

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING DOG PRODUCT
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Registration #: 65331-5

Registrant: Merial Limited

Subregistrant(s): NA

Product Name(s): Frontline Plus for Dogs

Active Ingredient: Fipronil (9.8%), PC Code: 129121 , CAS # 120068-37-3

Active Ingredient: S-Methoprene (8.8%), PC Code: 105402 , CAS # 65733-16-6

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.
<u>≤ 22 pounds</u>	<u>Apply 0.67 mL.</u>
<u>23 - 44 pounds</u>	<u>Apply 1.34 mL.</u>
<u>45 - 88 pounds</u>	<u>Apply 2.68 mL.</u>
<u>89 - 132 pounds</u>	<u>Apply 4.02 mL.</u>

Age: Dogs and puppies 8 weeks and older.

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 # 65331-5 containing Fipronil (9.8%), and S-Methoprene (8.8%). The product is a topical spot-on pesticide for dogs and puppies 8 weeks of age and older and is applied monthly to control fleas, ticks, and chewing lice.

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 2,469 incidents in dogs from all routes of exposure were evaluated for severity. Most were classified as minor (1,872 incidents or 76% of all incidents). There were 511 (21%) moderate incidents, 47 (2%) major incidents and 39 (<2%) deaths. (See Appendix for description of major, moderate and minor categories).

There were 96 incidents in cats, of which 48 (50%) were classified as moderate. There were 5 deaths in cats.

For dogs, 390 incidents (almost 25% of the total number of incidents), including 9 deaths, occurred in animals of less than 1 year of age. Four deaths occurred in puppies less than 3 months of age (some of these deaths may have involved misuse, as the label states the product is to be used only on animals 8 weeks or older). Five deaths occurred in dogs 3-6 months of age, while 6 occurred in dogs >11 years of age. As a total of 15/26 (or 58%) deaths occurred in animals <6 months or >11 years of age, and these dogs accounted for a total of 226 incidents (less than 15% of the total of 1,571), very young and old dogs may be at greater risk for death.

There were only 90 incidents (out of a total of 1,677) in which the dog weight was less than the product weight range.

Approximately 41% (688/1677) of the incidents occurred in dogs weighing less than 21 pounds. However, 360 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 2,354 incidents. Of these, mixed breed dogs (all sizes) were involved in 456 incidents, with large (>20 kg) having 206 incidents, small (<10 kg) with 127 incidents and medium (10-20 kg) with 123 incidents. Among purebreds, Labrador Retrievers (166 incidents) and Yorkshire Terriers (116 incidents) were the two top breeds in incidents, consistent with their rankings of 1 and 2 in annual registrations with the American Kennel Club. Golden Retrievers were 4th with 84 incidents, consistent with their AKC ranking of 4. However, the Shih Tzu (3rd with 87 incidents), Bichon Frise (5th with 63 incidents) and Chihuahua (6th with 59 incidents) were overrepresented with respect to their AKC rankings (10th, 35th and 12th, respectively). Conversely, beagles (used in the companion animal safety studies to register this product) ranked 15th with 30 incidents despite an AKC ranking of 5.

The majority of the reactions in dogs involved application site, skin and appendages and systemic 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)

As depicted in Tables 1-4, there were a total of 2469 incidents reported in dogs receiving the product by various routes of administration. The majority of the incidents were classified as being of moderate and minor significance. Two percent of the incidents were classified as major and slightly less than 2% were reported as deaths. The deaths were reported in animals receiving the product through the dermal route of exposure. Oral exposure did not result in death or the occurrence of incidents characterized as being of major significance.

Table 1 (Reg # 65331-5).**Severity: Dermal, Oral and Unspecified Routes of Exposure in Dogs, 2008.**

Severity*	# of Incidents	Per Cent
Death	39	<2
Major	47	2
Moderate	511	21
Minor	1872	76
TOTAL	2469	

* See appendix for explanation of severity categories

Table 2 (Reg # 65331-5). Severity: Dermal Exposure in Dogs*, 2008

Severity**	# of Incidents	Per Cent
Death	39	2%
Major	46	2%
Moderate	488	21%
Minor	1781	76%
TOTAL	2354	

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

** See appendix for explanation of severity categories

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

Severity**	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	10	17
Minor	49	83
TOTAL	59	

*Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

Table 4 (Reg # 65331-5).**Severity: Unspecified Routes of Exposure in Dogs, 2008.**

Severity*	# of Incidents	Per Cent
Death	0	
Major	1	2
Moderate	13	23
Minor	42	75
TOTAL	56	

* See appendix for explanation of severity categories

Cat exposed to dog product

Tables 5-8 provide information on the incidents and severity when the dog product is used on cats. A total of 96 cases were reported. Five deaths were reported following dermal exposure and 4 incidents were reported as being of major significance. This represents a misuse of the product; however, the total number of cases are considerably low when compared to the number of cases in dogs.

