

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING CAT PRODUCT

Registration #: 2596-147
Registrant: Hartz
Subregistrant(s): NA
Product Name(s): Control One-Spot for Cats
UltraGuard One Spot
Active Ingredient: S-methoprene (2.9 %), PC Code: 105402, CAS # 65733-16-6
Application Method: Apply product between the shoulders
Sales Method: Retail
Species: Cats
Weight Ranges: None
Age: Cats and kittens over 12 weeks of age
Primary Reviewer: Princess Campbell, D.V.M. **Signature:** *Princess Campbell* **Date:** 3/12/10
Secondary Reviewer: Byron Backus, Ph.D. **Signature:** *Byron Backus* **Date:** 3/12/10

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for Registration #2596-147 (%) containing S-methoprene 2.9 (%) as its sole active ingredient.

The product is a topical spot-on pesticide for cats and kittens 12 weeks of age and older. This product is packaged in applicator tubes containing 1 mL. Application is on a monthly basis.

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 who 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.

This product is sold in retail stores.

Conclusions:

A total of 274 incidents (242 by dermal exposure and 32 by the oral route) had a severity code assigned and were evaluated in this review. Of these 135 incidents (49%) were minor, while an additional 100 (36%) were moderate. There were 5 incidents (2%) classified as major and 34 deaths (12%).

For dermal exposure, age was reported for 223 incidents, including 31 deaths. Six of the deaths involved kittens younger than 3 months; the label states that this product is for use on cats and kittens older than 12 weeks of age. Eight additional deaths involved kittens 3-6 months of age. There were a total of 50 (22%) incidents involving kittens less than 6 months of age. There was 1 death and 65 incidents (29%) in cats 6 months to 3 years old. There were 5 deaths and 34 incidents in cats 3-5 years old, and 5 deaths and 28 incidents in cats 5-7 years old.

For dermal exposure, age was reported for 151 incidents, of which 16 were deaths. Only 3 deaths were reported for animals weighing less than 5 lbs, which is somewhat surprising as there were 6 deaths in kittens less than 3 months of age and 8 in kittens 3-6 months of age. There were 10 deaths and a total of 53 incidents (53/151=35%) in cats weighing 5-11 pounds, and 3 deaths and a total of 72 incidents (72/151=48%) in cats weighing 11-21 pounds.

Incidents occurred with approximately equal frequency in males and females.

For body systems affected, neurologic (nervous symptom) signs were observed 172 times, gastrointestinal 130 times, and dermal 122 times. The renal system was involved only 5 times (and the urinary system was also involved 5 times), but this is of importance as it possibly indicates a solvent issue. For clinical signs, lethargy occurred in 98 incidents, dermatitis/pruritus/sores in 85, anorexia in 68, hair loss in 68, vomiting in 46, ataxia in 36, and vocalization in 35.

The domestic shorthair (DSH) was affected in 131/242 (54%) of the incidents in which breed was reported. This is probably because the DSH is the most common type of household cat. There were 2 incidents (severity not specified) involving dermal exposure to dogs. The label includes the statement (under Directions for Use): "Use ONLY on cats or kittens over 12 weeks of age. DO NOT USE ON OTHER ANIMALS." There were 3 incidents (classified as moderate) involving oral exposure in dogs.

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

As can be seen in Tables 1, 2 and 3, the majority of incidents reported were minor or moderate in nature.

Table 1 (Reg # 2596-147) Severity: Dermal plus Oral routes of exposure in Cats, 2008

Severity*	# of Incidents	Per Cent
Death	34**	12
Major	5	2
Moderate	100	36
Minor	135	49
TOTAL	274	

* See appendix for explanation of severity categories

**8/34 were euthanized

Of the 33 deaths reported following only dermal exposure, 16 animals were treated by a veterinarian. Eight of these animals were euthanized. Label directions were not followed for five of the 33 deaths.

Data were not submitted for Exposure in Cats by Unspecified route or any route other than dermal or oral).

