

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING CAT PRODUCT
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Registration #: 65331-4

Registrant: Merial Limited

Subregistrant(s): NA

Product Name(s): Frontline Plus for Cats

Active Ingredient: S-Methoprene (11.8%), PC Code: 105402 , CAS # 65733-16-6

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

Application Method: directly on skin between the shoulder blades

Sales Method: Veterinary and Retail

Species: Cat

Weight Ranges: not specified

Age: 8 weeks or older

Primary Reviewer: Sanyvette Williams, DVM

Signature:

Date:

Secondary Reviewer: Princess Campbell, DVM

Signature:

Date:

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for Registration # 65331-4 containing S-Methoprene (11.8%), and Fipronil (9.8 %). The product is a topical pesticide for cats and kittens 8 weeks of age or older.

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 to 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:

There were 1305 incidents in cats with 32 deaths. Cats exhibited mainly minor signs (84%). There was no apparent gender difference and no breed predilection reported.

Most incidents were reported in cats less than 1 year of age (20%) with 8% of the incidents occurring between 9-12 months. Incidents began to decline after 3 years of age.

Cats in the 5 – 11 pound weight range had the greatest total number of incidents (263) at 46% with 38% being of minor severity and 8% moderate severity. Cats in the 11-16 pound weight range had 34% incidents reported with 29% of those being of minor severity.

Application site disorders were the most frequent observation (25%), followed by digestive tract disorders (23%) and systemic disorders (15%). Behavioral systems were reported as 11% of affected systems.

A total of 4325 occurrences of clinical signs were reported. Hypersalivation (12%) and erythema/inflammation/pruritis/sores/necrosis (12%) were the primary signs observed (the sites were not specified in the data). Though not as frequent, alopecia (10.7%), lethargy (8.9%), and death (1%) were some of the other clinical signs. Some other signs that occurred at less than 0.5% included twitching, pain head shaking, tachycardia, weight loss, recumbency agitation, conjunctivitis, and gagging. There were a total of 1335 incidents that involved the application site. The incidents at the application site and the hypersalivation could be related to treatment with the Frontline product.

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

The combined routes of exposure (dermal, oral and unspecified) in Table 1 totaled 1305 incidents. There were 32 deaths in cats. Animals exhibited mainly minor signs (82%). There were 8 (moderate – 75%) incidents of oral exposure in the cats and a total of 31 (minor – 77%) incidents of unknown route (Tables 3 and 4).

Table 1 (Reg #65331-4).**Severity: Dermal, Oral and Unspecified Routes of Exposure in Cats, 2008.**

Severity*	# of Incidents	Per Cent
Death	32	2%
Major	21	2%
Moderate	179	14%
Minor	1073	82%
TOTAL	1305	

* See appendix for explanation of severity categories

Table 2 (Reg # 65331-4). Severity: Dermal Exposure in Cats*, 2008

Severity**	# of Incidents	Per Cent
Death	32	3
Major	20	2
Moderate	171	14
Minor	1043	84
TOTAL	1266	

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

** See appendix for explanation of severity categories

Table 3 (Reg #65331-4). Severity: Oral Exposure in Cats*, 2008

Severity**	# of Incidents	Per Cent
Death	0	
Major	1	13%
Moderate	1	13%
Minor	6	75%
TOTAL	8	

*Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

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

Severity*	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	7	23%
Minor	24	77%
TOTAL	31	

* See appendix for explanation of severity categories

Cat product used on dogs

There were 9 incidents of the cat product used on dogs (Table 5). Most were classified minor. All incidents are considered misuse.

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

Cat product used on dogs

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

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

** See appendix for explanation of severity categories

Table 6 (Reg #65331-4). Severity: Oral Exposure in Dogs*, 2008

Cat product used on dogs

Severity**	# of Incidents	Per Cent
Death	0	
Major	0	
Moderate	0	
Minor	1	
TOTAL	1	

*Some animals may have had dermal exposure as well

** See appendix for explanation of severity categories

There were no incidents reported in dogs that had an unspecified route of exposure.

Severity: GENDER

As can be seen in Table 7, there is no apparent gender difference.

Table 7 (Reg #65331-4). Gender: Dermal Exposure in Cats, 2008

Sex	# of Incidents	Per Cent	Per Cent*
Female	549	43	51
Male	532	42	49
Unknown	185	15	NA
TOTAL	1266 (1081*)		

Note: Gender was not reported for all incidents.

