

DATA EVALUATION RECORD FOR ENHANCED SPOT-ON REPORTING DOG PRODUCT
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Registration #: 11556-132, -133, -134, & -135
Registrant(s): Bayer HealthCare LLC
Product Name (s): K9 Advantix® 10, K9 Advantix® 20, K9 Advantix® 100, K9 Advantix® 55

Active Ingredient: Permethrin (44.0%), PC Code: 109701, CAS #52645-53-1
Active Ingredient: Imidacloprid (8.8%), PC Code: 129099, CAS #138261-41-3

Application Method: <10 lbs: Apply contents of one tube (0.4 mL) directly to the skin between the shoulder blades.
 11-20 lbs: Apply contents of one tube (1.0 mL) directly to the skin between the shoulder blades.
 21-55 lbs: Entire contents of one tube (2.5 mL) should be applied evenly directly to the skin at three or four spots on the top of the back from the shoulder to the base of the tail.
 >55 lbs: Entire contents of one tube (4.0 mL) should be applied evenly to three or four spots on the top of the back to the base of the tail. At each spot, part the hair until the skin is visible. Place the tip of the tube on the skin and gently squeeze to apply directly to the skin.

Sales Method: Sold by veterinarians

Species: Puppies (>7 weeks) & Adult Dogs **Weight Ranges:** <10, 11-20, 21-55, >55 lbs

Primary Reviewer: Byron T. Backus, Ph.D. **Signature:** *Byron T. Backus* **Date:** 3/12/2010
Secondary Reviewer: Kit Farwell, DVM **Signature:** *Kit Farwell* **Date:** 3/12/2010

EXECUTIVE SUMMARY:

Product: This report is a review of incident data for EPA Registrations #11556-132, -133, -134 & -135 (Permethrin: 44.0%, Imidacloprid: 8.8%, other ingredients: 47.2%).

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, or applying on a different species). The

total number of reported incidents may be influenced by many external factors, such as negative publicity on web sites and ease or difficulty in reporting due to information presented on the product label which may vary between registrants.

This report includes only incidents for which a registration number was available. The total number of affected animals may differ between the tables in this report because incidents with multiple animals were sometimes not counted when it was difficult to tell which animal the description applied, or because age, weight, breed, or route of exposure were not always reported. Data were reported differently by the different registrants and simplifying assumptions were sometimes made and in other cases ambiguous data were not considered.

The intent of this report was not just to report the total number of incidents, but to describe the nature of the incidents and to identify any susceptible subpopulations or use patterns which may predispose to toxicity so that mitigation could be implemented if appropriate. The focus of this report is on dermal exposure for which there was no indication of misuse. However, the consequences of misuse or for oral exposure by grooming are also reported.

Conclusions: For 2008, there were a total of 1377 incidents reported in dogs following dermal exposure to this formulation. These included 7 deaths and 3 major (life-threatening) incidents. The great majority (>99%) of the incidents were moderate (>14%) or minor (>84%). A considerable number of the symptoms observed were dermal and/or behavioral, consistent with information in the NPIC Permethrin Technical Fact Sheet that dermal exposures in dogs may cause temporary paresthesia and neurological signs as evidenced by paw flicking or ear, tail or skin twitching, or rolling on the ground. Dermal exposure in humans may cause irritation, itching or paresthesia (a tingly, prickly sensation) at the site of contact, but these symptoms rarely last more than 24 hours, and are consistent with exposure to a pyrethroid.

Certain smaller breeds of dogs may be more susceptible than others to the dermal effects of these registered products. For purebreds, the Shih Tzu and Bichon Frise ranked one and two with 97 and 96 incidents, respectively, despite AKC rankings of 10 and 35. Yorkshire Terriers (AKC ranking 2) came in at number 3 with 59 incidents. Maltese and Chihuahua dogs (4th and 5th) were also involved in disproportionate numbers of incidents (56 and 53) relative to their AKC rankings of 20 and 12. Conversely, the beagle, which was the breed used in the companion animal safety studies that supported these registrations, was associated with only 14 incidents despite an AKC ranking of 5. The only effect noted in the companion animal (beagle) safety studies was a decrease in food consumption in 5X puppies relative to their solvent controls on the days following the first, second and third (but not the fourth) application; for the adults both the 5X and solvent control groups showed food consumption decreases on the days following application.

