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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0052290

MEMORANDUM

DATE: 04/12 /2004

SUBJECT: Hartz Flea and Tick Treatment for Cats (EPA Reg. Nos. 2596-148, 2596-151); Incident Data Reviews I014030, I014303, I014641, and I014665

DP Barcode: D297438
Submission #: S337006
PC Code: 069005 (phenothrin), 105402 (s-methoprene)

PRAT Case#:
Tox. Chem. No.:069005
MRID No.:none

TO: Ann Sibold, Risk Manager
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Health Effects Division (7509C)

THRU: Susan Hummel Susan V. Hummel 4/12/04
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Background and Request: Registration Division requests that RRB4 review the recently submitted incident reports for Hartz cat treatment products containing d-phenothrin. The executive summary for the reviewed data is attached.

EXECUTIVE SUMMARY: Incidents of alleged adverse events in cats (I014030, I014303, I014334, I014641 and I014665) for the period January 1 through September 30, 2003, 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 recovered, repackaged and relabeled as part of the agreement.

For product **2596-148**, a total of 737 cases (with reported clinical signs) in categories D-A (death), D-B (major effect) and D-C (moderate effect) were reported by both Hartz and the ASPCA for the 9 month-period . 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**, a total of 899 cases (with reported clinical signs) in categories D-A, D-B and D-C were reported by both Hartz and the ASPCA for the 9 month-period. 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.

The adverse events reports from January through September 2003 for products 2596-148 and 2596-151 demonstrate that there are still safety concerns about their use in cats. The number and types of clinical signs observed after the label revisions are essentially unchanged or worse than with the old label.

DATA EVALUATION RECORD

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

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

INCIDENT DATA REVIEW
I014030, I014303, I014334, I014641 and I014665

Prepared for

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Office of Pesticide Programs
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Disclaimer

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

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

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TXR#: 0052290

DATA EVALUATION RECORD

REVIEW TYPE: **INCIDENT DATA REVIEW**

PC CODE: 069005 (phenothrin), 105402 (s-methoprene) **DP BARCODE: D297438**
SUBMISSION NO.: S337006

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 (I014030, I014303, I014334, I014641 and I014665) for the period January 1 through September 30, 2003, 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 recovered, repackaged and relabeled as part of the agreement.

For product **2596-148**, a total of 737 cases (with reported clinical signs) in categories D-A (death), D-B (major effect) and D-C (moderate effect) were reported by both Hartz and the ASPCA for the 9 month-period . 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**, a total of 899 cases (with reported clinical signs) in categories D-A, D-B and D-C were reported by both Hartz and the ASPCA for the 9 month-period. 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.

The adverse events reports from January through September 2003 for products 2596-148 and 2596-151 demonstrate that there are still safety concerns about their use in cats. The number and types of clinical signs observed after the label revisions are essentially unchanged or worse than with the old label.

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.

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 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).

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.

INCIDENT DATA REVIEWED: Reports for the first three quarters of 2003 were submitted by Hartz (I014030 and I014334: January-March; I01430: April-June; I014641 and I014665: July-September). 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 category. It is noted that clinical signs are missing from some cases in the D-A, D-B and D-C categories. Also, the total number of cases reported in the summary tables does not always match the number in the clinical signs tables.

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 clinical signs 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

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

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: shaking, trembling, twitching, tremors, neurological symptoms, muscle spasms, fasiculations, jerking, quivering, flicking, muscle jumping and nervous system reaction. Pet owners may use various terms to describe the clinical signs, especially tremors. Phenothrin is a synthetic pyrethroid. Permethrin, another synthetic pyrethroid, is known to produce muscle tremors, ataxia, seizures and death in cats within hours of exposure to concentrated topical spot-on products for use on dogs.[2]

RESULTS: Only the results for the D-A, D-B and D-C categories will be discussed. Data from the D-D category were analyzed to demonstrate that neurological signs were also observed in these cases. See the Reporting Deficiencies section of this review for more discussion.

ASPCA DATA (TABLE 1): For product **2596-148,** the total number of cases (January through September) with clinical signs reported, number of cases with seizures, number of cases with other neurological signs and certainty category were tabulated.

