DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING DOG PRODUCT

Registrant: The Hartz Mountain Corporation
Subregistrant: N/A
Product Name(s): Hartz Reference 118
Hartz® Advanced Care Brand® Flea & Tick Drops Plus + for Dogs and Puppies
Hartz® Advanced Care® 4 in 1 Flea & Tick Drops Plus + for Dogs and Puppies
Hartz® Advanced Care® 5 in 1 Flea & Tick Drops Plus + for Dogs and Puppies
Hartz® UltraGuard™ plus Drops for Dogs and Puppies
Pet Principles by Hartz® Flea & Tick Drops for Dogs and Puppies

Active Ingredient: Phenothrin (85.7 %), PC Code: 069005, CAS # 26002-80-2
Active Ingredient: (s)-Methoprene (2.3 %), PC Code: 105402 , CAS # 65733-16-6

Application Method: Dermal along back

Species: Dog **(specifically says DO NOT USE ON CATS OR KITTENS)**
Weight Ranges: 4-15, 16-30, 31-45, 46-60, 61-90, >90 pounds. Parts of the label have different weight ranges listed.
Specifically says: **Do not use on puppies less that 12 weeks old, do not use on debilitated, aged, medicated, pregnant, nursing animals…with out consulting a veterinarian.**
Sales Method: Retail

Primary Reviewer: Jean W. Holmes, D.V.M. **Signature:** Kit Dell for Holmes **Date**: 3/12/2010
Secondary Reviewer: Melba Morrow, D.V.M. **Signature:** Byron T. Boden for Morrow **Date**: 7/12/2010

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for Registration # 2596-150 containing Phenothrin,(85.7%) and (S) – Methoprene (2.3%). The label was accepted with comments 4/17/07 in an EPA letter dated 9/4/07. The product is a topical pesticide to be applied along the back of dogs and puppies over 12 weeks of age. It is applied by individual tubes which represent the net contents of each weight class. The weight classes are 4-15 lbs, 16-30lbs., 31-45 lbs., 46-60lbs, 61-90lbs, and over 90lbs. The label indicates that the product kills and repels fleas, flea larvae, ticks and mosquitoes. The label states that this product should not be used on cats or kittens and that a Veterinarian should be consulted before using it on debilitated, aged, medicated, pregnant or nursing animals. The label also recommends that in addition to using this product, the animal's bedding and surroundings should be treated with other products registered for these uses.

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.

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, applying on a different species, or too frequent application). 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 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 9 deaths and 17 major incidents in dogs which accounted for 8% of the incidents. The majority of incidents were minor (56%) followed by moderate incidents (36%) and major incidents (5%). Oral exposure was involved in 8% of the incidents and none of the incidents involved an unidentified route of exposure. The oral exposure incidents were secondary to dermal application of the product. Neurological, gastrointestinal, and dermatological symptoms were disproportionately noted in the incidents, representing 78% of the symptoms observed in the incidents. In the incidents which resulted in death or were classified as "major" approximately 72% exhibited neurological signs, 44% exhibited gastrointestinal signs, and none exhibited dermal symptoms.

There were several incidents (36) in cats (Table 3) considering that the label specifically states that the product should not be used on cats and kittens. 83% (30) were classified as "moderate", 14% (5) were classified as "minor" and one resulted in death. These incidents could be due to misuse or inadvertent exposure through contact with a dog that had been recently treated with this product. The incidents were associated with all of the weight ranges of the dog product.

The greatest number of incidents (approximately 25%) was reported for animals in the 1-2 year old age group, followed by approximately 16% in the 2-3 year old age group. This age distribution is common with other spot-on products.

The data results suggest that a dog's weight and breed may be important factors contributing to the incidents associated with these products.

o The greatest number of incidents by weight was reported for animals 10 lbs and under (30%), the next two weight ranges had reported incidents ranging between 16% to 17% in increasing order. All of the other weight categories had incident rates less than 9%. It also should be noted that approximately 68% of the incidents in which the weight range of the product was identified was due to misuse. Of the incidents that resulted in death or that were classified as "major", misuse was associated with all the labeled weight ranges.

o Of the identified breeds, it appears that the larges numbers of incidents have been observed in small breed dogs (table 8). 52% were in small breeds, 34% in large breed dogs, and 13% in medium breed dogs. It must be noted that the breeds associated with 93 of the 296 incidents (31%) have not been identified. Also, certain smaller breeds of dogs may be more susceptible than others to the dermal effects of these products. Chihuahuas which have an AKC ranking of 12, represented about 13% of the incidents of the identified breeds. The breed that had the next highest number of incidents is the Labrador Retriever (9%) which has an AKC ranking of 1.

