

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING CAT PRODUCT
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Registration #:	2724-504	2724-504-270	2724-504-2596
Registrant:	Wellmark	--	--
Subregistrant:	--	Farnam	Hartz

Brand names listed on the Wellmark label:

- 1) ZODIAC® Spot On® Plus Flea & Tick Control for Cats 5 lbs. and Over
- 2) ZODIAC® Spot On® Plus Flea & Tick Control for Cats & Kittens Under 5 lbs.
- 3) ZODIAC® Multi-Cat Spot On® Plus Flea & Tick Control for Cats 5 lbs and Over

Active ingredients are the same for the three registrations

Active Ingredient: Etofenprox (40 %), PC Code: 128965 , CAS # 80844-07-1

Active Ingredient: S-Methoprene (3.6 %), PC Code: 105402 , CAS # 65733-16-6

The following product information is taken from the label of 2724-504 and should apply to both subregistrations.

Application Method: Apply directly to the skin on the back of the neck at the base of the skull

Sales Method: retail

Species: Cat

Weight Ranges:

- 1) Cats and kittens under 5 pounds
- 2) Cats and kittens 5 pounds and greater

Age: Cats and Kittens 12 weeks of Age or older

Primary Reviewer: Jean Holmes, D.V.M.

Signature:

Date:

Secondary Reviewer: Melba Morrow, D.V.M.

Signature:

Date:

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for Registration # 2724-504 (Wellmark), and subregistrations # 2724-504-270 (Farnam) and # 2724-497-2596 (Hartz) containing the following active ingredients: S-Methoprene (3.6 %) and Etofenprox (40 %). The Wellmark and Farnam data were submitted by Wellmark, whereas the Hartz data were submitted separately.

Background: The data were submitted in response to an Agency request 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 to the Agency.

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 age, weight, breed, or route of exposure was 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:

Due to differences in reporting style among Wellmark, Farnam and Hartz the severity of incidents was evaluated by combining all routes of exposure (table 1). When the dermal, oral and unknown exposures are combined, there is little difference among the 3 registrations. Deaths accounted for 4% of the total incidents, majors were also 4%, moderate effects accounted for 12 %, and the majority of incidents, 79 %, were minor effects.

The systems most frequently affected were the integumentary, nervous and digestive. There were frequent reports of behavioral and general disorders. The most common signs included pruritus/dermatitis, alopecia, anorexia, salivation and lethargy. These accounted for about 40 % of all the signs reported following dermal exposure. It should be noted that signs were individually counted even when there were multiple signs in a single animal.

The highest per cents of incidents from dermal exposure occurred in the cats that were between 1 and 3 years of age (approximately 13-14% on a yearly basis) followed by 3-5 years of age (approximately 8% on a yearly basis). There were 30 reported incidents that resulted in death or were classified as "major" in kittens less than 3 months of age (for all three registrations combined) following dermal exposure. This is a misuse of the product. The label indicates that this product should be used on cats or kittens 12 weeks of age or older.

Companion animal safety studies used to support this registration was conducted on 12 week old kittens using a formulation containing 40.0% etofenprox and 3.6% S-Methoprene and 12 week old kittens and adult cats using a formulation containing 56.03% etofenprox and 2.26% pyriproxyfen. Excessive salivation was noted as a clinical sign in both studies. Hypersalivation was clinical sign that was frequently reported in the incident data.

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

Many of the dermal incident reports also had oral exposure. However, these were assessed as oral exposure.

Due to differences in reporting style among Wellmark, Farnam and Hartz, the most appropriate table of severity is where all routes and unknown routes are combined (Table 1). When the dermal, oral and unknown exposures are combined, there is little difference in the number of reported incidents among the 3 registrations. However, when only the dermal exposure was evaluated there were 20 (6 %), 28 (6 %) and 25 (20 %) deaths reported (for Wellmark, Farnam and Hartz, respectively). When the incidents from the unknown route of exposure is included with the dermal exposure incidences, reported deaths associated with the Hartz product dropped to 11% while the percent incidents did not change with the other products (Tables 2, 3 and 4).

As can be seen in the Table 1, deaths were 4% of the total incidents, majors were also 4%, moderate effects accounted for 12 %, and the majority of incidents, 79 %, were minor effects. The Registrant’s tables listed most of the deaths and major effects as unlikely due to the product. However, based on the information provided regarding time after application and the fact that many of the signs are similar, it can’t be ruled out that many could have been due to treatment.

