product

Table 5 provides information on the incidents of cats receiving the canine product. There were a total of 19 incidents, none of which resulted in death and only one of which could be classified as an incident of major severity.

Table 5 (Reg #65331-3). Severity: Dermal Exposure in Cats*, 2008

Cat exposed to dog product

Severity**	# of Incidents	Per Cent
Death	0	
Major	1	5
Moderate	7	37
Minor	11	58
TOTAL	19	

*Animals that had both oral and dermal exposures were not included in this table

** See appendix for explanation of severity categories

There were no reported incidents in cats due to oral or unknown routes of exposure.

Gender

There did not appear to be any predilection for adverse effects to occur in one sex or the other (see Table 6). When considering only known females and males the incidences were similar (52 and 48 %, respectively). There were several entries designated as animals having “mixed sexes” and since hermaphroditism is not common in dogs, one can make the assumption that the incidents may have involved both male and female animals. Of the 241 animals appearing in the report 113 were females (76 neutered; 36 intact, 1 lactating) and 105 were males (66 neutered and 39 intact).

Table 6 (Reg # 65331-3). Gender: Dermal Exposure in Dogs, 2008

Sex	# of Incidents	Per Cent	Per Cent*
Female	113	47	52
Male	105	44	48
Unkown	23	10	NA
TOTAL	241 (218*)		

Note: Gender was not reported for all incidents.

*Values for Males and Females only

Age

Ages were reported in 164 incidents involving dogs. Animals less than 1 year of age accounted for approximately 26% of the total number of incidents. The greatest number of incidents was reported for any one year occurred for animals less than 1 year (26 %). The incidence gradually decreased as the animals got older when considered on a per year basis, 15% for 1-2 years, 11 % for 2-3 years, 6 %/year for 3/5 years and so on. The majority of the incidents for any age were minor (62 %) followed by moderate at 34 %. There were only 3 deaths reported (2 %). Animals between the ages of 3-5 years had a higher incidence of major effects but these only amounted to 2 % total. There were no incidents reported in animals less than two months of age, indicating that the product was used in accordance with label instructions when age was considered.

Table 7 (Reg # 65331-3). Age: Dermal Exposure in Dogs, 2008 # of Incidents (%)

Severity* Age	Death	Major	Moderate	Minor	Total (%)
< 3 Months**	0	0	1(<1)	5 (3)	6 (4)
3 – 6 month	0	0	2 (1)	7 (4)	9 (5)
6 – 9 months	1(<1)	0	4 (2)	7 (4)	12 (7)
9- 12 months	0	0	8 (5)	9 (5)	17 (10)
[total for 0 – 1 year]	[1 (<1)]	0	[15 (9)]	[28 (17)]	[44 (26)]
1 – 2 year	0	0	8 (5)	17 (10)	25 (15)
2 – 3 years	0	0	6 (4)	12 (7)	18 (11)
3 – 5 years	0	2 (1)	5 (3)	12 (7)	19 (12)
5 – 7 years	2 (1)	2 (1)	7 (4)	10 (6)	21 (13)
7 – 9 years	0	0	4 (2)	9 (5)	13 (8)
9 – 11 years	0	0	6 (4)	10 (6)	16 (10)
> 11 years	0	1(<1)	4 (2)	3 (2)	8 (5)
Subtotal	3 (2)	5 (3)	55 (34)	101 (62)	
TOTAL incidents	164				

Note: Not all ages were reported.

* Severity key (See appendix for explanation of severity categories)

** These incidences were for animals greater than 2 months old.

BODY WEIGHT

Dose ranges: up to 22, 23-44, 45-88, 89-132 pounds

Body weights were reported for a total of 165 animals (see table 8). The greatest number of incidents by weight was reported for animals, in the 11 to 21 pound group (23%) followed by animals greater than 60 pounds (20%). Animals in the 5 to 11 pound group also comprised 19% of the reported incidents. Animals weighing from 41 to 51 pounds had an incident rate of 11% and 51-61 has 7%. Interestingly, animals weighing less than 5 pounds had the lowest number of reports, (4%), indicating that low body weights were not a major factor in the manifestation of adverse reactions. A single death was reported in the 31 to 41 pound group.