Also from the NPIC Permethrin Technical Fact Sheet is the statement that: "Ingestion of permethrin may cause sore throat, abdominal pain, nausea and vomiting." In at least four of the reported dog fatalities there was vomiting prior to death suggesting that the animal may have ingested some of the formulation, although all deaths were attributed to dermal rather than oral exposure.

Cats are very susceptible to the toxic effects of permethrin. Despite labeling stating that this formulation is not to be used on cats, there were 10 reported deaths and 14 major incidents out of a total of 535 involving this species, both from dermal application (8 deaths, 13 major incidents) or by unspecified exposure type (2 deaths, 1 major incident).

According to NPIC, signs of toxicity in rats following oral ingestion of imidacloprid include lethargy, respiratory disturbances, decreased movement, staggering gait, occasional trembling and spasms. It effectively blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in impairment of normal nerve function. Imidacloprid has a higher binding strength to insect nerve receptors than to mammalian receptors. Presumably it is the permethrin (present at 44%) rather than the imidacloprid (8.8%) in these products that is responsible for most of the toxicity seen in these incidents, although there may be some contribution from the imidacloprid.

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

Most (>99%) of the reported incidents in dogs were minor or moderate.

Table 1 (Reg #11556-132, -133, -134 & -135).**Severity: Dermal, Oral and Unknown Routes of Exposure in Dogs*, 2008**

Severity*	# of Incidents	Per Cent
Death	7	<1
Major	3	<1
Moderate	244	15
Minor	1391	85
TOTAL	1645	

* See appendix for explanation of severity categories

Table 2. (Reg #11556-132, -133, -134 & -135).**Severity: Dermal Exposure in Dogs*, 2008**

Severity**	# of Incidents	Per Cent
Death	7	<1
Major	3	<1
Moderate	199	14
Minor	1168	85
TOTAL	1377	

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

** See appendix for explanation of severity categories

There were very few reported incidents involving oral exposure in dogs (see Table 3).

Table 3 (Reg #11556-132, -133, -134 & -135).**Severity: Oral Exposure in Dogs*, 2008**

Severity**	# of Incidents	Per Cent
Death	0	0
Major	0	0
Moderate	0	0
Minor	2	100
TOTAL	2	

*Some of these animals may have also had dermal exposure

** See appendix for explanation of severity categories

**Table 4 (Reg #11556-132, -133, -134 & -135).
Severity: Unknown Route of Exposure in Dogs*, 2008**

Severity*	# of Incidents	Per Cent
Death	0	0
Major	0	0
Moderate	45	17
Minor	221	83
TOTAL	266	

* See appendix for explanation of severity categories

Use of Dog product on cats

(See Tables 5, 6 and 7) These products are not registered for use on cats, and the labels include the statement: “DO NOT USE ON CATS.” In addition, the label includes the following: “Due to their unique physiology and inability to metabolize certain compounds, this product must not be used on cats. If applied to a cat, or ingested by a cat which actively grooms a recently treated dog, this product may have serious harmful effects. If this occurs contact your veterinarian immediately.”

Despite the label warnings, the cumulative (dermal + unspecified route of exposure) number of deaths in cats was greater than that reported for dogs (10 vs. 7), the number of major events was greater for cats than for dogs (14 vs. 3), and the number of moderate events was also greater in cats than dogs (535 vs. 244) (see Tables 3, 4 and 5). The number of reported minor effects for cats was less than that reported for dogs (99 vs. 1389). Cats are known to be very sensitive to permethrin.

**Table 5 (Reg #11556-132, -133, -134 & -135).
Severity: Dermal Exposure in Cats* 2008**

Severity**	# of Incidents	Per Cent
Death	8	2
Major	13	3
Moderate	318	75
Minor	84	20
E ^a	2	<1
TOTAL	425	

^a Symptoms 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 also be used for reporting evidence that known exposures have not resulted in symptoms.

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

** See appendix for explanation of severity categories

In a number of reported incidents, cats were affected or exposed. These reports could include secondary exposure to treated dogs, so it cannot be stated that the products were misused.