Table 5 (Reg # 65331-5).**Severity: Dermal, Oral and Unspecified Routes of Exposure in Cats, 2008.****Cat exposed to dog product**

Severity*	# of Incidents	Per Cent
Death	5	5
Major	4	4
Moderate	48	50
Minor	38	40
unknown or not specified	1	1
TOTAL	96	

* See appendix for explanation of severity categories

Table 6 (Reg #65331-5). Severity: Dermal Exposure in Cats*, 2008
Cat exposed to dog product

Severity**	# of Incidents	Per Cent
Death	5	5%
Major	4	4%
Moderate	47	51%
Minor	36	39%
unknown or not specified	1	1%
TOTAL	93	

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

** See appendix for explanation of severity categories

Table 7 (Reg # 65331-5). Severity: Oral Exposure in Cats*, 2008
Cat exposed to dog product

Severity**	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	0	
Minor	1	100%
unknown or not specified	0	
TOTAL	1	

*Some animals may have had dermal exposure as well

** See appendix for explanation of severity categories

Table 8 (Reg # 65331-5). Severity: Unspecified Exposure Route in Cats, 2008.
Cat exposed to dog product

Severity*	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	1	50
Minor	1	50
unknown or not specified		
TOTAL	2	

* See appendix for explanation of severity categories

GENDER

There did not appear to be any predilection for adverse effects to occur in one sex or the other. Of the 2354 animals appearing in the report 1052 were females (726 neutered; 324 intact, 2 pregnant) and 1076 were males (669 neutered).

Table 9 (Reg # 65331-5). Gender: Dermal Exposure in Dogs, 2008

Sex	# of Incidents	Per Cent	Per Cent*
Female	1052	45%	49%
Male	1076	46%	51%
Unknown	226	10%	NA
TOTAL	2354 (2128*)		

Note: Gender was not reported for all incidents.

* values without Unknown

AGE

Ages were reported for 1571 animals (Table 10). The ages that were reported in the raw data were further stratified into tighter age bands by the reviewer. The greatest number of incidents was reported for animals less than one year of age. In this group, a total of 390 (25%) incidents were reported. The next greatest number of reactions was reported in animals between 1 and 2 months (264 animals, 17%) and those between 1 to 2 years of age (264 animals, 17%). Animals in age groups from 5 to 7 years of age represented 12% of the incidents. The number of cases in animals less than 2 months of age was included in the number of animals that were designated as being less than 3 months of age. Since this entire group comprised only 3% of the total age-related incidents, there did not appear to be a propensity for misuse of this particular spot on product in under-age animals.

Table 10 (Reg # 65331-5). Age: Dermal Exposure in Dogs, 2008 # of Incidents (%)

Severity* / Age	Death	Major	Moderate	Minor	Total (%)
< 3 Months**	4 (<1)	1 (<1)	11 (1)	29 (2)	45 (3)
3 – 6 month	5 (<1)	2 (<1)	14 (1)	82 (5)	103 (7)
6 – 9 months	0	1 (<1)	17 (1)	70 (4)	88 (6)
9- 12 months	0	1 (<1)	32 (2)	148 (9)	181 (12)
[<1 year]	[9 (<1)]	[5 (<1)]	[74 (5)]	[302 (19)]	[390 (25)]
1 – 2 year	1 (<1)	5 (<1)	47 (3)	211 (13)	264 (17)
2 – 3 years	0	6 (<1)	34 (2)	124 (8)	164 (10)
3 – 5 years	2 (<1)	6 (<1)	65 (4)	176 (11)	249 (16)
5 – 7 years	3 (<1)	4 (<1)	43 (3)	133 (8)	183 (12)
7 – 9 years	3 (<1)	7 (<1)	41 (3)	85 (5)	136 (9)
9 – 11 years	2 (<1)	2 (<1)	27 (2)	49 (3)	80 (5)
> 11 years	6 (<1)	3 (<1)	20 (1)	49 (3)	78 (5)
Subtotal	26	38	351	1156	
TOTAL incidents	1571				

Note: Not all ages were reported.