Table 8 (Reg # 65331-3). Body Weight: Dermal Exposure in Dogs, 2008. # of incidents (%)

Severity* Body Wt (pounds)	Death	Major	Moderate	Minor	Total %
< 5	0	0	2 (1)	4 (2)	6(3)
5 – 11	0	0	13 (8)	18 (11)	31 (19)
11 – 21	0	3 (2)	7 (4)	28 (17)	38 (23)
21 – 31	0	0	7 (4)	12 (7)	19 (11)
31 – 41	1 (<1)	0	0	7 (4)	8 (5)
41 – 51	0	1 (<1)	5 (3)	12 (7)	18 (11)
51 – 61	0	0	3 (2)	9 (5)	12 (7)
≥61	0	1 (<1)	11 (7)	21 (13)	33 (20)
subtotal	1 (<1)	5 (3)	48 (29)	111 (67)	
TOTAL incidents	165				

Note: Not all body weights were reported.

Weight range (x – y) indicates weight from x up to but not including y

Table 9 indicates that product misuse is only responsible for 7 % of the incidents.

Table 9 (Reg # 65331-3). Product Weight Range: Dermal Exposure Dogs, 2008

Product Weight Range	# Incidents	Per Cent
Dog weight < product weight range*	12	7
TOTAL incidents	165	

*This table indicates product misuse and is a summary of all product use weight ranges

NOTE: not all body weights or product used were reported

BREEDS

Breeds (mixed or specific) were reported for 241 incidents. Mixed breed dogs were involved in 56 incidents (19 involving small dogs <10 kg; 9 for medium dogs 10-20 kg; 11 for large dogs >20 kg; and 17 unknown). Among purebreds, Labrador Retrievers (23 incidents), Yorkshire Terriers (13 incidents) and Golden Retrievers (11 incidents) were the three top breeds in incidents, consistent with their rankings of 1, 2 and 3 in annual registrations with the American Kennel Club (AKC).

However, Maltese, Shih Tzu and Pugs were each involved in 8 incidents, and so were overrepresented with respect to their AKC rankings (20th, 15th and 10th, respectively). Conversely, beagles (used in the companion animal safety studies to register this product) were tied for 14th with 4 incidents despite an AKC ranking of 5.

Table 10 (Reg #65331-3). Dermal Exposure in Dogs, 2008 by Breed Size

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Mixed/unknown*	various	56	23	NR
Labrador retriever	large	23	10	1
Yorkshire terrier	small	13	5	2
Golden retriever	large	11	5	4
Maltese	small	8	3	20
Pug	small	8	3	15
Shi Tzu	small	8	3	10
Chihuahua	small	7	3	12
Boxer	large	6	2	6
Havanese	small	5	2	36
Lhasa Apso	small	5	2	54
Pomeranian	small	5	2	13
German Shepherd	large	5	2	3
Dachshund	Small/medium	4	2	7
Cocker Spaniel	medium	4	2	21
English bulldog	large	4	2	8
Jack Russell Terrier	small	4	2	
Beagle	medium	4	2	5
Standard Poodle	large	4	2	9
Shetland Sheepdog	small	3	1	19
Bichon Frise	small	3	1	35
Siberian Husky	large	3	1	23
Great Dane	large	2	1	22
West Highland	small	2	1	34
Vizsla	large	2	1	42
Collie	large	2	1	38

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Boston Terrier	medium	2	1	17
Toy Poodle	small	2	1	9
Terrier breeds		2	1	
Bedlington terrier	medium	2	1	124
Pit Bull	large	2	1	55
Miniature Schnauzer	small	2	1	11
Shar Pei	medium	2	1	45
Others		26	11	
Total		241		

Note: Not all breeds were reported.

AKC Rank is the number of new registrations for 2008 by the American Kennel Club.

NR – Not AKC ranked

a Dachshunds are listed as #7 by AKC, but ranking for Miniature and Standard sizes are not named separately.

NR: not ranked

b Poodles are listed as #9 by AKC, but Toy, Miniature, and Standard breeds are not named separately.

c Pit Bulls include Bull Terriers (#55), American Staffordshire Terriers (#69), and Staffordshire Bull Terriers (#76). American Pit Bull Terrier is not listed by AKC.