* Male and female values only

Severity: AGE

Most incidents were reported in cats less than 1 year of age (20%) with 8% of the incidents occurring between 9-12 months. Incidents began to decline after 3 years of age. Deaths occurred in 3% of the cats with no apparent age predilection.

Table 8 (Reg #65331-4). Age: Dermal Exposure in Cats, 2008 # of Incidents (%)

Severity* \ Age	Death	Major	Moderate	Minor	Total (%)
< 3 Months**	2 (<1)	0	10 (1)	19 (3)	31 (4)
3 – 6 month	1(<1)	2(<1)	10 (1)	28 (4)	41 (6)
6 – 9 months	1(<1)	0	5(<1)	17 (2)	23 (3)
9- 12 months	2(<1)	1(<1)	9(1)	45 (6)	57 (8)
[0 – 1 year]	[6(<1)]	[3(<1)]	[34]	[109](15)	[152 (20)]
1 – 2 year	5(<1)	1(<1)	7(<1)	72 (10)	85 (12)
2 – 3 years	2(<1)	0	6(<1)	58 (8)	66 (9)
3 – 5 years	2(<1)	3(<1)	9(1)	82 (11)	96 (13)
5 – 7 years	3(<1)	1(<1)	13 (2)	63 (9)	80 (11)
7 – 9 years	2(<1)	3(<1)	14 (2)	57 (8)	76 (10)
9 – 11 years	1(<1)	0	7(<1)	67 (9)	75 (10)
> 11 years	4(<1)	3(<1)	25 (3)	76 (10)	108 (15)
Subtotal	25 (3)	14 (2)	115 (16)	584 (79)	
TOTAL incidents	738				

Note: Not all ages were reported.

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

**May be some misuse, label say only 8 weeks or older

BODY WEIGHT

Based on the reported 691 incidents, animals in the 5 – 11 pound weight range (Table 9) had the greatest total number of incidents (336) at 46% with 38% being of minor severity and 8% moderate severity. Cats in the 11-16 pound weight range had 34% incidents reported with 29% of those being of minor severity.

Dose ranges: none specified

Table 9 (Reg #65331-4). Body Weight: Dermal Exposure in Cats, 2008. # of Incidents (%)

Severity* Body Wt (pounds)	Death	Major	Moderate	Minor	Total (%)
< 5	2 (<1)	1 (<1)	15 (2)	21 (3)	39 (6)
5 – 11	11 (2)	9 (1)	53 (8)	263 (38)	336 (46)
11 – 16	4 (<1)	3 (<1)	26 (4)	203 (29)	236 (34)
16 – 21	1 (<1)	1 (<1)	5 (<1)	53 (8)	60 (9)
≥21	0	0	1 (<1)	19 (3)	20 (3)
Subtotal	18 (3)	14 (2)	100 (14)	559 (81)	
TOTAL incidents	691				

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)

BREEDS

Information on breed distribution not presented.

BODY SYSTEMS

Of the 1960 reports of effects seen on body systems after dermal exposure to the product, application site disorders were the most frequent observation (25%), followed by digestive tract disorders (23%) and systemic disorders (15%) (see Table 9). Behavioral systems were reported as 11% of affected systems.

Table 9 (Reg #65331-4). Body System: Dermal Exposure in Cats, 2008

Body System	# of Incidents	Per Cent
Application site disorders	486	25%
Digestive tract disorders	446	23%
Systemic disorders	297	15%
Behavioral disorders	225	11%
Skin and appendages disorders	167	9%
Neurological disorders	142	7%
Respiratory tract disorders	68	3%
Eye disorders	43	2%
Ear and labyrinth disorders	16	(<1%)
Blood and lymphatic system disorders	15	(<1%)
Musculoskeletal disorders	14	(<1%)
Renal and urinary disorders	11	(<1%)
Immune system disorders	10	(<1%)
Cardio-vascular system disorders	9	(<1%)
Hepato-biliary disorders	5	(<1%)
Metabolism and nutrition disorders	2	(<1%)
Endocrine system disorders	1	(<1%)
No signs	1	(<1%)
Reproductive system disorders	1	(<1%)
Mammary gland disorders	1	(<1%)
Total	1960	

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

CLINICAL SIGNS

A total of 4325 occurrences of clinical signs were reported (see Table 10). After reviewing the data, hypersalivation (12%) and erythema/inflammation/pruritis/sores/necrosis (12%) were the primary signs observed (the sites were not specified in the data). Though not as frequent, alopecia (10.7%), lethargy (8.9%), and death (1%) were some of the other clinical signs. Some other signs that occurred at less than 0.5% included twitching, pain head shaking, tachycardia, weight loss, recumbency agitation, conjunctivitis, and gagging. There were a total of 1335 incidents that involved the application site.