Table 6 (Reg #11556-132, -133, -134 & -135).**Severity: Unspecified Route of Exposure in Cats,* 2008**

Severity*	# of Incidents	Per Cent
Death	2	2
Major	1	1
Moderate	92	84
Minor	15	14
TOTAL	110	

^a Symptoms 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 also be used for reporting evidence that known exposures have not resulted in symptoms.

* See appendix for explanation of severity categories

There are no records of oral exposure in cats from use on cats.

The cumulative numbers of incidents and their severity in cats from all exposure routes (dermal + unspecified route of exposure) are given below:

Table 7 (Reg #11556-132, -133, -134 & -135).**Severity: Cumulative (Dermal + Unspecified Route) Exposure in Cats, (from Product Misuse), 2008**

Severity*	# of Incidents	Per Cent
Death	10	2
Major	14	3
Moderate	410	77
Minor	99	19
E ^a	2	<1
TOTAL	535	

* See appendix for explanation of severity categories

^a Symptoms 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 also be used for reporting evidence that known exposures have not resulted in symptoms.

There is no indication of any adverse incidents following misuse of these products on other species.

GENDER

For dogs, males and females are about equally represented in the incident reports (see Table 8).

Table 8 (Reg #11556-132, -133, -134 & -135).**Gender: Dermal Exposure in Dogs, 2008**

Sex	# of Incidents	Per Cent
Female	628	46.7
Male	718	53.3
TOTAL	1346	

Note: Gender was not reported for all incidents.

AGE

For those incidents in which the dog's age was known, two deaths occurred in dogs less than 6 months old. The remainder (4/6) involved dogs >5 years of age (see Table 9). As only 34% of the total number of incidents occurred in dogs >5 years of age, the possibility exists that these particular animals may have had underlying conditions that made them more susceptible to the formulation (assuming that exposure to the formulation caused the deaths).

Table 9 (Reg #11556-132, -133, -134 & -135).**Age: Dermal Exposure in Dogs, 2008. # of Incidents**

Severity* Age	Death	Major	Moderate	Minor	Total	% Total
< 3 Months	1	0	2	24	27	2
3 – 6 month	1	0	9	47	57	4
6 – 9 months	0	0	4	61	65	5
9 - 12 months	0	0	4	27	31	2
[<1 year]	[2]	[0]	[19]	[159]	[180]	[13]
1 - 2 years	0	1	27	162	190	14
2 – 3 years	0	0	41	199	240	18
3 – 5 years	0	1	46	223	270	20
5 – 7 years	1	0	21	159	181	14
7 – 9 years	3	0	19	114	136	10
9 – 11 years	0	0	13	55	68	5
> 11 years	0	0	9	62	71	5
TOTAL (%)	6 (<1)	2 (<1)	195 (15)	1133 (85)	1336	

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

Note: Not all ages were reported.

BODY WEIGHT

Dose ranges: <10, 11-20, 21-55, >55 lbs

Three of the five reported deaths occurred in dogs weighing between 11 and 20 pounds, but two occurred in dogs weighing more than 60 pounds (see Table10). More than half (720/1211 or >59%) of the incidents occurred in dogs weighing less than 20 pounds, but a considerable number (179/1211 or >14%) occurred in dogs weighing more than 60 pounds.

**Table 10. (Reg #11556-132, -133, -134, -135).
Body Weight: Dermal Exposure in Dogs, 2008**

Severity Body Wt (pounds)	Death	Major	Moderate	Minor	Total	Per Cent
< 5	1	0	9	38	48	4
> 5 – 11	1	0	37	225	263	22
11 – 21	2	1	56	351	410	34
21 – 31	0	0	18	131	149	12
31 – 41	0	0	11	47	58	5
41 – 51	0	0	10	36	46	4
51 – 61	1	0	9	50	60	5
≥61	2	1	32	144	179	15
TOTAL (%)	7 (<1)	2 (<1)	182 (16)	1022 (84)	1213	

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 11, there were 105 reported incidents in which the dog weight was below the range specified by the product label. These incidents may represent misuse.

