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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0052555

MEMORANDUM

DATE:9/14/2004

SUBJECT: Hartz Flea and Tick Treatment for Cats: Review of Incident Data

DP Barcode: D302791
Submission #:None
PC Code: 069005

PRAT Case#:
Tox. Chem. No.:
MRID No.:

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Insecticide Branch
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Background and Request: The review of the incidence data for the Hartz Cat products is atttached.

DATA EVALUATION RECORD

HARTZ ADVANCED CARE BRAND FLEA & TICK DROPS PLUS+ FOR CATS & KITTENS [PHENOTHRIN/(S)-METHOPRENE]

HARTZ ADVANCED CARE BRAND ONCE-A-MONTH FLEA & TICK DROPS FOR DOGS & CATS (PHENOTHRIN)

INCIDENT DATA REVIEW
I015000

Prepared for

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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

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TXR#: 0052555

DATA EVALUATION RECORD

REVIEW TYPE: INCIDENT DATA REVIEW

PC CODE: 069005 (phenothrin), 105402 (s-methoprene) DP BARCODE: D302791
SUBMISSION NO.:

PRODUCTS: Hartz Advanced Care Brand Flea & Tick Drops Plus+ for Cats & Kittens [EPA Reg. No. 2596-148; 85.7% phenothrin/ 2.9% (s)-methoprene]

Hartz Advanced Care Brand Once-a-Month Flea & Tick Drops for Dogs & Cats (EPA Reg. No. 2596-151; 85.7% phenothrin)

SPONSOR: The Hartz Mountain Corporation, 400 Plaza Drive, Secaucus, New Jersey 07003

EXECUTIVE SUMMARY: Incidents of alleged adverse events in cats (I015000) for the period January 1 through March 31, 2004, reported by the Hartz Mountain Corporation for two products, Hartz Advanced Care Brand Flea & Tick Drops Plus+ for Cats & Kittens [EPA Reg. No. 2596-148; 85.7% phenothrin/ 2.9% (s)-methoprene)] and Hartz Advanced Care Brand Once-a-Month Flea & Tick Drops for Dogs & Cats (EPA Reg. No. 2596-151; 85.7% phenothrin), were evaluated. The incident reports consisted of a summary of the total number of adverse events in each of the 6(a)(2) domestic animal severity categories (D-A, D-B, D-C, D-D and D-E) and tables of clinical signs in affected cats. Data were collected by both the ASPCA's National Animal Poison Control Center and Hartz's Consumer Relations Department. For each adverse event, the ASPCA provided an assessment of whether the product was responsible for the clinical signs. This expanded incident reporting is part of a November 2002 agreement between the company and EPA due to safety concerns in cats exposed to products 2596-148 and 2596-151. The products were relabeled with new directions for use as part of the agreement.

For product **2596-148**, a total of 207 cases were reported during January through March, 2004, in the following severity categories: D-A=14; D-B=25; D-C=101; and D-D=67. Of the 140 cases in the D-A, D-B and D-C cases (68% of the total number of cases), 26 (19%) had seizures and 93 (66%) had other neurological signs. Misuse, which usually involved use of the wrong size product, was reported in 16 cases that had seizures and other neurological signs.

For product **2596-151**, a total of 222 cases were reported in the following severity categories: D-A=8; D-B=27; D-C=96; and D-D=91. Of the 131 cases in the D-A, D-B and D-C cases (59% of the total number of cases), 22 (17%) had seizures and 94 (72%) had other neurological signs. Misuse was reported in 17 cases with seizures and other neurological signs.

For product **2596-148**, the ASPCA assigned the following certainty categories to the 39 cases with seizures and other neurological signs: low suspicion in 4 cases (10%); medium suspicion in 11 (28%); high suspicion in 19 (49%); and doubtful/not related in 5 (13%). For product **2596-151**, the ASPCA assigned the following certainty categories to the 20 cases with seizures and other neurological signs: low suspicion in 4 cases (20%); medium suspicion in 3 (15%); high suspicion in 12 (60%); and doubtful/not related in 1 (5%).