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

May be misuse, label says **8 weeks or older only

BODY WEIGHT

Dose ranges: <22 lbs, 23-44 lbs., 45-88 lbs. 89-132 lbs

Body weights were reported for a total of 1677 animals (Table 11). The greatest number of incidents was reported in animals weighing 11 to 21 pounds (21%). Animals in the 5 to 11 pound group comprised 16% of the reported incidents and the 21 to 30 pound group had an incident rate of 10%. All of the other weight stratifications had incident rates less than 10%. Interestingly, animals weighing less than 5 pounds had the lowest number of incidents (5%), indicating that low body weights were not a major factor in the manifestation of adverse reactions. In Table 12, the number of incidents in animals below the recommended weight range is reported as 5% of the total number of incidents. Based on this, there does not appear to be a tendency for product misuse with regard to animal weight.

Table 11 (Reg # 65331-5).**Body Weight: Dermal Exposure in Dogs, 2008. # of Incidents (%)**

Severity* Body Wt (pounds)	Death	Major	Moderate	Minor	Total %
< 5	4 (<1)	1 (<1)	12 (<1)	47 (3)	64 (5)
5 – 11	3 (<1)	7 (<1)	60 (4)	194 (12)	264 (16)
11 – 21	4 (<1)	8 (<1)	74 (4)	274 (16)	360 (21)
21 – 31	5 (<1)	6 (<1)	40 (2)	118 (7)	169 (10)
31 – 41	2 (<1)	2 (<1)	27 (2)	82 (5)	113 (7)
41 – 51	0	2 (<1)	30 (2)	93 (6)	125 (7)
51 – 61	1 (<1)	0	18 (1)	105 (6)	124 (7)
61 – 71	4 (<1)	3 (<1)	28 (2)	106 (6)	141 (8)
71 – 81	1 (<1)	2 (<1)	37 (2)	95 (6)	135 (8)
≥81	2 (<1)	5 (<1)	41 (2)	134 (8)	182 (11)
subtotal	26 (2)	36 (2)	367 (22)	1248 (74)	
TOTAL incidents	1677				

Note: Not all body weights were reported.

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

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

Table 12 (Reg # 65331-5). Product Weight Range: Dermal Exposure Dogs, 2008

Product Weight Range	# Incidents	Per Cent
Dog weight < product weight range*	90	5
TOTAL incidents	1677	

*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 2,354 incidents. Of these, mixed breed dogs (all sizes) were involved in 456 incidents, with large (>20 kg) having 206 incidents, small (<10 kg) with 127 incidents and medium (10-20 kg) with 123 incidents. Among purebreds, Labrador Retrievers (166 incidents) and Yorkshire Terriers (116 incidents) were the top two breeds in incidents, consistent with their rankings of 1 and 2 with the American Kennel Club (AKC). Golden Retrievers were 4th with 84 incidents, consistent with their AKC ranking of 4. However, the Shih Tzu (3rd with 87 incidents), Bichon Frise (5th with 63 incidents) and Chihuahua (6th with 59 incidents) were overrepresented with respect to their AKC rankings (10th, 35th and 12th, respectively). Conversely, beagles (used in the companion animal safety studies to register this product) ranked 15th with 30 incidents despite an AKC ranking of 5.

Table 13 (Reg #65331-5). Dermal Exposure in Dogs, 2008 by Breed Size

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Retriever Labrador	Large	166	7.1%	1
Yorkshire Terrier	Small	116	4.9%	2
Shih Tzu	Small	87	3.7%	10
Retriever (Golden)	Large	84	3.6%	4
Bichon Frise	Small	63	2.7%	35
Chihuahua	Small	59	2.5%	12
German Shepherd Dog	Large	50	2.1%	3
Maltese	Small	47	2.0%	20
Terrier (Jack Russell)	Small	44	1.9%	NR
Pomeranian	Small	43	1.8%	13
Boxer	Large	40	1.7%	6
Schnauzer (Miniature)	Small	38	1.6%	11
Pug	Small	33	1.4%	15
Dachshund	Medium	31	1.3%	7a
Beagle	Medium	30	1.3%	5
Spaniel (Cocker)	Small	28	1.2%	21
Pit Bull	medium	26	1.1%	55 c
West Highland White	Small	26	1.1%	34
Poodle (Miniature)	Small	25	1.1%	9 b
Shetland Sheep Dog (Sheltie)	Medium	25	1.1%	19
Poodle (Toy)	Small	24	1.0%	9 b
Bulldog	Large	21	0.9%	8
English Bulldog	Large	21	0.9%	?
Australian Shepherd	Medium	21	0.9%	29
Boston Terrier	Small	19	0.8%	17
Poodle (Standard)	Large	18	0.8%	9 b
Rottweiler	Large	17	0.7%	14
Border Collie	Large	16	0.7%	51
Siberian Husky	Large	15	0.6%	23
Papillon	Small	15	0.6%	37
Dachshund (Miniature)	Small	15	0.6%	7a
Eskimo (Spitz)	Medium	13	0.6%	??
Great Pyrenees	Large	11	0.5%	60
Cockapoo	Small	11	0.5%	NR
Lhasa Apso	Small	11	0.5%	50
mixed/unknown, Breeds <0.5%*	various	1045	44.4%	NR

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Total incidents		2354		

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.