* Small (<10 kg) mixed = 19, large (>20 kg) mixed = 11, medium (10-20 kg) = 9, unknown = 17

BODY SYSTEMS

There were a total of 409 reports involving various body systems for 241 incidents. These incidents are captured in Table 11. This clearly indicates that some of the animals had more than one symptom involving multiple systems. Of the reported systems involvement, 18 % were designated as systemic disorders. Systemic disorders were followed by disorders of the skin and appendages (16%), digestive tract disorders (15%) application site disorders (13%) neurological disorders (12% and behavioral disorders (11%). All other observations occurred at a frequency of less than 10% of the total observations reported.

Table 11 (Reg # 65331-3). Body System: Dermal Exposure in Dogs, 2008

Body System	# of Reports	Per Cent
Systemic disorders	75	18%
Skin and appendages disorders	64	16%
Digestive tract disorders	62	15%
Application site disorders	54	13%
Neurological disorders	51	12%
Behavioural disorders	46	11%
Respiratory tract disorders	16	4%
Immune system disorders	13	3%
Eye disorders	7	2%
Musculoskeletal disorders	5	1%
Ear and labyrinth disorders	4	<1%
Cardio-vascular system disorders	4	<1%
Blood and lymphatic system disorders	4	<1%
Renal and urinary disorders	2	<1%
Metabolism and nutrition disorders	1	<1%
Endocrine system disorders	1	<1%
TOTAL	409	

Note: Not all incidents had a body system reported and some incidents had multiple body systems reported.

CLINICAL SIGNS

Table 12 provides information on the clinical signs following dermal exposure. The most commonly reported signs involved the skin and appendages and were characterized as pruritis, erythema, dermatitis, irritation and sores (16%). Lethargy was reported in 11% of the incidents, followed by emesis (9%), anorexia (5%) and seizures (4%). Other clinical signs were reported at a lower frequency of occurrence. The following select lesions that occurred at >1% including vocalization, tachypnea, dyspnea, anxiety, panting self mutilation, tachycardia, weakness were not recorded individually, but when totaled, they accounted for 26% of the total reported clinical signs. A total of 128 (13%) of all signs were related to the application site.

Table 12 (Reg # 65331-3). Clinical Signs: Dermal Exposure in Dogs, 2008

Signs	# of Incidents	Per Cent
Pruritus/Erythema/Dermatitis/Irritation/Sores	153	16%
Lethargy and related signs	105	11%
Emesis	83	9%
Anorexia	48	5%
Seizures	38	4%
Behavioural disorder NOS	33	3%
Application site hair change	30	3%
Diarrhea	30	3%
Salivation	28	3%
tremor/trembling	28	3%
Alopecia	27	3%
Ataxia	25	3%
Agitation	20	2%
Fever	16	2%
Pyoderma	13	1%
Application site reaction NOS	12	1%
Pain	12	1%
Adipsia	11	1%
Urticaria	10	1%
See footnote*	251	26%
TOTAL	973	

Note: Not all incidents had clinical signs reported and some incidents had multiple clinical signs reported

** 251 (26 %) incidents were signs with <1% incidence

TOXICITY SUMMARY FOR 65331-3:**BRIEF SUMMARY OF TOXICITY:****Active ingredients:**

From an HED memorandum dated 9/22/09, fipronil (5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S) (trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile) is a broad-spectrum insecticide belonging to the pyrazole class of insecticides. Fipronil is neurotoxic in both rats and dogs as evidenced by signs in the acute and subchronic screening batteries in the rat, in developmental neurotoxicity and chronic carcinogenicity studies in the rat, and in two chronic dog studies. In a chronic toxicity study in dogs (MRID 42918645) the NOAEL in males was 1.0 mg/kg/day and in females was 0.3 mg/kg/day; the respective LOAELs were 2.0 mg/kg/day and 1.0 mg/kg/day based on clinical signs of neurotoxicity. In a rat acute neurotoxicity screening battery (MRID 42918635) the NOAEL was 0.5 mg/kg and the LOAEL was 5.0 mg/kg based on decreased hindlimb splay; in a subsequent rat neurotoxicity screening battery study (MRID 44431801) the NOAEL was 2.5 mg/kg and the LOAEL was 7.5 mg/kg based on decreased hindlimb splay in males and changes in a number of parameters for females. Fipronil is also associated with alterations in the thyroid-pituitary hormonal status, resulting in alterations in thyroid hormonal levels and thyroid follicular cell tumors. The rat and mouse showed evidence of liver and/or thyroid alterations at all time periods (chronic only for the mouse).