The incident data comments indicated that most of the products involved in the adverse events contained the new label. **Although the data are limited in that only three months of incident data are provided for a relatively low use period of the products (January through March), a comparison of 2003 and 2004 was made. The total number of cases for both products was increased from 2003 to 2004 (139 to 207 for product 2596-148 and 129 to 222 for product 2596-151). The percentage of cases in the D-A, D-B and D-C categories and the percentage with seizures and other neurological signs were essentially the same for both years. There is no indication that the pattern of neurological effects with use of the products has changed.**

Background

Under the current 6(a)(2) summary reporting practices for incident data, adverse events in domestic animals exposed to a pesticide product may be accumulated for three months and submitted to EPA two months later. Incidents are categorized according to severity as follows:

D-A: Domestic Animal Death (death or euthanasia)
D-B: Domestic Animal Major (clinical signs which may have been life-threatening or resulted in residual disability)
D-C: Domestic Animal Moderate (clinical signs which are more pronounced, more prolonged or of a more systemic nature than minor signs)
D-D: Domestic Animal Minor (clinical signs which are minimally bothersome)
D-E: Signs Unknown, Unspecified or May Appear in the Future (clinical signs are unknown or not specified)

Registrants are required to report only the number of animals in each category. Neither the species of animal nor the nature of the alleged adverse event is included. However, if EPA has concern about the number of incidents reported for a product, detailed information may be requested. In a March 13, 2001 letter, EPA requested detailed information on several Hartz Mountain Corporation's (Hartz) products because of concern about the use of the products in cats.

As part of the EPA investigation into the alleged adverse events reported for products containing phenothrin, the Agency requested that Hartz analyze the incident data for products 2596-148 and 2596-151 to provide the number of cats with neurological signs (defined by EPA's Health Effects Division as tremors, seizures or convulsions) in categories D-A, D-B and D-C.

For all Hartz's products, adverse events reports are collected by the ASPCA/National Animal Poison

Control Center (NAPCC) and the company directly. (Hartz has a contract with the NAPCC to collect incident data.) The NAPCC is a 24-hour emergency hotline for animals similar to human poison control centers. It is staffed by veterinary toxicologists who provide diagnostic and treatment recommendations. Complete records on each call, including follow-up conversations to determine the outcome of a case, are maintained in a database. Causality categories assigned to cases include the following: high suspicion, medium suspicion, low suspicion, doubtful and unrelated.

In November 2002, EPA and Hartz agreed to enact measures to reduce risks from these products in cats based on the adverse events incidents investigated by EPA.[1] Hartz agreed to recover, repackage and relabel available stock of the products. The relabeled products have revised use directions to apply the products as a single spot to the back of the animal's neck. The initial use directions instructed that the products should be applied as a stripe down the animal's back which increased the possibility of ingestion. New precautionary labeling also lists clinical signs which could be observed with the product, including skin irritation or hair loss at the application site, salivation, tremors (twitching of muscles), and in some circumstances, severe full body tremors. The company also agreed to take additional measures, including among others, the conduct of a new companion animal safety study and expanded incident data reporting. For the calendar years 2003 and 2004, Hartz agreed to submit separate quarterly reports of alleged adverse events involving cats including a list of clinical signs for each incident in the D-A, D-B and D-C severity categories. In addition, for each incident collected by the ASPCA, the certainty category will be reported.

Multiple EPA reviews of incident data on Hartz products 2596-148 and 2596-151 have been conducted previously. For product 2596-148, during the period January 1 through September 30, 2001, neurological signs were observed in 734/1774 (41%) of all incidents in cats or 734/981 (75%) of all D-A, D-B and D-C incidents (EPA Memorandum dated June 6, 2002; D283433: TXR# 0050782). For the same product, during the period January 1 through September 30, 2003, a total of 737 cases in categories D-A , D-B and D-C were reported by both Hartz and the ASPCA for the 9 month-period (D297438; TXR# 0052290). Of these, a total of 607 (82%) had seizures or other neurological signs. For the 154 cases in the D-A, D-B and D-C categories collected by the ASPCA during this period, 119 (77%) had seizures or other neurological signs. The ASPCA assigned the following causality categories to these cases: 8/119 (7%) low suspicion; 19/119 (16%) medium suspicion; 79/119 (66%) high suspicion; and 13/119 (11%) doubtful suspicion or not related.

For product 2596-151, during the year 2001, neurological signs were observed in 340/973 (35%) of all incidents in cats or 296/450 (66%) of incidents in the D-A, D-B and D-C categories (EPA Memorandum dated September 3, 2002; D285022; TXR# 0051077). For the period January 1 through September 30, 2003, a total of 899 cases in categories D-A, D-B and D-C were reported by both Hartz and the ASPCA (D297438; TXR# 0052290). Of these, a total of 724 (81%) had seizures or other neurological signs. For the 121 cases in the D-A, D-B and D-C categories collected by the ASPCA during this period, 91 (75%) had seizures or other neurological signs. The ASPCA assigned the following causality categories to these cases: 11/91 (12%) low suspicion; 17/91 (19%) medium suspicion; 56/91 (62%) high suspicion; and 7/91 (8%) doubtful suspicion or not related.

Incident Data Reviewed

[1] United States Environmental Protection Agency, Press Advisory, *Label Instructions Tightened on Flea & Tick Control Products for Pets*, dated November 27, 2002.