D-A: Of 15 cases, 4 (27%) had seizures and 3 (20%) had other neurological signs. The ASPCA certainty categories for these signs were: 2/7 (29%) low suspicion; 1/7 (14%) high suspicion; and 4/7 (57%) doubtful suspicion/not related.

D-B: Of 27 cases, 17 (63%) had seizures and 3 (11%) had other neurological signs. The certainty categories for these signs were: 3/20 (15%) low and medium suspicion; 10/20 (50%) high suspicion; and 4/20 (20%) doubtful suspicion/not related.

D-C: Of 112 cases, 1 (1%) had seizures and 91(81%) had other neurological signs. The certainty categories for these signs were: 3/92 (3%) low suspicion; 16/92 (17%) medium suspicion; 68/92 (74%) high suspicion; and 5/92 (5%) doubtful suspicion/not related.

A total of 154 D-A, D-B and D-C cases were reported for the 9 month period. Of these, 119 (77%) had seizures or other neurological signs. The causal category was low suspicion in 8 cases (7%), medium suspicion in 19 (16%), high suspicion in 79 (66%) and doubtful suspicion/not related in 13 (11%).

[2] Hansen SR: Pyrethrins and Pyrethroids. *In* Peterson ME, Talcott PA (eds): Small Animal Toxicology. Philadelphia, W.B. Sauders Company, 2001, pp 687-694.

TABLE 1: Summary of adverse events in cats reported to the ASPCA, January through September 2003

Time period	Number of cases	Number with clinical signs reported	Number with neurological signs			ASPCA certainty category for cases with neurological signs			
			Seizures	Other	Total	Low	Medium	High	Doubtful/ Not Related
Product 2596-148									
First quarter									
D-A	1	1	0	0	0	0	0	0	0
D-B	5	5	4	1	5	2	1	1	1
D-C	14	14	0	10	10	1	3	6	0
D-D	4	4	0	3	3	1	0	2	0
Second quarter									
D-A	5	5	2	1	3	0	0	0	3
D-B[a]	6	6	5	1	6	1	0	3	2
D-C	40	40	1	30	31	0	5	23	3
D-D	23	23	0	7	7	1	3	3	0
Third quarter									
D-A	9	9	2	2	4	2	0	1	1
D-B	16	16	8	1	9	0	2	6	1
D-C	58	58	0	51	51	2	8	39	2
D-D	30	30	0	10	10	0	4	6	0
Total (January through September)									
D-A	15	15	4	3	7	2	0	1	4
D-B	27	27	17	3	20	3	3	10	4
D-C	112	112	1	91	92	3	16	68	5
Total D-A, D-B, D-C	154	154	22	97	119	8	18	79	13
D-D	57	57	0	20	20	2	7	11	0
Product 2596-151									
First quarter[b]									
D-A	2	2	1	0	1	0	0	0	1
D-B	0	0	0	0	0	0	0	0	0
D-C[c]	6	6	0	4	4	2	0	2	0
D-D	6	0	0	0	0	0	0	0	0
Second quarter									
D-A	8	8	2	1	3	0	1	1	1
D-B	3	3	2	0	2	0	0	2	0
D-C	36	36	0	30	30	1	8	20	1
D-D	19	19	0	5	5	1	1	3	0

Time period	Number of cases	Number with clinical signs reported	Number with neurological signs			ASPCA certainty category for cases with neurological signs			
			Seizures	Other	Total	Low	Medium	High	Doubtful/ Not Related
Third quarter									
D-A	7	7	2	1	3	2	0	1	0
D-B	14	14	12	0	12	2	1	6	3
D-C[d]	45	45	0	36	36	4	7	24	0
D-D	20	20	0	9	9	1	4	4	0
Total (January through September)									
D-A	17	17	5	2	7	2	1	2	2
D-B	17	17	14	0	14	2	1	8	3
D-C	87	87	0	70	70	7	15	46	2
Total D-A, D-B, D-C	121	121	19	72	91	11	17	56	7
D-D	45	45	0	14	14	2	5	7	0

[a] One case with "unknown" certainty category classified as Doubtful.
[b] Includes two cases (1 D-C, 1 D-D) from VPRP Manufacturer Reports
[c] One case with "possible" certainty category classified as Low.
[d] Certainty category missing for one case.

The comments section noted that there was misuse in 22 cases in which seizures and other neurological signs were reported. Most misuse involved application of the wrong size product.