**Table 11. (Reg #11556-132, -133, -134, -135).
Product Weight Range: Dermal Exposure in Dogs, 2008**

Dog wt. vs. Product wt. range	# Incidents	Per Cent
Dog weight < product weight range	105	10
TOTAL	1018	

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

BREEDS

Many of the reported incidents were in mixed and crossbred dogs (see table 10). Several small breeds were involved in disproportionately high numbers of incidents relative to their AKC rankings (see Table 12), with the Bichon Frise (96 incidents) having the second highest number of incidents among purebreds despite an AKC ranking of 35. The Shih Tzu (with an AKC ranking of 10) ranked highest with 97 incidents. Other small breeds with high numbers were Yorkshire Terriers (59 incidents), Maltese (56), Chihuahuas (53) and Pomeranians (51). The only large dog involved in more than 50 incidents was the Labrador Retriever (53), which has an AKC ranking of 1.

Table 12. (Reg #11556-132, -133, -134, -135). Dermal Exposure Incidents in Dogs, 2008 by Breed

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
Shih Tzu	Small (10-16 lbs)	97	7	10
Bichon Frise	Small (7-12 lbs)	96	7	35
Yorkshire Terrier	Small (<7 lbs)	59	4	2
Maltese	Small (4-7 lbs)	56	4	20
Chihuahua	Small (3-7 lbs)	53	4	12
Labrador Retriever	Large	53	4	1
Pomeranian	Small (3-7 lbs)	51	4	13
Poodle	Large (45-70 lbs)	41	3	(9) Not separated ^a
Golden Retriever	Large	29	2	4
Miniature Poodle	Small-Medium	27	2	(9) Not separated ^a
Schnauzer	Small-Large	25	2	(97) Not separated ^b
Pug	Small (13-20 lbs)	24	2	15
Lhasa Apso	Small (13-15 lbs)	18	1	54
(Cavalier) King Charles Spaniel	Small (10-18 lbs)	18	1	25
Toy Poodle	Small	17	1	(9) Not separated ^a
Jack Russell Terrier	Small (14-18 lbs)	17	1	Not listed
Beagle	Medium (20-25 lbs)	14	1	5
Miniature Schnauzer	Small (10-15 lbs)	13	<1	(97) Not separated ^b
Cocker Spaniel	Medium (15-30 lbs)	9	<1	21
Cockerpoo	Small-Medium(<6- >19 lbs)	9	<1	Not listed ^c
Dachshund (Standard) -Kurzhaar	Standard = 15-28 lbs	9	<1	7 ^d
Border Collie	Medium	9	<1	51
West Highland White Terrier	Small (15-22 lbs)	8	<1	34
Rottweiler	Large	7	<1	14
Schipperke	Small (12-18 lbs)	7	<1	89
Cairn Terrier	Small (13-18 lbs)	6	<1	49
Papillon	Small (7-12 lbs)	6	<1	37
Miniature Pinscher	Small (8-11 lbs)	6	<1	32
Boston Terrier	Small-Medium (10-25 lbs)	6	<1	17

Breed	Breed Size	# Incidents	% Incidents	AKC Ranking
German Shepherd Dog	Large	6	<1	3
Brittany	Large (36-50 lbs)	5	<1	30
Greyhound	Large (60-80 lbs)	5	<1	127
American Bulldog	Large (60-120 lbs)	5	<1	8 ^e
Old English Sheepdog	Large (60-100+ lbs)	5	<1	73
Italian Greyhound	Small (6-10 lbs)	4	<1	59
Great Dane	Large	4	<1	22
French Bulldog	Medium (19-28 lbs)	4	<1	26
Basset Hound	Large (45-65 lbs)	4	<1	33
Weimaraner	Large (50-70 lbs)	4	<1	31
Bernese Mountain Dog	Large (65-120 lbs)	4	<1	40
Scottish Terrier	Medium (19-23 lbs)	4	<1	47
Other breeds, crossbred, mixed or not specified	various sizes	490	36	Not applicable
TOTAL		1377		

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.

^a Poodles are listed as #9 by AKC, but Toy, Miniature, and Standard breeds are not named separately.

^b Miniature schnauzer not ranked separately from schnauzer.

^c Not listed as a purebred by AKC; originated as cross between poodle and cocker spaniel with 4 distinct sizes currently noted: Teacup (<6 lbs); Toy (<12 lbs); Miniature (13-18 lbs); Maxi (>19 lbs)

^d Ranking for dachshunds; miniature and standard sizes are not ranked separately.

^e Ranking for bulldogs.