Reports for the first month of 2004 were submitted by Hartz (I015000). The summary reports include tables for each Hartz product which provide the total number of incidents in each severity category. For products 2596-148 and 2596-151, there are also monthly tables of data from both the ASPCA and Hartz's Consumer Relations Department listing the report number, pet owner's name, exposure designation (severity category), clinical signs and comments (weight designation, etc.). The comments section also contains information on misuse and whether new or old product label was used. It is unclear how many cats are involved with each report number and owner's name. Often multiple cats in a household are treated with flea products at the same time. Although not required by the EPA agreement, clinical signs are reported for some of the cases in the D-D severity categories.

Data from the ASPCA and Hartz's Consumer Relations Department were analyzed separately since certainty categories were included for the ASPCA data only. Using the clinical signs tables, the ASPCA data were analyzed for the number of cases reported, the number with neurological signs and the ASPCA certainty category (Table 1). The Hartz data were analyzed in the same manner without the certainty category (Table 2). The applicable ASPCA and Hartz data were then combined (Table 3). In the neurological signs analysis, the number of cases with seizures or other neurological signs were reported separately. A case with both seizures and other neurological signs was counted only once in the seizure category. Seizures were listed in the clinical signs tables as seizures or convulsions. Other neurological signs included the following terms or forms thereof in the clinical signs tables: tremors, shaking, fasciculations, twitching, trembling, muscle spasms, quivering and flicking. Pet owners may use various terms to describe the clinical signs, especially tremors.

Results

ASPCA Data (Table 1):

For product **2596-148,** the total number of cases (January through March) with clinical signs reported, number of cases with seizures, number of cases with other neurological signs and certainty category were tabulated. A total of 66 cases were assigned the following severity categories: D-A=8; D-B=13; D-C=34 and D-D=11. Of the 55 cases in the D-A, D-B and D-C categories (83% of total), 14 (25%) had seizures and 25 (45%) had other neurological signs. In the 39 cases with seizures and other neurological signs, the ASPCA certainty categories were low suspicion in 4 cases (10%), medium suspicion in 11 (28%), high suspicion in 19 (49%) and doubtful/not related in 5 (13%). The comments section noted that there was misuse in 4 cases in which seizures and other neurological signs were reported. Most misuse involved application of the wrong size product. Of the total number of cases (66), new label was used in 58 cases and old label in 5 cases; no notation was provided in 3 cases.

For product **2596-151**, the following results were obtained using a similar analysis. A total of 33 cases were reported in the following severity categories: D-A=4; D-B=3; D-C=16 and D-D=10. (One

D-D case involved a dog and was not counted.) Of the 23 cases in the D-A, D-B and D-C categories (70% of total), 3 (13%) had seizures and 17 (74%) had other neurological signs. In the 20 cases with seizures and other neurological signs, the ASPCA certainty categories were low suspicion in 4 cases (20%), medium suspicion in 3 (15%), high suspicion in 12 (60%) and doubtful/not related in 1 (5%). Misuse was reported in 2 cases with seizures and other neurological signs. Of the total 33 cases, new label was used in 32 cases and old label in one case.

Hartz Data (Table 2):

For product **2596-148**, a total of 141 cases were reported in the following severity categories: D-A=6; D-B=12; D-C=67; and D-D=56. (Nine cases were categorized as D-E but no other information was provided.) Of the 85 cases in the D-A, D-B and D-C categories (60% of total), 12 (14%) had seizures and 68 (80%) had other neurological signs. Misuse was reported in 12 cases with seizures and other neurological signs. Of the total 141 cases, new label was used in 127 cases and old label in 13 cases; no notation was provided in one case.

For product **2596-151**, at total of 189 cases were reported in the following severity categories: D-A=4; D-B=24; D-C=80; and D-D=81. (Thirteen cases were categorized as D-E but no other information was provided.). Of the 108 cases in the D-A, D-B and D-C categories (57% of total), 22 (20%) had seizures and 77 (71%) had other neurological signs. Misuse was reported in 15 cases with seizures and other neurological signs. Of the total number of 189 cases, new label was used in 164 cases and old label in 25 cases.

Combined ASPCA and Hartz Data (Table 3):

For product **2596-148**, a total of 207 cases were reported in the following severity categories: D-A=14; D-B=25; D-C=101; and D-D=67. (D-E cases were not counted.) Of the 140 cases in the D-A, D-B and D-C cases (68% of the total), 26 (19%) had seizures and 93 (66%) had other neurological signs. Three cases with neurological signs were reported in the D-D category. Misuse was reported in 16 cases that had seizures and other neurological signs. Of the total 207 cases, new product was used in 185, old label in 18 and there was no notation in 4.