For product **2596-151**, the following results were obtained using a similar analysis.

D-A: Of 17 cases, 5 (29%) had seizures and 2 (12%) had other neurological signs. The certainty categories for these signs were: 2/7 (29%) each for low suspicion, high suspicion and doubtful suspicion/not related; and 1/7 (14%) medium suspicion.

D-B: Of 17 cases, 14 (82%) had seizures; none had other neurological signs. The certainty categories for this sign were: 2/14 (14%) low suspicion; 1/14 (7%) medium suspicion; 8/14 (57%) high suspicion; and 3/14 (21%) doubtful suspicion/not related.

D-C: Of 87 cases, none had seizures; 70 (80%) had other neurological signs. The certainty categories for these signs were: 7/70 (10%) low suspicion; 15/70 (21%) medium suspicion; 46/70 (66%) high suspicion; and 2/70 (3%) doubtful suspicion/not related.

A total of 121 D-A, D-B and D-C cases were submitted for the 9 month-period. Of these, 91 (75%) had seizures or other neurological signs. The causality categories were low suspicion in 11 cases (12%), medium suspicion in 17 (19%), high suspicion in 56 (62%) and doubtful suspicion/not related in 7 (8%).

Misuse was reported in 13 cases with seizures and other neurological signs.

HARTZ DATA (TABLE 2):

For product **2596-148**, the following results for the 9 month-period were obtained in the various severity categories.

D-A: Of 26 cases, 9 (35%) had seizures and 5 (19%) had other neurological signs.

D-B: Of 55 cases with clinical signs reported, 37 (67%) had seizures and 13 (24%) had other neurological signs.

D-C: Of 502 cases with clinical signs reported, 58 (12%) had seizures and 366 (73%) had other neurological signs.

Misuse was reported in 45 cases with seizures and other neurological signs.

TABLE 2: Summary of adverse events in cats reported to Hartz, January through September 2003

Time period	Number of cases	Number of cases with clinical signs reported	Number with neurological signs		
			Seizures	Other	Total
Product 2596-148					
First quarter					
D-A	4	4	1	2	3
D-B	4	4	1	3	4
D-C	55	55	13	31	44
D-D	52	38	0	8	8
Second quarter					
D-A	6	6	3	1	4
D-B	13	13	12	1	13
D-C	202	199	15	153	168
D-D	186	124	1	20	21
Third quarter					
D-A	16	16	5	2	7
D-B	39	38	24	9	33
D-C	250	248	30	182	212
D-D	181	168	0	23	23
Total (January through September)					
D-A	26	26	9	5	14
D-B	56	55	37	13	50
D-C	507	502	58	366	424
D-D	419	330	1	51	52

Time period	Number of cases	Number of cases with clinical signs reported	Number with neurological signs		
			Seizures	Other	Total
Product 2596-151					
First quarter					
D-A	8	7	2	2	4
D-B	7	7	7	0	7
D-C	58	58	9	36	45
D-D	42	20	0	7	7
Second quarter					
D-A	9	8	1	1	2
D-B	29	29	25	3	28
D-C	285	282	37	202	239
D-D	107	104	0	18	18
Third quarter					
D-A	20	15	3	0	3
D-B	61	59	45	9	54
D-C	317	313	42	209	251
D-D	209	196	0	45	45
Total (January through September)					
D-A	37	30	6	3	9
D-B	97	95	77	12	89
D-C	660	653	88	447	535
D-D	358	320	0	70	70

For product **2596-151**, the following results were obtained for the various severity categories.

D-A: Of 30 cases with clinical signs reported, 6 (20%) had seizures and 3 (10%) had other neurological signs.

D-B: Of 95 cases with clinical signs reported, 77 (81%) had seizures and 12 (13%) had other neurological signs.

D-C: Of 653 cases with clinical signs reported, 88 (13%) had seizures and 447 (68%) had other neurological signs.

Misuse was reported in 85 cases with seizures and other neurological signs.

COMBINED DATA (TABLE 3):

For product **2596-148**, the following results were obtained for the various severity categories.

D-A: Of 41 cases with clinical signs reported, 13 (32%) had seizures and 8 (20%) had other neurological signs.

D-B: Of 82 cases with clinical signs reported, 54 (66%) had seizures and 16 (20%) had other neurological signs.