SYSTEMS and CLINICAL SIGNS

Most of the symptoms observed (pruritus, scratching, attempts to lick or bite the skin, development of alopecia) were dermal, and were at or near the application site. Some of the signs (digestive) included vomiting, and are suggestive of ingestion of the product (see Table 13).

**Table 13. (Reg #11556-132, -133, -134, -135).
Clinical Signs: Dermal Exposure in Dogs, 2008**

Symptoms - short description	Count Of Symptoms (%)
Dermal	1212 (34)
Behavioral	798 (26)
Systemic disorders	334 (9)
General Signs	310 (9)
Neurological	284 (8)
Digestive	205 (6)
Lethargy	188 (5)
Immune System	52 (1)
Respiratory	43 (1)
Salivation	29 (<1)
Ear	20 (<1)
Convulsions	19 (<1)
Eye	10 (<1)
Death	4 (<1)
Musculoskeletal	3 (<1)
Renal	3 (<1)
Cardio-vascular	2 (<1)
Total	3516

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

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

Permethrin [(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a synthetic type I pyrethroid with the primary target organ being the nervous system. The neurotoxic effects are consistently characterized by tremors, hyperactivity, and altered Functional Observational Battery parameters. According to a Health Effects Division memorandum dated April 1, 2009, the acute neurotoxicity NOAEL in the rat is 25 mg/kg/day and the LOAEL is 75 mg/kg/day based on observations of clinical signs (aggression, abnormal and/or decreased movement) and increased body temperature. The technical is classified in toxicity category III for acute oral and acute dermal toxicity.

NPIC Permethrin Technical Fact Sheet: According to this NPIC document (<http://npic.orst.edu/factsheets/Permttech.pdf>): “Dermal exposures to cats and dogs may cause temporary paresthesia and neurological signs as evidenced by paw flicking or ear, tail or skin twitching, or rolling on the ground.”

“Cats exposed dermally to some permethrin products may experience hyperexcitability, depression, ataxia, vomiting, anorexia, tremors or convulsions. Symptoms can begin within a few minutes or up to 3 days after exposure. Some permethrin products contain high concentrations of the active ingredient and are labeled for use only on dogs. Close physical contact with a recently treated dog may also lead to symptoms in cats. If symptoms are severe and untreated, they may result in death.”

“A report of 11 cats intentionally treated with products containing 45-65% permethrin described adverse effects including muscle tremors, seizures, incoordination and agitation after exposure. Of the 11 cats that were treated, all were hospitalized, and 4 died after the exposure. Symptoms were found to develop within 24 hours of exposure, with some cats experiencing seizures within 2 hours. In one additional case, a cat was in proximity of two large dogs treated with a permethrin product 48 hours after treatment. Between 18 and 24 hours after being near the dogs, the cat developed signs including agitation, tremors, seizures and ataxia.”

“Animals may also display drooling or lip-smacking. This is believed to be the result of licking at the application site and thought to be caused either by the taste or a tingling sensation in the mouth.”

“Cattle which have been treated topically with permethrin may show signs of parasthesia including twitching the skin on their backs, trying to rub their backs, and general restlessness.”

“Dermal exposure [in humans] may cause irritation, itching or paresthesia (a tingly, prickly sensation) at the site of contact. These symptoms rarely last more than 24 hours. Ocular exposures may result in pain, redness, or a burning sensation.”

“Ingestion of permethrin may cause sore throat, abdominal pain, nausea and vomiting.”

Imidacloprid is a member of the pyridylmethylanine class of compounds. Its mode of action is the disruption of the nervous system by acting as an inhibitor at nicotinic acetylcholine receptors. Imidacloprid blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in normal nerve function impairment.

Different mammalian species have varying susceptibilities to imidacloprid as the mouse has an oral LD₅₀ (see <http://pmep.cce.cornell.edu/profiles/extoxnet/haloxyp-methylparathion/imidacloprid-ext.html>) of 131 mg/kg, considerably lower than the value for the rat (424 mg/kg for male rats and between 450 and 475 mg/kg in female rats).

From a Health Effects Division memorandum dated July 30, 2009, an acute neurotoxicity study in the rat gave a LOAEL of 42 mg/kg, based on decreased motor and locomotor activities observed in females.