Table 10 (Reg #65331-4). Clinical Signs: Dermal Exposure in Cats, 2008

Signs	# of Incidents	Per Cent
Dermatitis/inflammation/pruritus/sores/necrosis/erythema	521	12.0%
Salivation	521	12.0%
Alopecia	463	10.7%
Application site hair change	384	8.9%
Lethargy	359	8.3%
Emesis	231	5.3%
Anorexia	199	4.6%
Behavioral disorder NOS	127	2.9%
Hyperactivity	76	1.8%
Ataxia/ paresis/paralysis	67	1.5%
Tremor/tremb - Muscle tremor	62	1.4%
Application site lesion	58	1.3%
Fever – Pyrexia	55	1.3%
Self mutilation	54	1.2%
Seizure – Convulsion	48	1.1%
Dead and Death by euthanasia	42	1.0%
Application site reaction NOS	40	0.9%
Adipsia	39	0.9%
Licking at application site	36	0.8%
Application site scab	35	0.8%
Vocalisation	33	0.8%
Diarrhoea	32	0.7%
Dyspnoea	28	0.6%
Excessive licking and/or grooming	21	0.5%
Grooming disorder	21	0.5%
Aggression	20	0.5%
Panting	20	0.5%
Tachypnoea	20	0.5%
See footnote*	713	16.5%
TOTAL	4325	

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

** 713 (16.5 %) 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 0011405: In this domestic animal safety study (MRID # 434449-04), 4 male and 4 female domestic short hair kittens (≤ 8 weeks of age) were administered a single topical treatment of RM1601C (0.25% fipronil) at 6 ml/kg (recommended dosage) once every month for three months. Another group of 6 male and 6 female kittens were treated in a like manner with five times the recommended dosage. A group of 4 male and 4 female kittens served as a control group and were treated with the formulation vehicle at 5X the recommended dosage. The following parameters were evaluated: physical examinations, clinical observations, body weight, food consumption, hematology, clinical chemistry and gross necropsy examination of the abdominal cavity. There was no evidence of a treatment-related effect on any of the parameters. The study demonstrated that the RM1601C (0.25% fipronil) has at least a 5X margin of safety in kittens.

From TXR 0010923: Domestic Animal Safety study (MRID 143121112): Groups of three adult male cats were topically administered six treatments of the 0.25% fipronil formulation 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 cats is 3-6 ml/kg.) Food consumption was significantly decreased in the 15 ml/kg group as compared to the control group at weeks 2 and 4 after the first treatment. All other time points were comparable. The incidences of vomiting and soft/liquid feces were higher in the treated animals as compared to the controls.

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, except for cats weighing less than 2 kg."

Cat Bodyweight (kg)	Spot Treatment Total Dose (mg)	Spray Treatment Total Dose (mg)
2	50	30
4	50	60
8	50	120

"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 kittens with a formulation containing as actives fipronil (10%) and (S)-methoprene (12%). The following is a summary of this study:

In a companion animal safety study, MRID 44942009, Fipronil/s-Methoprene solution for cats (Active Ingredients: Fipronil:10% w/v; (S)-methoprene:12% w/v) was topically applied at dose levels of 0.5 mL (1X), 1.5 mL (3X) or 2.5 mL (5X times the maximum recommended dose) to groups of 6 male and 6 female kittens (52-59 days old at the initiation of the study). Controls were not dosed. Animals were treated on Study Day 0 and again on Study Day 28. The report includes results of the study up to Day 42.