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

There were 9 deaths and 17 major incidents in dogs which accounted for 8% of the incidents (Table 1). The majority of incidents were minor (56%) followed by moderate incidents (36%). Oral exposure was involved in 8% of the incidents (Table 3) and none of the incidents involved an unidentified route of exposure.

Table 1 Reg # 2596-150).
Severity: Dermal and Oral Exposure in Dogs*, 2008

Severity*	# of Incidents	Per Cent
Death	9	3
Major	17	5
Moderate	116	36
Minor	180	56
TOTAL	322	

* See appendix for explanation of severity categories

Table 2 Reg # 2596-150).
Severity: Dermal Exposure in Dogs*, 2008

Severity**	# of Incidents	Per Cent
Death	8	3
Major	17	6
Moderate	111	38
Minor	160	54
TOTAL	296	

*Animals that had both oral and dermal exposure were not included in this table
** See appendix for explanation of severity categories

Table 3 (Reg #2596-150).
Severity: Oral Exposure in Dogs*, 2008

Severity**	# of Incidents	Per Cent
Death	1	4
Major	0	
Moderate	5	19
Minor	20	77
TOTAL	26	

* Some of these animals may have also had dermal exposure
** See appendix for explanation of severity categories

Cats or other species exposed to dog product.

There were 36 incidents in cats (Table 4). 83% (30) were classified as "moderate", 5 were classified as "minor" and one resulted in death. These incidents could be due to misuse or inadvertent exposure through contact with a dog that had been recently treated with this product.

Table 4 (Reg # 2596-150).
Severity: Dermal Exposure in Cats*, 2008. Cat exposed to dog product

Severity**	# of Incidents	Per Cent
Death	1	3
Major	0	
Moderate	30	83
Minor	5	14
TOTAL	36	

* Some of these animals may have also had dermal exposure
** 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. Males accounted for a slightly higher per cent of incidents (54% versus 46% for females) (see Table 5). However, there is no way to determine whether males were treated at a higher rate.

Table 5 (Reg #2596-151). Gender: Dermal Exposure in Dogs, 2008

Sex	# of Incidents	Per Cent of all incidents	Per Cent*
Female	127	43	46
Male	152	51	54
Unknown	17	6	NA
TOTAL	296 (279*)		

Note: Gender was not reported for all incidents.
NA – calculation not applicable
* total of only those where gender was specified

AGE

Ages were reported for 271 dogs which involved incidents associated with dermal exposure to the product (Table 6). The label indicates that dogs need to be over 12 weeks of age to be treated. There was 4 % of misuse in puppies younger than this age. The greatest number of incidents (approximately 25%) was reported for animals in the 1-2 year old age group, followed by approximately 16% in the 2-3 year old age group. This age distribution is common with other spot-on products.

Table 6 (Reg #2596-150).
Age: Dermal Exposure in Dogs, 2008. # of Incidents (%)

Severity* / Age	Death	Major	Moderate	Minor	Total (%)
< 3 Months**	1 (<1 %)	0	3 (1 %)	10 (4 %)	14 (4)
3 – 6 month	2 (<1 %)	0	10 (4 %)	8 (3 %)	20 (7)
7 – 9 months	0	0	5 (2 %)	14 (5 %)	19 (7)
9- 12 months	0	0	5 (2 %)	0	5 (2)
[<1 year]	[3 (1 %)]	[0]	[23 (9 %)]	[32 (12 %)]	[58 (21 %)]
1 – 2 year	2 (<1 %)	3 (1 %)	16 (6 %)	27 (10 %)	48 (25)
2 – 3 years	1 (<1 %)	3 (1 %)	16 (6 %)	23 (9 %)	43 (16)
3 – 5 years	0	5 (2 %)	21 (8 %)	18 (7 %)	44 (16)
5 – 7 years	1 (<1 %)	1 (<1 %)	9 (3 %)	14 (5 %)	25 (7)
7 – 9 years	0	2 (<1 %)	6 (2 %)	16 (6 %)	24 (9)
9 – 11 years	0	0	5 (2 %)	7 (3 %)	12 (4)
> 11 years	1 (<1 %)	2 (<1 %)	6 (2 %)	8 (3 %)	17 (5)
Subtotal	8	16	102	145	
TOTAL incidents	271				