From TXR 009960, there was a NOEL of 1250 ppm (41 mg/kg/day) and a LOEL of 2500 ppm (72 mg/kg/day) from a chronic dog feeding study (MRID 42273002) with technical (94.9%) imidacloprid. Adverse effects included increased cholesterol levels in the blood and some stress to the liver (indicated by elevated hepatic cytochrome P-450 levels). From the review: "Although the NOEL for decreased food consumption was 500 ppm...it is probably due to palatability and will not be used for regulatory purposes." A 1 kg dog dosed with 0.4 mL of the 9.1% formulation would receive a dermal dose of 0.04 g imidacloprid, or 40 mg/kg, which is comparable to the 41 mg/kg/day for the 1250 ppm NOEL in the chronic oral study.

According to information from NPIC on imidacloprid (<http://npic.orst.edu/factsheets/imidacloprid.pdf>), signs of toxicity in rats following oral ingestion of imidacloprid include lethargy, respiratory disturbances, decreased movement, staggering gait, occasional trembling and spasms. It effectively blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in impairment of normal nerve function. Imidacloprid has a higher binding strength to insect nerve receptors than to mammalian receptors. Presumably it is the permethrin (present at 44%) rather than the imidacloprid (8.8%) in these products that is responsible for most of the toxicity seen in these incidents, although there may be some contribution from the imidacloprid.

Companion animal safety studies:

The companion animal safety studies that were used as supporting data to register these products are in MRID 45563002 (an adult dog study) and 45563003 (a study with puppies, 7 weeks old at the start of the study). Summaries of the two studies are given below:

MRID 45563002: Imidacloprid (8.8% w/w) and Permethrin (44.0% w/w) was administered via syringe to the dorsal midline of each dog in a group of 6 male and 6 female young adult (10-11 months old) beagles at 5X the proposed use dosage rate on days 0, 7, 14 and 21. A second (control) group of 6 male and 6 female dogs of the same age received a weekly 5X application of the test substance less the active ingredients on days 0, 7, 14 and 21. No mortality occurred. The report states that there was no evidence of adverse or irreversible clinical signs demonstrated by the dogs on the days of dosing or at other times during the study. However, there were

noticeable reductions in mean food consumption for both the placebo and 5X groups on days -12, -5, 1, 22, 39 and, to a lesser extent, for days 8 and 15 (the vehicle or test material was administered on days 0, 7, 14 and 21). The reduced food consumptions on days -12, -5, 1, 22 and 39 were presumably largely due to blood taking and/or overnight fasting, which (for days 1 and 22) would have masked any effects from exposure to the test material. However the reductions for days 8 and 15 (day 8 relative to day 7: vehicle males: -24.9%; 5X males: -11.4%; vehicle females: -14.9%; 5X females: -15.0%; Day 15 relative to day 14: vehicle males: -41.2%; 5X males: -46.0%; vehicle females: -15.0%; 5X females: -31.9%) were presumably associated with administration of the vehicle and test material (the vehicle is not toxicologically inert). Mean food consumption values recovered in all groups for days 9 and 15.

There were sporadic occurrences of vomiting and mucoid feces, with a “clustering” of these around day 1. These may have been from stress on the animals from the combination of fasting, blood taking and exposure to the vehicle or test material.

A number of dogs in both the vehicle and 5X groups showed a “few” to “multiple” pinpoint-sized red areas at the base of hair shafts at the dose site on days 7, 14 and/or 21. In one case, these red areas persisted for several days.

All animals survived to the end of the study.

It is noted that not only were the dogs treated at a 5X single-dose application rate, but that they received four 5X treatments in a 21-day period (as the label specifies once-a-month treatment at the 1X rate, these dogs then received a cumulative of 20X the monthly dose specified on the label).

MRID 45563003: Imidacloprid (8.8% w/w) and Permethrin (44.0% w/w) was administered as a single 2 mL (5X the proposed use dosage rate of 0.4 mL) dose to the dorsal cervical area of each puppy in a group of 6 male and 6 female young (≤ 7 weeks old at initiation of dosage) on days 0, 7, 14 and 21 (the proposed 1X rate is 0.4 mL for dogs and puppies weighing ≤ 10 lbs). A second (control) group of 6 male and 6 female puppies of the same age received an application of 1.0 mL vehicle (formulation without active ingredients) on days 0, 7, 14 and 21.