Table 1 Severity: Dermal, Oral and Unknown Routes of Exposure in Cats, 2008

Severity*	Reg #2724-504		Reg # 2724-504-270		Reg # 2724-504-2596		Total % Across Registrations
	# of Incidents	%	# of Incidents	%	# of Incidents	%	
Death	24	4	35	4	23	10	4
Major	10	2	34	4	19	8	4
Moderate	49	8	74	9	77	32	12
Minor	538	87	640	82	118	50	79
TOTAL	621		783		237		

* See appendix for explanation of severity categories

Table 2 Severity: Dermal Exposure in Cats*, 2008

Severity**	Reg #2724-504		Reg # 2724-504-270		Reg # 2724-504-2596	
	# of Incidents	Per Cent	# of Incidents	Per Cent	# of Incidents	Per Cent
Death	20	6	28	6	25	20
Major	9	3	30	6	15	12
Moderate	38	11	59	13	14	11
Minor	289	81	351	75	72	57
TOTAL	356		468		126	

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

** See appendix for explanation of severity categories

Table 3 Severity: Oral Exposure in Cats*, 2008

Severity**	Reg #2724-504		Reg # 2724-504-270		Reg # 2724-504-2596	
	# of Incidents	Per Cent	# of Incidents	Per Cent	# of Incidents	Per Cent
Death	3	1	1	<1	2	4
Major	1	<1	4	2	3	6
Moderate	11	5	11	4	3	6
Minor	218	94	239	94	44	85
TOTAL	233		255		52	

*Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

Table 4 Severity: Unknown Route of Exposure in Cats, 2008

Severity*	Reg #2724-504		Reg # 2724-504-270		Reg # 2724-504-2596	
	# of Incidents	Per Cent	# of Incidents	Per Cent	# of Incidents	Per Cent
Death	1	3	6	10	1	2
Major	0		0		1	2
Moderate	0		4	7	57	97
Minor	31	97	50	83	1	2
TOTAL	32		60		59	

* See appendix for explanation of severity categories

GENDER

Table 5 indicates that there is little difference between the three registrations based on gender, but there was a slightly higher rate in females (ranging from 2-4 % for Wellmark and Farnam and 15 % for Hartz). It must be noted that this assessment only pertains to dermal exposure in which the gender is reported. It does not include oral or unspecified exposures which account for 691 incidents.

Table 5 Gender: Dermal Exposure in Cats, 2008

Sex	Reg #2724-504		Reg # 2724-504-270		Reg # 2724-504-2596	
	# of Incidents	Per Cent	# of Incidents	Per Cent	# of Incidents	Per Cent
Female	183	52	235	51	64	58
Male	167	48	224	49	47	43
TOTAL	350		459		111	

Note: Gender was not reported for all incidents.

AGE

Most of the moderate and minor incidents were reported between the ages of 1 and 3 years of age (13-14 % on a yearly basis) followed by 3-5 years of age (approximately 8% on a yearly basis).

Table 6 Age: Dermal Exposure in Cats, 2008. # of Incidents (%)

Severity* Age	Reg #2724-504				Reg # 2724-504-270				Reg # 2724-504-2596				Total % Across severity
	D-A	D-B	D-C	D-D	D-A	D-B	D-C	D-D	D-A	D-B	D-C	D-D	
<3 months**	2 (<1)	2 (<1)	4 (1)	24 (7)	5 (1)	2 (<1)	5 (1)	24 (5)	1 (<1)	0	0	5 (4)	8 %
3-6 months	2 (<1)	2 (<1)	0	17 (5)	1 (<1)	4 (<1)	2 (<1)	9 (2)	1 (<1)	3 (2)	0	2 (2)	4 %
6-9 months	0	0	0	7 (2)	1 (<1)	2 (<1)	2 (<1)	11 (2)	2 (2)	0	0	5 (4)	3 %
9-12 months	1 (<1)	3(<1)	0	5 (1)	1 (<1)	1 (<1)	0	4 (<1)	1 (<1)	0	0	2 (2)	2 %
[<1 year]	[5]	[7]	[4]	[53]	[8]	[9]	[9]	[48]	[5]	[3]	[0]	[14]	[17%]
1-2 years	2 (<1)	0	2 (<1)	46 (13)	3 (<1)	4 (<1)	14 (3)	53 (11)	1 (<1)	1 (<1)	0	7 (6)	14 %
2-3 years	0	0	9 (3)	42 (12)	4 (<1)	5 (1)	9 (2)	34 (7)	5 (4)	2 (2)	0	12 (10)	13 %
3-5 years	1 (<1)	2 (<1)	6 (2)	55 (15)	3 (<1)	4 (<1)	6 (1)	53 (11)	3 (2)	4 (3)	4 (3)	12 (10)	16 %
5-7 years	2 (<1)	0	4 (1)	39 (11)	1 (<1)	3 (<1)	5 (1)	50 (11)	2 (2)	2 (2)	1 (<1)	6 (5)	12 %
7-9 years	4 (1)	0	1 (<1)	13 (4)	4 (<1)	0	7 (1)	33 (7)	1 (<1)	1 (<1)	3 (2)	6 (5)	7 %
9-11 years	1 (<1)	0	4 (1)	21 (6)	3 (<1)	2 (<1)	5 (1)	26 (5)	2 (2)	0	1 (<1)	7 (6)	7 %
>11 years	5 (1)	0	8 (2)	20 (6)	2 (<1)	3 (<1)	4 (<1)	54 (12)	5 (4)	2 (2)	4 (3)	8 (6)	12 %
													Total
TOTAL Incidents	356				468				124				948