Note: Not all ages were reported.
* Severity key (See appendix for explanation of severity categories)
** Misuse, label says use only on puppies and dogs older than 12 weeks

BODY WEIGHT

Body weights were reported for a total of 224 animals (Table 7). The labeled weight classes for dogs are 4-15 lbs, 16-30 lbs, 31-60 lbs, and >60 lbs. The greatest number of incidents by weight was reported for animals 10 lbs and under (30%), the next two weight ranges had reported incidents ranging from 16% to 17% in increasing order. All of the other weight stratifications had incident rates less than 9%.

Table 7 (Reg #2596-150).
Body Weight: Dermal Exposure in Dogs, 2008. # of Incidents (%)

Severity* / Body Wt (pounds)	Death	Major	Moderate	Minor	Total (%)
<5	4 (2 %)	1 (<1 %)	13 (6 %)	33 (15 %)	51 (23 %)
5-11	2 (<1 %)	7 (3 %)	21 (9 %)	30 (13 %)	60 (27 %)
11 – 21	1 (<1 %)	1 (<1 %)	13 (6 %)	21 (9 %)	36 (16 %)
21 – 31	1 (<1 %)	2 (<1 %)	18 (8 %)	17 (8 %)	38 (17 %)
31 – 41	0	0	10 (5 %)	11 (5 %)	21 (9 %)
41 – 51	0	1 (<1 %)	5 (2<1 %)	6 (3 %)	12 (5 %)
51 – 61	0	0	2 (<1 %)	1 (<1 %)	3 (1 %)
≥61	0	1 (<1 %)	2 (<1 %)	0	3 (1 %)
Subtotal	8	13	84	119	
TOTAL incidents	224				

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)

As can be seen in Table 8, approximately 68% of the incidents in which the weight range of the product was identified, were due to treatment of dogs under the labeled product weight range (misuse). Of the incidents that resulted in death or that were classified as "major", misuse was associated with all the labeled weight ranges.

Table 8 (Reg #2596-150).
Product Weight Range: Dermal Exposure in All Dogs, 2008

Product Weight Range	# Incidents	Per Cent
Dog weight < product weight range*	101	68
TOTAL animals reported	150	

* This table indicates product misuse and is a summary all product use weight ranges
NOTE: not all body weights or product used were reported

BREEDS

Chihuahuas which have an AKC ranking of 13, represent about 13% of the incidents of the identified breeds (see Table 9). The breed that had the next highest number of incidents is the Labrador Retriever (9%) which has an AKC ranking of one. Of the identified breeds, the small size dog breeds appear to be associated with more incidents than the other sizes. There were incidents in 106 small breed dogs (52%), 70 large breed dogs (34%), and 26 medium (13%) breed dogs. It must be noted that the breeds associated with 93 of the 296 incidents (31%) have not been identified. Of the incidents that have resulted in death or have been classified as "major" approximately 52% were small breed dogs. For this group of incidents, an evaluation of the breed size of dogs for dogs in which the breed was not specified was conducted based on age and weight of dog. When these numbers were included, approximately 44% small breed dogs, instead of 52% , resulted in death or were classified as "major".

Table 9 (Reg #2596-151). Dermal Exposure in Dogs, 2008 by Breed Size

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Mixed Breed, Other, Unknown	Various sizes	93	31%	NR
Chihuahua	Small	27	9%	12
Labrador Retriever	Large	20	7%	1
Yorkshire Terrier (Yorkie)	Small	18	6%	2
Boxer	Large	13	4%	6
Shih Tzu	Small	13	4%	10
Dachshund	Small/Medium	10	3%	7
Golden Retriever	Large	9	3%	4
Pit Bull Terrier	Large	9	3%	55
Pomeranian	Small	8	3%	13
Beagle	Medium	6	2%	5
Miniature Pinscher	Small	5	2%	32
Schnauzer	Medium	5	2%	94
Jack Russell Terrier	Small	4	1%	NR
Bulldog	Large	3	1%	8
Maltese	Small	3	1%	20
Rottweiler	Large	3	1%	14
Boston Terrier	Small	3	1%	17
Amer. Staffordshire Terrier	Large	3	1%	69
Other breeds of 1 or 2 incidents		41		
TOTAL		296		