* 1045 (or 44 %) incidents were either unspecified breeds, mixed breeds or breeds with <0.5 % incidence.

Size - Small < 20#, Medium ~ 20-50#, Large > 50#

Body Systems

There were a total of 3816 incidents involving various body systems. Some of the animals had multiple symptoms involving multiple systems. Of the reported systems involvement, 18% were application site disorders (pruritis, hair loss, erythema, irritation and non-specific reactions). Seventeen percent (17%) were designated as systemic disorders and another 17% of the incidents were characterized as disorders of the skin and appendages. The digestive system was reported as being involved in 15% of the incidents, followed by behavior and neurological disorders, at 12% and 10%, respectively. From the results reported in Table 14, incidents in other reported body systems were not as prevalent, with some being involved in less than 1% of the total.

Table 14 (Reg # 65331-5). Body System: Dermal Exposure in Dogs, 2008

Body System	# of Incidents	Per Cent
Application site disorders	677	18%
Skin and appendages disorders	643	17%
Systemic disorders	641	17%
Digestive tract disorders	543	14%
Behavioral disorders	469	12%
Neurological disorders	391	10%
Respiratory tract disorders	145	4%
Immune system disorders	89	2%
Eye disorders	46	1%
Musculoskeletal disorders	41	1%
Ear and labyrinth disorders	34	<1%
Blood and lymphatic system disorders	30	<1%
Renal and urinary disorders	27	<1%
Cardio-vascular system disorders	20	<1%
Hepato-biliary disorders	13	<1%
Reproductive system disorders	4	<1%
Endocrine system disorders	1	<1%
No signs	1	<1%
Metabolism and nutrition disorders	1	<1%

TOTAL	3816	
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Note: Not all incidents had a body system reported and some incidents had multiple body systems reported.

CLINICAL SIGNS

Clinical signs were reported in 8,047 incidents indicating that some animals had more than one observation reported. Clinical signs in which the skin was the primary organ involved (pruritis, dermatitis, erythema, sores, irritation) were reported at a higher frequency (19%). Lethargy and emesis were both reported in 9% of the total incidents. Other clinical signs were reported at a lower frequency of occurrence. Fever, vocalization, dyspnea, self mutilation, adipsia, restlessness, pain, anxiety, aggression, recumbency and weakness each occurred at less than 1% incidence.

Table 15 (Reg # 65331-5). Clinical Signs: Dermal Exposure in Dogs, 2008

Signs	# of Incidents	Per Cent
Pruritus/Dermatitis/Sores/Erythema/Irritation	1536	19%
Lethargy and similar observations	755	9%
Emesis	727	9%
Anorexia	377	5%
Alopecia	373	5%
Application site hair change	303	4%
Behavioural disorder NOS	258	3%
Seizures	231	3%
Diarrhea and /bloody diarrhea	222	3%
Ataxia	186	2%
Hyperactivity	146	2%
Tremors/trembling	130	2%
Application site reaction NOS	112	1%
Pyoderma	111	1%
Rash	106	1%
Application site lesion (<i>not specified</i>)	102	1%
Salivation	102	1%
Tachypnoea	83	1%
See footnote*	2187	27%
TOTAL	8047	

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

** 2187 (27 %) incidents were signs with <1% incidence

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.

(S)-Methoprene is a juvenile hormone analog which can be used as an insecticide because of its insect growth regulator activity. Methoprene does not kill adult insects. Instead, it mimics natural juvenile hormone of insects. Juvenile hormone must be absent for a pupa to molt to an adult, so methoprene-treated insect larvae will be unable to successfully change from a pupa to the adult. Methoprene is essentially nontoxic to humans when ingested or inhaled.

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 (nyctagmus, 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 65331-5:

The following studies were conducted on a formulation containing 10% fipronil and 12% (S)-methoprene. EPA Reg. No. 65331-5 has a label declaration of 9.8% fipronil and 8.8% (S)-methoprene.

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.