In acute toxicity studies, technical fipronil exhibits low to moderate toxicity, depending on the route of exposure and species. In rats it has oral LD₅₀ values of 92 mg/kg (males) and 103 mg/kg (females), indicating toxicity category II by this exposure route (MRID 42918628). By the dermal route, it is of moderate toxicity in rabbits (II, with an LD₅₀ value of 354 mg/kg, MRID 42918630), and low toxicity in rats (III, with an LD₅₀ >2000 mg/kg). It is in toxicity category II by the inhalation exposure route (LC₅₀ in male rats: 0.36 mg/L; in female rats: 0.42 mg/L, MRID 43544401). Fipronil technical is relatively non-irritating to the skin (IV, MRID 42918633) and eye (III (MRID 42918632) of rabbits and is not a dermal sensitizer (MRID 42918634). Dermal absorption in rats is estimated to be 1% or less based on a dermal absorption study (MRID 43737308).

NPIC Fipronil Technical Fact Sheet (<http://npic.orst.edu/factsheets/fiptech.pdf>): Fipronil's mode of action involves blockage of the GABA_A-gated chloride channels in the central nervous system. Fipronil's disruption of the GABA_A receptors prevents the uptake of chloride ions resulting in excess neuronal stimulation and death of the target insect. Fipronil-sulfone, the primary biological metabolite of fipronil, is reported to be twenty times more active at mammalian chloride channels than at insect chloride channels. Fipronil-sulfone is reportedly six times more potent in blocking vertebrate GABA-gated chloride channels than fipronil, but demonstrates similar toxicity to the parent compound in mammals. Fipronil-desulfinyl, the primary photoproduct of fipronil, is 9-10 times more active at the mammalian chloride channel than the parent compound, reducing the selectivity between insects and humans when exposed to this metabolite. Signs of toxicity in rats and mice given single doses of fipronil by the oral or inhalation exposure routes generally include changes in activity or gait, hunched appearance,

tremors, convulsions and seizures. Clinical signs and symptoms reported after ingestion of fipronil by humans include sweating, nausea, vomiting, headache, abdominal pain, dizziness, agitation, weakness, and tonic-clonic seizures. Clinical signs of exposure to fipronil are generally reversible and resolve spontaneously.

Companion animal safety studies:

From TXR 0051187: In this domestic animal safety study (MRID # 43863802), 4 male and 4 female pure-bred beagle dogs (approximately 10 weeks of age) were administered a single topical treatment of RM1601E/62 (9.7% fipronil) of either 1x, 3x or 5x the recommended dose (0.133 mg/kg/spot) once every month for a total of six treatments. A group of 4 male and 4 female dogs served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. A similar group served as an untreated control. The following parameters were evaluated: clinical observations, body weight, food consumption, water consumption, hematology and clinical chemistry. As there was no ante-mortem evidence of any treatment-related effects, necropsy examinations were only of the application sites. There was an increase in the number of animals in the vehicle control and treated groups which were observed to scratch and rub at the treated areas after application. On microscopic examination of the skin at the application sites, there was an increase in the number of females in the 3x and 5x groups which had superficial dermal inflammatory cells as compared to the untreated controls. The study demonstrated that RM1601E/62 (9.7% fipronil) has at least a 5X margin of safety in dogs greater than 10 weeks of age. The product label should state that there may be temporary irritation after application.

From TXR 0010923: MRID # 43121110: Groups of three male and three female beagle dogs were topically administered six treatments of 0.25% fipronil at dosages of either 0, 3, 9 or 15 mL/kg (0, 7.5, 22.5 and 37.5 mg/kg, respectively) at 28-day intervals. (The proposed recommended dose for the product is 3-6 mL/kg.) There was a statistically significant increase in the number of animals judged to have abnormal eye examinations in the 9 mL and 15 mL groups after the second treatment and in the 9 mL group after the sixth treatment. The increases were not dose-responsive and were not considered to be treatment-related. Two treated dogs, one in the 3 mL group and another in the 9 mL group, were noted to have skin lesions at 21 days after the last treatment. Additional treatment did not exacerbate the lesions. There was no other evidence of treatment-related toxicity.