Note: Not all breeds were reported. Small < 20#, Medium ~ 20-50#, Large > 50#
AKC Rank is the number of new registrations for 2008 by the American Kennel Club.
NR not AKC ranked or not applicable

BODY SYSTEM

There were a total of 549 incidents involving various body systems for affected 296 dogs (see Table 10). In numerous cases more than one body system was affected; however, neurological, gastrointestinal, and dermatological symptoms were disproportionately noted in the incidents. They represent 78% of the symptoms observed in the incidents. In the incidents which resulted in death or were classified as "major" approximately 72% exhibited neurological signs, 44% exhibited gastrointestinal signs, and none exhibited dermal symptoms.

Table 10 (Reg #2596-150). Body System: Dermal Exposure in Dogs, 2008

Body Systems	# of Incidents	Per Cent
Dermal	151	28%
Gastrointestinal	137	25%
Neurological	137	25%
Miscellaneous/unable to determine	47	9%
Respiratory	21	4%
Asymptomatic	17	3%
Ocular	14	3%
Urinary (renal)	13	2%
Heme/Hepatic	6	1%
Hepatic	3	<1%
Cardiovascular	2	<1%
Hematopoietic	1	<1%
TOTAL	549	

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

CLINICAL SIGNS

The majority of the clinical signs demonstrate an adverse affect to the neurological, gastrointestinal, and dermatological body systems (Table 11).

Table 11 (Reg #2596-150). Clinical Signs: Dermal Exposure in Dogs, 2008

Signs	# of Incidents	Per Cent
Vomiting	89	11%
Lethargy	85	11%
Pruritus/Sores	74	9%
Alopecia	45	6%
Anorexia	45	6%
Erythema	40	5%
Diarrhea	39	5%
Tremor/Trembling	20	3%
Seizure	18	2%
Recumbant/Can't stand up	14	2%
Vocalization /Abnormal mentation	14	2%
Shaking/Shivering	13	2%
Salivation	12	2%
Ataxia	11	1%
Gagging/Nausea	10	1%
Agitated	9	1%
Dyspnea	9	1%
Rash	9	1%
Weakness	9	1%
Hyperthermia	8	1%
See footnote*	207	27%
TOTAL incidents	780	

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

* 207 (or 27%) were signs with <1% incidence

BRIEF SUMMARY OF TOXICITY:

EPA Reg. No. 2596-150:

From a Health Effects Division memorandum dated July 2, 2008 phenothrin, ([(3-phenoxyphenyl)methyl] 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate), also known as sumithrin, is a type I pyrethroid insecticide. Pyrethroids are synthetic esters structurally similar to naturally occurring pyrethrins (insecticides derived from the extract of chrysanthemum flowers). Type I pyrethroids act on axons in the peripheral and central nervous system by interacting with sodium channels in mammals and/or insects. Technical phenothrin is composed of both cis and trans forms. Phenothrin and other pyrethroids are usually combined with synergists which enhance insecticidal activity by preventing enzymatic break down of the pyrethroid.

A rabbit developmental study provides evidence of (developmental) neurotoxicity. Spina bifida was observed in 1 fetus at 100 mg/kg/day and microphthalmia was seen in 1 fetus at 300 mg/kg/day. Hydrocephaly was observed in four rabbit fetuses within 3 litters at the highest dose tested (500 mg/kg/day). While spina bifida and microphthalmia were seen only in a single fetus each, the co-occurrence of these effects with hydrocephaly is suggestive because each is an indicator of neurotoxicity. Generally, other specific neurotoxic clinical signs were absent in other acute, subchronic and chronic phenothrin studies in rats and dogs at dose up to 20,000 pm (limit dose).

Technical phenothrin has an oral LD_{50} >5000 mg/kg (MRID 40908302), placing it in toxicity category IV by this exposure route. It has a dermal LD_{50} >2000 mg/kg (MRID 40908303), placing it in toxicity category III by this route. It is in toxicity category III in terms of eye irritation (MRID 40908304) and in toxicity category IV for dermal irritation (MRID 40908304). It is not a dermal sensitizer (MRID 40908305).