Table 2 (Reg # 2596-147) Severity: Dermal Exposure in Cats*, 2008

Severity****	# of Incidents	Per Cent
Death	33**	14%
Major	5	2%
Moderate	92	38%
Minor	112	46%
TOTAL	242	

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

**8/33 were euthanized

*** See appendix for explanation of severity categories

Table 3 (Reg # 2596-147) Severity: Oral Exposure in Cats*, 2008

Severity**	# of Incidents	Per Cent
Death	1	3%
Major	0	
Moderate	8	25%
Minor	23	72%
TOTAL	32	

* Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

****NOTE:** The one death reported was an 8 year old mixed breed cat which exhibited lethargy, anorexia, weight loss and renal failure 24 hours to one week after ingesting the product. The cat was treated by a veterinarian and euthanized.

Dogs exposed to cat product:

There were very few reported incidents in dogs due to exposure to this product. Tables 4 and 5 indicate a misuse of the product since the label states "DO NOT USE ON OTHER ANIMALS"

Table 4 (Reg # 2596-147) Severity: Dermal Exposure in Dogs, 2008

Dogs exposed to cat product

Severity**	# of Incidents	Per Cent
Death		
Major		
Moderate		
Minor		
TOTAL	2*	

*Severity not specified

** See appendix for explanation of severity categories

Table 5 (Reg # 2596-147) Severity: Oral Exposure in Dogs*, 2008

Dogs exposed to cat product

Severity**	# of Incidents	Per Cent
Death		
Major		
Moderate	3	100
Minor		
TOTAL	3	

* Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

GENDER

Incidents seem to be equally divided between male and female cats (see Table 6). Thus, gender did not play a role in the occurrence of incidents after the use of the product.

Table 6 (Reg # 2596-147) Gender: Dermal Exposure in Cats, 2008

Sex	# of Incidents	Per Cent of all incidents	Per Cent*
Female	117	49	53
Male	102	42	46
Unknown	22	9	NA
TOTAL	241 (219*)		

Note: Gender was not reported for all incidents.

NA – calculation not applicable

* total of only those where gender was specified

AGE

The majority of the deaths occurred during the first 6 months of life with 6 (3 %) occurring before 3 months which is a misuse of the product (see Table 7). Eight deaths (4 %) occurred between 3-6 months of age. There were no reported deaths between 6 months and 2 years of age. After the 1 to 2 year increment, the incidence ranged from <1 % to 2 %. The majority of the incidents was moderate to minor in severity (accounting for 84 %) and was most frequent in the 1-3 year olds.

Table 7 (Reg # 2596-147) Age: Dermal Exposure in Cats, 2008. # of Incidents (%)

Severity* \ Age	Death	Major	Moderate	Minor	Total (%)
< 3 Months**	6 (3 %)	0	8 (4 %)	7 (3 %)	21 (9)
3 – 6 month	8 (4 %)	0	12 (5 %)	9 (4 %)	29 (13)
6 – 9 months	0	0	2 (<1 %)	5 (2 %)	7 (3)
9- 12 months	0	0	0	1 (<1 %)	1 (<1)
[<1 year]	[14 (6)]	[0]	[22 (10)]	[22 (10)]	[58 (26)]
1 – 2 year	0	1 (<1 %)	17 (8 %)	15 (7 %)	33 (15)
2 – 3 years	1 (<1 %)	0	8 (4 %)	15 (7 %)	24 (11)
3 – 5 years	5 (2 %)	2 (<1 %)	8 (4 %)	19 (9 %)	34 (15)
5 – 7 years	5 (2 %)	1 (<1 %)	9 (4 %)	13 (6 %)	28 (13)
7 – 9 years	3 (1 %)	1 (<1 %)	9 (4 %)	7 (3 %)	20 (9)
9 – 11 years	1 (<1 %)	0	8 (4 %)	3 (1 %)	12 (5)
> 11 years	2 (<1 %)	0	7 (3 %)	5 (2 %)	14 (6)
Subtotal	31 (14)	5 (2)	88 (39)	99 (44)	
TOTAL incidents	223				

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

** Misuse, label says 12 weeks and older only.

Note: Not all ages were reported.