Note: Not all ages were reported.

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

- D-A = Death
- D-B = Major
- D-C = Moderate
- D-D = Minor

** Misuse, label says 12 weeks (~ 3 months) and older only.

BODY WEIGHT

The majority of deaths appear to be in animals <11 pounds. Few deaths occurred in animals 16 pounds and greater, but there may be fewer cats in this weight category. (see Table 7)

Table 7 Body Weight: Dermal Exposure in Cats, 2008. # of Incidents (%)

Severity* Weight	Reg #2724-504				Reg # 2724-504-270				Reg # 2724-504-2596				Total % Across severity
	D-A	D-B	D-C	D-D	D-A	D-B	D-C	D-D	D-A	D-B	D-C	D-D	
<5 pounds	8 (<1)	5 (1)	7 (2)	65 (18)	9 (2)	12 (3)	13 (3)	53 (11)	3 (3)	2 (2)	0	21 (21)	26 %
5-10 pounds	11 (3)	3 (<1)	17 (5)	145 (41)	12 (3)	12 (3)	20 (4)	126 (27)	5 (5)	4 (4)	4 (4)	32 (32)	42 %
11-15 pounds	1 (<1)	1 (<)	12 (<1)	59 (17)	6 (1)	3 (<1)	19 (4)	149 (32)	5 (5)	3 (3)	2 (2)	13 (13)	30 %
16-20 pounds	0	0	2 (<1)	18 (5)	0	0	4 (<1)	16 (3)	1 (<1)	2 (2)	1 (<1)	1 (<1)	5 %
>21 pounds	0	0	0	2 (<1)	1 (<1)	3 (<1)	3 (<1)	7 (2)	1 (<1)	1 (<1)	0	0	2 %
													Total
TOTAL incidents	356				468				101				925

Note: Not all body weights were reported.

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

- D-A = Death
- D-B = Major
- D-C = Moderate
- D-D = Minor

BODY SYSTEM

The primary systems (see Table 8) affected are the dermal and nervous systems, with a high incidence also reported in general and behavioral disorders. The digestive system also has a high number of incidents reported. These effects appeared to be consistent among the 3 product registrations.

Table 8 Body System: Dermal Exposure in Cats, 2008

Reg #2724-504			Reg # 2724-504-270			Reg # 2724-504-2596		
System	# of Incidents	%	System	# of Incidents	%	System	# of Incidents	%
Integumentary	235	27	Integumentary	304	27	Nervous	78	25
Nervous	199	22	Nervous	291	25	Digestive	56	18
General Disorders	130	15	Behavioral Disorders	161	14	Integumentary	56	18
Behavioral disorders	129	15	Digestive	152	13	General disorders	44	14
Digestive	96	11	General Disorders	148	13	Behavioral	29	9
Sensory Disorders	26	3	Sensory Disorders	23	2	Respiratory	19	6
Respiratory	25	3	Respiratory	22	2	Musculoskeletal	12	4
Urinary	13	1	Urinary	17	1	Sensory Disorders	11	3
Musculoskeletal	10	1	See footnote**	28	2	Urinary	8	3
See footnote*	22	2				See footnote***	5	2
			TOTAL	1145				
TOTAL	885					TOTAL	318	

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

* 22 (or 2 %) incidents were either in unspecified systems and/or in systems with <1% incidence