(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:

Companion Animal Studies: The companion animal safety studies used to support this registration are in MRIDs 45006403 (adult dog) and 45006402 (puppy). These studies were conducted under the current 870.7200 OPPTS guidelines, and the reviews were signed off on 9/04/01. The following are summaries of these studies:

MRID 45006403: The test material (containing as active ingredients sumithrin (d-phenothrin) at 95.22% and (S)-methoprene at 2.41% was topically applied (from the neck to the base of the tail) at a 5X dose (1.3 mL every 60 minutes until a 5X dose was achieved) to a group of 6 male and 6

female adult (at least 6 months old) beagle dogs. A second group of 6 male and 6 females was similarly treated with safflower oil (1.3 mL every 60 minutes for a total of 5 doses). Males weighed from 9.1-13.5 kg and females from 6.7-10.8 kg at study initiation. No mortality was observed and there were no treatment-related or biologically significant effects on body weight, clinical chemistry or hematology. Several statistically significant clinical and hematology differences were observed between treated and control groups; however, these were within normal limits and were not considered toxicologically significant. It was assumed that the intended use dosage rate was one application of 1.3 mL per month, and with this dosage rate the required 5X margin of safety (in adult dogs) was demonstrated in this study.

MRID 45006402: The test material (two analyses: sumithrin (d-phenothrin) at 84.154 and 84.487%; (S)-methoprene at 2.323 and 2.319%) was topically applied at a 5X dose (1.3 mL every 60 minutes until a 5X dose was achieved) to a group of 6 male and 6 female beagle puppies. Controls were similarly treated with safflower oil. The test material or placebo was applied to the skin of the back from a point midway between the shoulder blades to the base of the tail. The puppies were 84-90 days old at study initiation, and weighed (males) from 2.1-5.1 kg and (females) from 2.8-4.7 kg. The puppies were observed for 14 days after treatment. No mortality occurred, and there were no treatment-related or biologically significant effects on body weight, clinical chemistry or hematology. Several statistically significant clinical chemistry differences were observed between the two groups, but these were within the reference ranges and were therefore not considered to be toxicologically significant. It was assumed that the intended dosage rate was one application of 1.3 mL per month, and with this dosage rate the required 5X margin of safety (in puppies) was demonstrated in this study.

Acute toxicity studies:

The acute oral LD50 study used to support this registration is in MRID 44864002. Five male and 5 female fasted Sprague-Dawley rats were orally dosed at 5000 mg/kg with a formulation containing approximately 90% technical Sumithrin and 3% (S)-Methoprene combined with a solvent. Following administration, all rats exhibited anogenital staining and one male also had ventral staining, with recovery by day 3. There were no mortalities and no gross abnormalities were seen at necropsy following the 14-day observation period. The oral LD50 > 5000 mg/kg (EPA Toxicity Category IV).

The acute dermal LD50 study used to support this registration is in MRID 44864003. Five male and 5 female New Zealand white rabbits received a 24-hour occluded dermal exposure to 5000 mg/kg of a formulation containing approximately 90% technical Sumithrin and 3% (S)-Methoprene combined with a solvent. One male lost weight between days 7 and 14 and one female failed to gain weight over the 14-day observation period. Except for dermal irritation (erythema and edema) noted at the dose site of all animals on day 2 (and continuing in some animals up to day 12), there were no signs of gross toxicity, adverse pharmacological effects or abnormal behavior. There were no mortalities and no gross abnormalities were seen at necropsy following the observation period. The dermal LD50 > 5000 mg/kg (EPA Toxicity Category IV).

In the eye irritation study (MRID 44864004) no corneal opacity or iritis was observed in any of the 3 rabbits. One of the rabbits was positive for conjunctival redness at 1 and 24 hours, and the formulation was assigned to EPA Toxicity Category III by this exposure route.

In the dermal irritation study (MRID 44864005) with 4-hour occluded exposure the primary dermal irritation index was 0.3, with only one of six rabbits showing slight (grade 1) erythema at 24 and 48 hours and all scores zero at 72 hours. The formulation is in EPA Toxicity Category IV by this exposure route.

In the dermal sensitization study (MRID 44864006) guinea pigs were tested using the Buehler Method. There was no indication of a dermal sensitization response, as no irritation was observed in 20 previously induced or 10 animals only exposed at challenge..

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.