BODY WEIGHT

More deaths occurred in animals weighing between 5 and 11 pounds (see table 8). However, it should be noted that minor signs seem to be more commonly reported (52 %) while the majority of all incidents occurred in the 11-21 weight range.

Table 8 (Reg # 2596-147) Body Weight: Dermal Exposure in Cats, 2008. # of Incidents (%)

Severity* Body Wt (pounds)	Death	Major	Moderate	Minor	Total (%)
<5	3 (2)	0	13 (9)	10 (7)	26 (17)
5- 11	10 (7)	3 (2)	18 (12)	22 (15)	53 (35)
11 -- 21	3 (2)	0	23 (15)	46 (30)	72 (48)
Subtotal	16 (11)	3 (2)	54 (35)	78 (52)	
TOTAL incidents	151				

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

As can be seen in Table 9, most incidents were reported for the DSH breed. This is most likely because the DSH is the most popular breed seen in American households.

Table 9 (Reg # 2596-147) Dermal Exposure in Cats, 2008 by Breed

Breed	# Incidents	% Incidents
Domestic Short Hair	131	54
Unknown	42	17
Domestic Long Hair	40	16.5
Mixed	12	4.9
Other	5	2.1
Himalayan	4	1.6
Siamese	3	1.2
Maine Coon	2	0.8
Ragdoll	1	0.4
Persian	1	0.4
Burmese	1	0.4
Total	242	

BODY SYSTEM

As can be seen in Table 10, gastrointestinal, neurological, and dermal signs each accounted for one quarter of the total number of signs reported.

Table 10 (Reg # 2596-147) Body System: Dermal Exposure in Cats, 2008

Body System	# of Incidents	Per Cent
Neurologic	172	32
Gastrointestinal	130	24
Dermal	122	23
Miscellaneous	41	8
Respiratory	26	5
Hematologic	12	2
Ocular	9	2
Unable to determine	6	1
Renal	5	<1
Urinary	5	<1
Cardiac	2	<1
Liver	1	<1
Total	531	

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

CLINICAL SIGNS

Of the total of 862 clinical signs, dermal symptoms (dermatitis, pruritus sores, hair loss, erythema and rough skin - 21 %) were most frequently reported (see Table 11). Lethargy was the next most observed sign, followed by signs which were neurological in nature. Neurological signs included tremors, seizures/ convulsions, and weakness. Even though the registrant provided data which showed that some of the clinical signs persisted until death, the length of time between product application and death could not be determined. In general it seems that clinical signs persisted for periods ranging from two hours to less than one month.

Table 11 (Reg # 2596-147) Clinical Signs: Dermal Exposure in Cats, 2008

Signs	# of Incidents	Per Cent
Lethargy	98	11
Dermatitis/Pruritus/Sores	85*	10
Anorexia	68	8
Hair Loss	68	8
Vomiting	46	5
Ataxia	36	4
Vocalization	35	4
Recumbent	30	3
Seizure of some type	30	3
Tremor	30	3
Salivation	20	2
Agitated	16	2
Diarrhea	13	2
Erythema	13	2
Rough skin	13	2
Weakness	13	2
Weight loss	12	1
Gagging	11	1
Sudden death	10	1
Dyspnea of various types	10	1
See footnote**	302	35
TOTAL	862	

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

* 38 of these 85 reported dermal signs were due to pruritus

** 302 (or 35%) were signs with <1% incidence

TOXICITY SUMMARY FOR 2596-147

BRIEF SUMMARY OF TOXICITY FOR 2596-147:

Active ingredient:

(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:

No companion animal safety studies were submitted for this product. (S)-methoprene is considered to be non-toxic to mammalian species, and it was registered on this basis.

Acute studies on 2596-147:

No acute toxicity studies were submitted for the formulation in 2596-147. The label indicates this formulation is in EPA toxicity category III for eye irritation, and toxicity category IV in terms of the oral LD₅₀ and dermal LD₅₀. The label also indicates that this formulation is in toxicity category IV for dermal irritation and is not 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.