The animals were observed hourly for 6 hr following each treatment, and twice daily on every study day (with the exception of Day -14 when they were observed only once). Clinical evaluations were conducted on Days -14 (or -13), on the day of each treatment (Day 0 and Day 28) and on Study Days 1, 3, 7, 14, 21, 29, 31, 35 and 42. Body weights were recorded at the start of acclimation on Study Day-14 (with the exception of 5 cats who were weighed on Day-13), prior to dosing on Study Days 0 and 28, and on Study Days -7, -1, 7, 14, 21, 35, and 42. Blood samples were obtained from the jugular vein on Study Days-4, or -3 (depending on the set) and thereafter on Days 14, 28 (before treatment) and 43.

No clinical signs of erythema, edema, alopecia or abnormal hair coat condition were observed 1-6 hr post-dosing in any of the treated animals or during any of the other observation periods from Study Day -14 to Study Day 42. Some animals in all treated groups (maximum of 9 of 12 in 5X group on Study Day 28) had skin flakes and off-white material at the application site, and four in the 5X group exhibited pruritus on Days 1, 2 or 3. No ocular, muscular, cardiovascular, or behavioral changes or abnormalities of the mucus membranes were observed in the treated cats. There were no morphological abnormalities in RBCs that could be attributed to treatment.

Overall, no treatment-related, biologically-significant effects on body weight, clinical biochemistry, or hematology, were reported. Although there were statistically-significant changes in hematology and clinical chemistry parameters in some treatment groups at some sampling times (i.e., reduction in mean corpuscular volume; reduction in % neutrophils, increase in % monocytes; increase in eosinophils, increase in reticulocytes, increase in urea), none of the changes followed a clear dose-response relationship and most were within the normal reference range.

This study deviated from the companion animal safety study Guidelines (OPPTS 870.7200), in that blood samples were collected prior to treatment on Days -3 or -4 and on Day 28 and not at 24 hrs following treatment, as specified by the guidelines. However, the HED Companion Animal Safety Committee suggested that this study could be classified as acceptable for the following reasons: 1) the remainder of the study was conducted according to the guidelines; 2) there was no evidence of toxicity in any of the animals; 3) as fipronil is registered at this concentration in other products, there are CAS studies with no evidence of toxicity at 5X. In addition, methoprene is used with many other chemicals in flea and tick products, and, in so far as the Committee is aware, there is no evidence that it interacts with these other chemicals,

although the proposed 12% concentration in this product may be somewhat higher than that of most of the other products listed in REFS.

It is also noted that doses are not stated on the proposed label. HED concludes that the final dosages, as indicated on the label or as packaged in the applicator tubes, must be consistent with (no more than) the 1 X application rate in this study (0.5mL/kg). With this stipulation, and assuming that there are no additional adverse effects reported in the final report, the study is classified as **Acceptable/Guideline** for a companion animal safety study (OPPTS 870.7200) in cats (kittens).

The last accepted (March 24, 2004) label for 65331-4 includes the statement: "Can also be used...on breeding, pregnant and lactating queens." The following is a summary of the study that was used to support this statement:

In a special (reproductive) companion animal safety study (MRID 45618502) ML-2,095,988 508Q (a topical formulation containing 10% w/v fipronil and 12% w/v (S)-methoprene) was administered at 0X (Group 1; sham-treated controls), 1X (Group 2) and 3X (Group 3) the recommended [use] dose (0.5 mL/cat) to groups of 12 adult female cats (queens) prior to and during pregnancy, through parturition and to weaning of the kittens. There were 3 groups, each containing 12 queens (all proven breeders, as each had had at least two previous successful pregnancies). The queens were dosed at the start (March 17, 1999) of the study, and then at 28-day intervals thereafter until mating, then were treated within 24 hours of their first mating session and every 28 days thereafter until their kittens were weaned (ages 42-44 days). Even if a queen was mated a few days following an application treatment, she was treated again on the day following mating (example: Queen #17 of Group 2 was treated on March 17, then again 28 days later on April 14, again 28 days later on May 12, and then on May 26, one day after mating which happened to be 14 days after the previous treatment, followed by treatments on June 23, July 21, and August 18).

Queens in Group 1 were sham treated. Queens in Groups 2 and 3 were treated by parting the hair and applying the formulation directly to the skin between the base of the skull and shoulder blades; queens in Group 2 were dosed (0.5 mL) at one spot; queens in Group 3 received three 0.5 mL treatments at each of three sites. Based on the body weights, initial doses ranged from 0.0096 to 0.022 mL/kg for queens in Group 2 and from 0.32 to 0.54 mL/kg in Group 3. The toms that were used for breeding were not treated with the test material.