For product **2596-151**, a total of 222 cases were reported in the following severity categories: D-A=8; D-B=27; D-C=96; and D-D=91. (D-E cases were not counted.) Of the 131 cases in the D-A, D-B and D-C cases (59% of the total), 22 (17%) had seizures and 94 (72%) had other neurological signs. Eight cases with other neurological signs were also reported in the D-D category. Misuse was reported in 17 cases with seizures and other neurological signs. Of the total 222 cases, new label was used in 196 and old label in 26.

Table 1: Summary of Adverse Events in Cats Reported to the ASPCA, January through March 2004

Product	Number of cases	Number with neurological signs			ASPCA certainty category for cases with neurological signs			
		Seizures	Other	Total	Low	Medium	High	Doubtful/Not Related
Product 2596-148								
D-A	8	4	2	6	2	1	0	3
D-B	13	10	0	10	2	1	6	1
D-C	34	0	23	23	0	9	13	1
Total D-A, D-B, D-C	55	14	25	39	4	11	19	5
D-D	11	0	2	2	0	0	2	0
Product 2596-151								
D-A	4	0	2	2	1	0	1	0
D-B	3	3	0	3	0	2	0	1
D-C	16	0	15	15	3	1	11	0
Total D-A, D-B, D-C	23	3	17	20	4	3	12	1
D-D	10	0	3	3	0	1	2	0

Table 2: Summary of Adverse Events in Cats Reported to Hartz, January through March 2004				
Product	Number of cases	Number with neurological signs		
		Seizures	Other	Total
Product 2596-148				
D-A	6	2	1	3
D-B	12	10	1	11
D-C	67	0	66	66
Total D-A, D-B, D-C	85	12	68	80
D-D	56	0	1	1
Product 2596-151				
D-A	4	0	2	2
D-B	24	22	0	22
D-C	80	0	75	75
Total D-A, D-B, D-C	108	22	77	99
D-D	81	0	5	5

Table 3: Summary of Adverse Events in Cats Reported to ASPCA and Hartz, January through March 2004				
Product	Number of cases	Number with neurological signs		
		Seizures	Other	Total
Product 2596-148				
D-A	14	6	3	9
D-B	25	20	1	21
D-C	101	0	89	89
Total D-A, D-B, D-C	140	26	93	119
D-D	67	0	3	3
Product 2596-151				
D-A	8	0	4	4
D-B	27	25	0	25
D-C	96	0	90	90
Total D-A, D-B, D-C	131	22	94	119
D-D	91	0	8	8

Discussion: For product **2596-148**, a total of 207 cases were reported in the following severity categories: D-A=14; D-B=25; D-C=101; and D-D=67. (D-E cases were not counted.) Of the 140 cases in the D-A, D-B and D-C cases (68% of the total number of cases), 26 (19%) had seizures and 93 (66%) had other neurological signs. Misuse was reported in 16 cases that had seizures and other neurological signs. Of the total 207 cases, new product was used in 185, old label in 18 and there was no notation in 4.

For product **2596-151**, a total of 222 cases were reported in the following severity categories: D-A=8; D-B=27; D-C=96; and D-D=91. (D-E cases were not counted.) Of the 131 cases in the D-A, D-B and D-C cases (59% of the total number of cases), 22 (17%) had seizures and 94 (72%) had other neurological signs.

For product **2596-148**, the ASPCA assigned the following certainty categories for the 39 cases with seizures and other neurological signs: low suspicion in 4 cases (10%); medium suspicion in 11 (28%); high suspicion in 19 (49%); and doubtful/not related in 5 (13%). For product **2596-151**, the ASPCA assigned the following certainty categories to the 20 cases with seizures and other neurological signs: low suspicion in 4 cases (20%); medium suspicion in 3 (15%); high suspicion in 12 (60%); and doubtful/not related in 1 (5%).

Although the data are limited in that only three months of incident data are provided for a relatively low use period of the products (January through March), a comparison to the incident data for 2003 and 2004 is provided in Table 4 below. While the total number of cases reported for the first quarter of 2004 was increased as compared to the first quarter of 2003, the percentage of cases in the D-A, D-B and D-C categories and the percentage with seizures and other neurological signs were essentially the same for both years. There is no indication that the pattern of neurological effects with use of the products has changed.

Table 4: Comparison of Incident Data for First Quarter 2003 and First Quarter 2004

Product/ Year	No. of cases reported	No. of D-A, D-B & D-C cases	No. of D-A, D-B & D-C cases with neurological signs	
			Seizures	Other Neurological Signs
Product 2596-148				
2003	139	83 (60%)	19 (23%)	47 (57%)
2004	207	140 (68%)	26 (19%)	93 (66%)
Product 2596-151				
2003	129	81 (63%)	19 (23%)	42 (52%)
2004	222	131 (54%)	22 (17%)	94 (72%)