From TXR 0011764 (dated January 24, 1996): "In the domestic animal safety studies, the 0.25% [spray-on] formulation was administered to adult and juvenile animals at five times the recommended dose (30 mL/kg). A comparison of the actual active ingredient applied to the animal at maximum rates illustrates that less active ingredient was applied with the 10% formulation..."

Dog Bodyweight (kg)	Spot Treatment Total Dose (mg)	Spray Treatment Total Dose (mg)
5	67	75
10	134	150
20	268	300

“The inerts in the two formulations differ. However, those found in the 10% formulation are listed on the Pesticide Product Inert Ingredients or the GRAS list. The vehicle control for this formulation was tested in an acute toxicity battery and showed the same level of toxicity as the formulation.”

Subsequently, the registrant conducted a companion animal safety study on beagle puppies with a formulation containing as actives fipronil (10%) and (S)-methoprene (9%). The following is a summary of this study:

In a companion animal safety study (MRID 44942104) Frontline Plus [Active Ingredients: fipronil:10% w/v; (S)-methoprene:9% w/v] was topically applied (between the base of the skull and the shoulder blades) at dose levels of 0.133 mL/kg, 0.399 mL/kg, and 0.665 mL/kg, to groups of 6 male and 6 female beagle puppies (52-60 days old at initiation) on test Day 1 and again on test Day 29. Controls received no treatment.

Clinical evaluations were conducted on approximately Day -14 (or soon after arrival if this was later than Day -14), and on Days 1 and 29 just prior to treatment. Following each treatment, the puppies were isolated for 6 hr and observed for the first 10 min, hourly for 6 hr and thereafter twice daily. Clinical evaluations were also conducted at 1, 3, 7, 14, and 21 days after each treatment. Clinical evaluations included: skin reaction at the application site (erythema, edema, alopecia, haircoat condition, and pruritus); rectal temperature; condition of the eyes (nystagmus, congestion, discharge, visual impairment); muscular disturbances (tremors, paralysis and atony); gastrointestinal disturbances (vomiting, consistency of stools); color of mucus membranes; and general behavior. Body weights were recorded on arrival, and thereafter weekly from approximately Day-7, and on the day of each treatment. Blood samples were obtained from fasted animals via the jugular vein once between Day -7 and Day-1 and on Days 15, 29 (prior to second treatment) and 43.

No mortality was observed during the study period, and there were no statistically significant, dose-related effects on body weight, clinical biochemistry, or hematology. Some control and test animals in all groups exhibited fecal abnormalities both before and during treatment (e.g., soft, creamy, or mucoid feces and red discharge in feces). Although these signs were considered by the study authors “not to be unusual for puppies”, it is possible that they represent an abnormal condition such as a parasitic infection. According to the report text, the puppies had received anthelmintic treatments prior to arrival, and received further treatments at the laboratory. However, the schedule of treatments (as well as the material administered) is not reported. One male in the high-dose group exhibited clinical signs (body weight loss early in the study (after fasting for blood collection) and subdued behavior on Day 18), and changes in hematology (stress leukogram, microcytosis and hypochromasia and anisocytosis on Days 15 and/or 29) and clinical chemistry (reduction in albumin and albumin: globulin ratio on Days 15, 29 and 43, and

elevated AST and ALT on Day 15). Most of the hematological and clinical chemistry changes observed in this one animal were of a transitory nature; however, the reduction in albumin level persisted throughout the study. Decreased albumin was also observed in one female in the 1X group on Day 15.

Overall, the observed clinical signs and changes in hematological and clinical chemistry parameters did not indicate significant treatment related adverse effects. The package labeling and application instructions indicate that the product is to be used on dogs or puppies 8 weeks or older and should not be used more frequently than once every 30 days.

It is concluded that the final dosages, as indicated on the label and as packaged in the applicator tubes, must be consistent with (no more than) the 1X application rate in this study (0.133 mL/kg).

Acute studies for 65331-3:

Note: the following studies were conducted on a formulation containing 10% fipronil and 12% (S)-methoprene. EPA Reg. No. 65331-3 has a label declaration of 9.7% fipronil.