D-C: Of 614 cases with clinical signs reported, 59 (10%) had seizures and 457 (74%) had other neurological signs.

There were a total of 737 cases in categories D-A, D-B and D-C. Of these, a total of 607 (82%) had seizures and other neurological signs.

For product **2596-151**, the following results were obtained for the various severity categories.

D-A: Of 47 cases with clinical signs reported, 11 (23%) had seizures and 5 (11%) had other neurological signs.

D-B: Of 112 cases with clinical signs reported, 91 (81%) had seizures and 12 (11%) had other neurological signs.

D-C: Of 740 cases with clinical signs reported, 88 (12%) had seizures and 517 (70%) had other neurological signs.

There were a total of 899 cases in categories D-A, D-B and D-C. Of these, a total of 724 (81%) had seizures and other neurological signs.

The comments section of the clinical signs tables for the second and third quarter reporting (mostly from Hartz's Consumer Relations Department) noted whether old or new labeled product was used. In 613 cases with seizures and other neurological signs reported in severity categories D-A, D-B and D-C, new label for both products 2596-148 and 2596-151 was used. This information is provided not as a quantitative measure but to demonstrate that serious adverse events were reported with use of the new labeled product.

TABLE 3: Summary of Adverse Events in Cats Reported to ASPCA and Hartz, January through September 2003					
	Number of cases	Number of cases with clinical signs reported	Number with neurological signs		
			Seizures	Other	Total
Product 2596-148					
D-A	41	41	13	8	21
D-B	83	82	54	16	70
D-C	619	614	59	457	516
Total D-A, D-B, D-C	743	737	126	481	607
D-D	476	387	1	71	72
Product 2596-151					
D-A	54	47	11	5	16
D-B	114	112	91	12	103
D-C	747	740	88	517	605
Total D-A, D-B, D-C	915	899	190	534	724
D-D	403	365	0	84	84

DISCUSSION: The adverse events reports from January through September 2003 for products 2596-148 and 2596-151 demonstrate that there are still safety concerns about their use in cats. The number and types of clinical signs observed after the label revisions are essentially unchanged or worse than with the old label. For product 2596-148 during January 1 through September 30, 2001, neurological signs (defined as seizures, convulsions and tremors) were reported in 734/981 (75%) of all D-A, D-B and D-C incidents. For the period January 1 through September 30, 2003, when the new label was in use, 607/737 (82%) of cases in these severity categories had seizures and other neurological signs. For product 2596-151, during the year 2001, 296/450 (66%) of all D-A, D-B and D-C incidents had neurological signs. For the first nine months of 2003, 724/899 (82%) of incidents in these severity categories had seizures and other neurological signs. The increased number of incidents for product 2596-151 may be partly explained by the fact that it was registered in November 2000. In 2001, the product may not have been as available commercially as in 2003. However, the percentage of incidents with neurological signs has increased from 2001.

Neurological signs were observed in the new companion animal safety study (MRID 46118301) conducted under the EPA agreement. Very slight ataxia was reported in one of 12 cats exposed to the recommended dose of product 2596-148. At 3X and 5X the recommended dose, there was a dose-responsive increase in the number and severity of unsteady gait, trembling and ataxia. (D296096; TXR# 0052259). Also in the companion animal safety study, one male in the 5X group had elevated liver enzymes (ALT, AST). In the incident reports, icterus, liver failure or elevated liver enzymes was reported in seven animals.

REPORTING DEFICIENCIES: Hartz's incident reporting lacked good quality control in the following areas:

1. **Assignment of severity categories:** Neurological signs, including seizures, were reported in all the different severity categories, even D-D, which is defined as a minor effect (clinical signs which are minimally bothersome). This category usually includes minor hair and skin effects. Hartz's criteria for assigning incidents to the various severity categories should be standardized.

2. **Summmary reporting**: In some instances, the number of cases reported in the aggregate incident form was not consistent with the total number in the clinical signs tables. For example, 10 deaths were reported for product 2596-148 during the third quarter (I014665). However, a total of 25 deaths was included in the clinical signs tables.

3. **Number of cats affected:** It is unclear from the clinical signs tables how many cats were affected with each report number. Multiple cats from a single household are often treated with pesticides at the same time.

4. **Editorial issues:** Numerous misspellings and miscounts were present in the clinical signs tables.