Clinical observations were conducted hourly for 6 hr following each treatment; on other days each cat was observed at least once a day. Daily clinical observations were conducted on kittens beginning within 24 hours of parturition. Queens were weighed before each treatment, at 42 days post-mating and within 3 days post-parturition. Kittens were weighed individually within 24-48 hours of parturition, at 14-15, 26-28, and 42-44 days post-parturition.

All queens became pregnant, although some required more than one mating. Those queens which were rebred were exposed to more applications of the test material. Individual queens in Groups 2 and 3 received from one to seven exposures to the test material before a mating resulting in pregnancy. Two of the 12 queens in Group 1 required two breeding sessions, and one

required three. Each of the 12 queens in Group 2 became pregnant as a result of one breeding session, while four of the 12 queens in Group 3 required two breeding sessions.

The only dose-related effects observed in queens were flaky skin at the application site (recorded 2 times in Group 1, 7 times in Group 2, and 10 times in Group 3), and slight to moderate salivation lasting from 1 to 5 minutes following dosage of the test material (not observed in Groups 1 or 2, observed 4 times in Group 3). There were no significant differences between queens from the different groups for mean body weights, or for a number of parameters measured on post-parturition day 42 (mean rectal temperatures, mean respiratory rates, or mean heart rates).

With respect to reproductive parameters, there was an increased incidence of stillborn kittens in Group 3 relative to the other two groups: Group 1: 2/40; Group 2: 2/36; and Group 3: 8 or 9/42 (one kitten in Group 3 from Queen #32 was found cannibalized from the waist up, and it was not possible to determine whether its lungs had ever expanded, and whether or not it had been stillborn). However, this increase was due in part to Queen #34, which had a gestation period of 72 days, compared to 63-69 days for the other 35 queens. Queen #34 delivered two stillborn kittens on day 72, then required a C-section to deliver two additional stillborn kittens. Queen #26 delivered two small stillborn kittens, at least one of which had been dead in utero, in addition to two normal kittens. These were sporadic findings which, in each case, were limited to one queen, and it is concluded then that there is no evidence that the increased incidence of stillborn kittens in Group 3 was a result of exposure to the test material. Also, it is noted that there was no indication of any post-natal adverse effect in Group 3 kittens (one Group 1 kitten died in the period between birth and weaning, as did two Group 2 kittens, but all Group 3 kittens survived to weaning); and there were no significant differences between kittens from the 3 groups with respect to physiological parameters (mean body weights, mean rectal temperatures, mean respiratory rates, mean heart rates) measured on post-parturition days 14, 28 and 42. While the sex ratio in Group 3 was somewhat skewed (27/42, or 0.643 of the kittens born were males), this was also incidental as the chances of having a ≥ 0.643 ratio of one sex out of 42 births, assuming an equal likelihood of male and female births, is approximately 8%, and there is no indication within the report of any kittens of ambiguous gender.

Although no queens were dosed at 5X level, and no blood was taken for clinical chemistry and hematology measurements, the purpose of this study was to allow a label claim for use of this registered product (EPA Reg. No. 65331-4) on breeding, pregnant and lactating female cats. TRB has previously reviewed (MRID 44942009; date of review: 12 April 2000) a companion animal (cat) study for this formulation which included a 5X dosage group and measurements of clinical chemistry and hematology parameters. The TRB review of 12 April 2000 was reviewed by the HED Companion Animal Safety Committee which noted, among other things that there was no evidence of toxicity in any of the animals and that “as fipronil is registered at this concentration in other products, there are CAS studies with no evidence of toxicity at 5X. In addition, methoprene is used with many other chemicals in flea and tick products, and, in so far as the Committee is aware, there is no evidence that it interacts with these other chemicals, although the proposed 12% concentration in this product may be somewhat higher than that of most of the other products listed in REFS.”

This study is classified as acceptable. The findings of this study are adequate to support the use of this registered product at the dosage rate of 0.5 mL/cat at 28-day intervals on breeding, pregnant and lactating female cat.

Acute studies for 65331-4:

Note: the following studies were conducted on a formulation containing 10% fipronil and 12% (S)-methoprene. EPA Reg. No. 65331-4 has a label declaration of 9.8% fipronil and 11.8% (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.