In an acute oral LD₅₀ study (MRID 44942004), groups of 5 male and 5 female rats were dosed with 0.5, 1.0 or 2.0 g/kg of the test material. At 0.5 g/kg, 2/5 males and 1/5 females died. At 1.0 g/kg, 2/5 males and 5/5 females died. At 2.0 g/kg, 4/5 males and 4/5 females died. Most deaths occurred with 2-3 days following test article administration. All dose groups showed hypoactivity, salivation, dyspnea, prostration, coma and discoloration around the mouth. The estimated oral LD₅₀ > 750 mg/kg, placing the formulation in toxicity category III by this exposure route.

In an acute dermal LD₅₀ study (MRID 44942005), 5 male and 5 female young adult rats were dermally exposed to 5000 mg/kg of the test formulation. There were no mortalities and no significant clinical signs. The formulation is in toxicity category IV by this exposure route.

In a rabbit eye irritation study (MRID 44942006), there was no positive irritation in any of 3 rabbit eyes at 24 hours. The formulation is in toxicity category IV for eye irritation potential.

In a dermal irritation study (MRID 44942007) the formulation was in toxicity category IV by this exposure route.

The test material was not a sensitizer in guinea pigs using a Buehler protocol (MRID 44942008).

APPENDIX

EXPOSURE TYPE AND SEVERITY CATEGORIES

Excerpted From Pesticide Registration Notice 98-3, April 3, 1998.

D-A - Domestic Animal Death

§159.184 (5)(ii)(A): "If the domestic animal died or was euthanized."

It was reported that the animal died or was euthanized as a result of exposure or as a direct complication of exposure to the pesticide.

D-B - Domestic Animal Major

§159.184 (5)(ii)(B): "If the domestic animal exhibited or was alleged to have exhibited symptoms which may have been life-threatening or resulted in residual disability."

Life-threatening effects include, but are not limited to, massive or internal hemorrhage, loss of consciousness, grand mal seizures, paralysis, cardio-respiratory depression and bronchoconstriction requiring immediate treatment. In general, life-threatening effects are any condition which, if untreated, would likely lead to death. Residual disability includes adverse effects which last for an extended period of time after the initial poisoning and may affect the life span for the animal. An example of an adverse effect which may last for an extended period of time is the case of a cat that developed severe weakness lasting for weeks to months after organophosphate exposure. An example of a residual disability that may affect the life span of an animal is the case of a dog which recovered from cholecalciferol rodenticide ingestion but is left with decreased renal function.

D-C - Domestic Animal Moderate

§159.184 (5)(ii)(C): "If the domestic animal exhibited or was alleged to have exhibited symptoms which are more pronounced, more prolonged or a more systemic nature than minor symptoms. Usually some form of treatment would have been indicated to treat the animal. Symptoms were not life-threatening and the animal has returned to its pre-exposure state of health with no additional residual disability."

Effects include, but are not limited to, corneal abrasion, difficulty breathing, hyperthermia, isolated focal seizures, gastrointestinal symptoms leading to dehydration, caustic injury to mouth or esophagus, severe muscle weakness, incoordination, tremors and hives. More prolonged effects are those that last one month or longer, such as a persistent skin rash.

D-D - Domestic Animal Minor

§159.184 (5)(ii)(D): "If the domestic animal was alleged to have exhibited symptoms, but they were minimally bothersome. The symptoms resolved rapidly and usually involved skin, eye or respiratory irritation."

Effects include, but are not limited to, excessive salivation, skin rash, itching, conjunctivitis, lethargy, transient cough, mild gastrointestinal symptoms of a short duration and minor behavioral changes such as agitation and hyperactivity.

D-E - Symptoms Unknown, Unspecified or May Appear in Future

§159.184 (5)(ii)(E): "If symptoms are unknown or not specified."

If a documented exposure occurred and, based on other available evidence, was likely to lead to an adverse effect, then a report would be filed under this category. This category can be used for reporting evidence that known exposures have not resulted in symptoms. This information is useful in establishing a No Observed Effect Level for the pesticide in different species of animals. Additionally, the reporting of exposures which do not lead to adverse effects provides a measure of a product's safety.