One female puppy in the 5X dose group died on Day 25. This puppy was necropsied and found to have had a congenital digestive/cardiac condition. However, it had been evident for some time that there was a problem (this puppy had weighed 1522 g on day 0, and had dropped to 1117 g on day 12; this puppy had also been noted as thin on day 9 and had subsequently been given occasional supplemental nutrition. It had also been single-housed starting on day 9, while the others were usually co-housed.

The report states that there was no evidence of adverse or irreversible clinical signs demonstrated by the puppies on the days of dosing or at other times during the study, and that the test substance and vehicle were well retained within the haircoat. However, while the report states (p. 26 of MRID 45563003) that: “Food consumption was not considered to have been influenced by compound administration (females or males) during the course of the study” mean food consumption for the 5X puppies on day 1 was considerably lower than that for their controls:

323.75 g vs. 478.25 g (both values are for combined males and females). On day 8 mean food consumption for the 5X puppies was 580.25 g vs. the control value of 686.25 g. The food consumption differences on days 1 and 8 (day 1: 5X puppies consumed 32.3% less than their controls; day 8: 5X puppies consumed 28.4% less food per pup than their controls) were the largest daily differences observed during this study. There was also a somewhat lower food consumption in the period from day 14 to 16, although this was not as pronounced as those following the first two application treatments. There is no evidence that there was lower food consumption in the 5X puppies following the fourth (day 21) treatment. It is also noted that 5X puppies recovered their appetites by the third day after each treatment.

There was a clustering of soft or mucoid red feces on day 20. In addition, red mucoid feces were noted in some puppies during the first four days of the study which were confirmed by fecal flotation as a mild subclinical coccidiosis, and all puppies were treated with Tribissen, 60 mg, sid for three days starting on day 4. Another puppy received a dose of kapectate on day 3.

It is noted that not only were these puppies treated at a 5X single-dose application rate, but that they were also given four 5X treatments in a 21-day period (as the label specifies once-a-month treatment at the 1X label, these puppies then received a cumulative of 20X the monthly dose specified on the label).

Acute Dermal Toxicity:

The acute dermal toxicity study used to support the registrations of these products is in MRID 45563005. A group of 6M and 6F young adult (8-12 weeks old) Wistar-Hanover rats was dermally exposed for 24 hours (occluded exposure) to 2000 mg/kg of the test material. A control group was exposed to a placebo which consisted of the test formulation excluding the active ingredients. However, the report does not indicate the amount of placebo material that was administered to the control group.

There was no mortality (dermal LD50 > 2000 mg/kg, or toxicity category III). One male and two females in the placebo group had lesions/sores within or close to the dose site, as did one male in the 2000 mg/kg test material dose group. Lacrimal and nasal staining from red discharge, as well as perigenital staining, occurred with similar incidences in both the control and test material-exposed groups. These were attributed to the use of Elizabethan collars.

Acute Oral Toxicity:

The acute oral toxicity study used to support the registrations of these products is in MRID 45563004. Groups of 6M and 6F young adult (8-12 weeks old) overnight fasted Wistar-Hanover were orally gavaged with 500, 1000 or 2000 mg/kg of the test material administered at a constant dose volume of 10 mL/kg in vehicle (0.5% aqueous carboxymethylcellulose). A control group was dosed with vehicle only.

There was one mortality (occurring the day after dosing) involving a female dosed at 1000 mg/kg. There were no deaths at any of the other doses (0, 500 or 2000 mg/kg). The vehicle (0.5% aqueous carboxymethylcellulose) controls showed no symptoms. Symptoms (persisting to

day 5 in 2000 mg/kg rats) in other groups included whole body tremors, nasal discharge and perigenital staining. All surviving rats showed body weight gains, although the mean weight gain in 2000 mg/kg males (65 g) was somewhat less (although apparently not significantly so) than that observed in other groups: controls: 79 g; 500 mg/kg: 77 g; 1000 mg/kg: 86 g).

Gross pathological findings in the rat which died included wet ventrum and nasal discharge; one 2000 mg/kg female had a single pinpoint crusty zone on the nose. No significant findings were observed in the other rats which survived to termination.

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.