** 28 (or 2 %) incidents were either in unspecified systems and/or in systems with <1% incidence

*** 5 (or 2 %) incidents were either in unspecified systems and/or in systems with <1% incidence

CLINICAL SIGNS

Individual cases may have more than one clinical sign reported. Therefore, individual animals may be represented multiple times in the total of incidents for signs. The most frequent signs involved the skin (pruritus/dermatitis and alopecia). This is consistent with table 6 above which shows that the integumentary system was one of the primary targets. Other signs that occurred with some frequency included lethargy, anorexia and hypersalivation. There were also frequent occurrences of anxiety/agitation and other neurologic/behavioral changes (hiding, tremors, ataxia, etc.). The pruritus/dermatitis/sores, alopecia, lethargy, anorexia and hypersalivation account for 36 to 42 % of all the signs. These effects appear to be consistent among the 3 product registrations.

Table 9 Clinical Signs: Dermal Exposure in Cats, 2008

Reg #2724-504			Reg # 2724-504-270			Reg # 2724-504-2596		
Signs	# of Incidents	%	Signs	# of Incidents	%	Signs	# of Incidents	%
Pruritus/Dermatitis/Sores	96	11%	Pruritus/Dermatitis	143	12%	Lethargy	28	9%
Alopecia	88	10%	Lethargy	109	10%	Hypersalivating	24	8%
Lethargy	84	9%	Alopecia	108	9%	Anorexia	23	7%
Anorexia	52	6%	Hypersalivation	73	6%	Alopecia	19	6%
Hypersalivation	43	5%	Tremors/Trembling	56	5%	Pruritus/Sores	18	6%
Anxiety/Agitation	41	5%	Anorexia	55	5%	Anxiety/Agitated	14	4%
Hiding	32	4%	Hiding	49	4%	Vomiting	14	4%
Tremors/Trembling	28	3%	Anxiety/Agitation	46	4%	Death	12	4%
Ataxia	25	3%	Vomiting	46	4%	Erythema	11	3%
Vomiting	25	3%	Seizure(s)	38	3%	Ataxia	10	3%
Erythema	23	3%	Fasciculation	27	2%	Tremor	10	3%
Paw Shaking	19	2%	Ataxia	26	2%	Twitching	8	3%
Death	15	2%	Death	19	2%	Vocalization	8	3%
Hyperesthesia	12	1%	Erythema	19	2%	Dyspnea	7	2%
Vocalization	11	1%	Hyperactivity	17	1%	Seizures	7	2%
Hyperactivity	10	1%	Vocalization	16	1%	Fasciculations	6	2%
Hyperthermia	10	1%	Diarrhea	13	1%	Hyperactivity	6	2%
Behavior Change	9	1%	Euthanized	11	1%	Recumbant	5	2%
Fasciculation	9	1%	See footnote **	274	24%	Weight loss	5	2%
Squinting	9	1%				Hiding	4	1%
See footnote*	244	28%	TOTAL	1145		Nasal discharge	4	1%
						Panting	4	1%
	885					Rigidity	4	1%
						See footnote***	61	19%
						TOTAL	317	

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

* 244 (or 28 %) were signs with <1% incidence

** 274 (or 24%) were signs with <1% incidence

*** 61 (or 19 %) were signs with <1% incidence

BRIEF SUMMARY OF TOXICITY:**Active ingredients:**

In mammalian species, the major targets of etofenprox are the liver, thyroid, kidney, and hematopoietic system. Results from subchronic and chronic feeding studies in rats indicate that males may be more sensitive to treatment-related effects of etofenprox than females; males often exhibited effects earlier and/or at lower doses.

From a Health Effects Division memorandum dated August 13, 2008, an acute neurotoxicity study in the adult rat (MRID 45932301) revealed no treatment-related effects for etofenprox.

Technical etofenprox has low acute oral ($LD_{50} \geq 5000$ mg/kg), dermal ($LD_{50} \geq 2100$ mg/kg) and inhalation ($LC_{50} \geq 5.9$ mg/mL) toxicity in dogs, rabbits and rats, respectively. Etofenprox is neither an acute eye nor skin irritant. Etofenprox is not a dermal sensitizer under the conditions of the guinea pig maximization test.

(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:

The companion animal safety studies that were used as supporting data to register these products are in MRIDs 46513409 (a study initiated with 12 week old kittens conducted with a formulation containing 40.0% etofenprox and 3.6% S-Methoprene) and 46161309 (an adult cat study conducted using a formulation containing 56.03% etofenprox and 2.26% pyriproxyfen) Summaries of the studies are given below:

MRID 46513409: Four groups, each containing six 12 week-old kittens/sex were treated at 0X (5.0 mL of the inerts in the formulation without active ingredients), or with 1X (1.0 mL), 3X (3.0 mL) or 5X (5.0 mL) of a formulation containing 40.0% etofenprox and 3.6% S-Methoprene. The control or test formulations were applied to an area on the mid-dorsal back on Day 0, with subsequent 14-day observation. There was no mortality and there was no indication of systemic toxicity. Clinical observations seen in all groups included sporadic diarrhea and soft feces. Observations of excessive salivation were seen in one male and one female of the control group a few minutes after dosing, and for one male in this group about 20 minutes after dosing. One control female had salivation at the 1-hour observation and one 5X female showed this at the 2-hour observation. These episodes of salivation lasted no more than 10 minutes and were ascribed to oral contact with the control or test material. As originally reported, a small (< 5 mm) sore or scabbing was noted at the application site on Day 7 or later for one 5X male and one 5X female, and in one 3X female. A subsequent clarification (in MRID 46725801) by the registrant stated that these lesions were not at the actual application sites; the reviewer's

conclusion was that these may have been from attempts by the kittens to scratch the application site. The study was classified as acceptable to support a 1.0 mL dosage on <5 lb kittens.

MRID 46161309: In this study a 56.03% etofenprox and 2.26% pyriproxyfen spot on was topically applied to a furrow in the skin starting high on the back of the neck to in front of the shoulder blades. There were 3 groups, each consisting of three male and three female 12 week old kittens and three male and three female adult (at least 1 year old) cats. For the 1X group doses were 0.6 mL for kittens and 1.2 mL for adult cats; for the 5X group cumulative doses were 3.0 mL for kittens and 6.0 mL for adult cats; for controls the kittens received a cumulative dose of 1.284 mL vehicle and adult cats received 2.568 mL. One vehicle control adult female was found dead on Day 3, with a probable cause of closed-cervix pyometra (a collection of pus in the uterine cavity). Cosmetic effects (wet, greasy and/or spiked fur and white deposits) were observed in all animals beginning at the one hour observation, and persisted through Day 2 in the 5X group. On Day 1 one 5X kitten showed trembling and salivation, and another 5X kitten showed activity decrease and rapid respiration. There was a definite drop in mean food consumption values in all groups on Day 1 compared with pretest means (1X: kittens: -24.3%; adults: -51.7%; 5X: kittens: -44.2%; adults: -51.0%; controls: kittens: -24.6%; adults: -38.9%) but kittens had recovered by Day 4 and adults by Day 8. 1X and 5X female kittens showed mean weight losses in the period from Day 0 to 7, but mean body weights for kittens in all groups were similar by Day 14. However, some of these effects may have been due to overnight fasting and/or blood collection on Day 1. The study was classified as acceptable to support a proposed dosage rate for this formulation of 0.6 mL for kittens and cats weighing less than 5 lbs and 1.2 mL for cats weighing more than 5 lbs.

In a review dated January 18, 2006 it was stated that in order for the study in MRID 46161309 to support 2724-504 (40.0% etofenprox and 3.6% S-methoprene) dosage for cats >5 lbs would have to be no more than 1.8 mL (not 2.0 mL, as originally proposed).

Acute studies on 2724-504:

In an acute oral LD₅₀ study (MRID 46513404), 5 male and 5 female rats received a single dose of 5010 mg/kg of a formulation containing 40.3% etofenprox and 3.55% S-methoprene. There were no mortalities; clinical signs included few feces, hunched posture, excessive salivation and red material around the nose, but all rats recovered by day 3. The formulation has an oral LD₅₀ > 5010 mg/kg (EPA Toxicity Category IV).

In an acute dermal LD₅₀ study (MRID 46513405), 5 male and 5 female rats were dermally exposed (with 24-hour exposure) to 5010 mg/kg of a formulation containing 40.3% etofenprox and 3.55% S-methoprene. There were no mortalities; clinical signs included red material around the nose and few or no feces, with recovery by day 3. The formulation has a dermal LD₅₀ > 5010 mg/kg (EPA Toxicity Category IV).

The formulation is in EPA Toxicity Category IV in terms of eye irritation (MRID 46513406), and EPA Toxicity Category IV for dermal irritation (MRID 46513407). In a dermal sensitization study using a modified Buehler design (MRID 46513408) there was no indication the formulation is a dermal sensitizer.

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.