



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

SEP 8 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: BLOCKADE cat and dog sprays

TO: Mr. George LaRocca, PM 15
Registration Division (TS-767C)

FROM: Byron T. Backus, Toxicologist *Byron T. Backus*
Toxicology Branch (TS-769C) *89/03/87*

THROUGH: Marcia van Gemert, Ph.D.
Section Head, Review Section III *M. van Gemert*
Toxicology Branch (TS-769C) *9/3/87*

and

Theodore M. Farber, Ph.D., D.A.B.T.
Branch Chief
Toxicology Branch (TS-769C)

Theodore M. Farber
9/3/87

EPA Record Nos. 197405, 197776

Project No. 7-0976

Tox. Chem. 346, 77A

EPA Reg. Nos. 2596-114 Hartz Blockade for Cats
2596-115 Hartz Blockade for Dogs

Action Requested:

The Registration Division has requested an expedited review of 6(a)(2) and toxicity data on a DEET + Fenvalerate formulation (Hartz Mountain Blockade) registered for spray-on use on cats and dogs. There have been a considerable number of reports of adverse effects on these animals following label-use exposure, and part of the material received is a computerized listing from the National Animal Poison Control Center reporting on 162 calls received on this product between March 10 through July 17, 1987.

Because this memorandum has been expedited, a comprehensive review of the registrant's toxicity data has not yet been made, although the data have been examined and what appear to be some of the more relevant problems are indicated in this memorandum.

Background:

What appears to be the same formulation is registered under two EPA registration numbers, 2596-114 (use on cats) and 2596-115 (use on dogs). In both cases the label declaration for active ingredients gives N,N-Diethyl-m-toluamide as 8.55% with other isomers 0.45%, Cyano (3-phenoxyphenyl)methyl-4-chloro-alpha-(1-methylethyl)benzeneacetate (also known as pydrin and fenvalerate) as 0.09%. The remaining 90.91% of the formulation is listed as "inerts." Precautionary statements and label use directions (with the exception of which species is to be treated) are identical.

Comments and Recommendations:

1. The rat oral LD₅₀ for N,N-diethyl-m-toluamide technical (90-100%) is reported (DEET Registration Standard) as 2.43 ml/kg for males and 1.78 ml/kg for females. Since the specific gravity of the technical is reported (Registration Standard) as 0.99-1.00, these values can also be expressed as 2.43 gm/kg and 1.78 gm/kg. If one ounce (28 grams) of this formulation is sprayed on a cat, this represents a total of $28 \times 0.0855 = 2.39$ gms of DEET. Assuming that cats are as susceptible to DEET as are rats (and in fact they may be even more so), the potential then exists for a cat - particularly a young animal weighing 1 kg or less - to ingest an LD₅₀ amount of this active by grooming. The label directions for use specify spraying the product over the entire body (avoiding the eyes), including feet and tail. However, there is no indication that the Agency has received information as to what sort of dose (amount sprayed on the animal) would be involved. In theory, given the label directions for use, the contents of the entire can (7 oz) could be sprayed on a cat and this would not constitute misuse.

In a study conducted at Leberco Testing, Inc. the rat oral LD₅₀ on the technical concentrate (14.286% DEET) of this Hartz product was reported as 6700 mg/kg, with 95% confidence limits of 5668 to 7919 mg/kg. However, this oral LD₅₀ is based on the combined mortality for both sexes; it is noteworthy that all females receiving doses of 7 g/kg or more died, while only 4/15 males did so, suggesting females are more susceptible. Symptoms of toxicity included moderate to severe ataxia even at the lowest dose level (5 g/kg).

While the BLOCKADE formulation also contains 0.09% Pydrin, the available information indicates that this contributes very little to the toxicity of the formulation (the lowest oral LD₅₀ value for technical Pydrin is approximately 75 mg/kg; for a product containing 0.09% as sole active this would extrapolate to approximately 10,000 times this value).

The IRB/TSS review of the reported incidents notes that "The most at-risk group would appear to be young kittens (especially female)."

2. The material submitted August 28, 1987 by the Hartz Mountain Corporation includes only two reports involving cats. Both were efficacy studies using the aerosol product; one with two treated animals and the other with only one. While no signs of adverse reactions were noted in either of these studies, the total number of animals involved (three) is clearly inadequate to demonstrate product safety for cats. Additionally, no information was provided as to the sexes or ages of these animals, or the dosage amounts of product applied.
3. While the labeling for the cat product makes a 21-day efficacy claim and states: "Under normal circumstances, repeat spray every 21 days" it is also stated that: "In areas or periods of heavy infestation it may be necessary to treat the animal more frequently." The implication is that a cat could be treated as often as necessary. This may, however, be a somewhat moot point as indications are that a single exposure to the product may be sufficient to kill a cat.
4. According to information on p. 123 of the ninth (1986) edition of Current Veterinary Therapy, DEET (in the form of DEET-containing products such as Off, Deep Woods Off) was associated with seven suspected cases of toxicosis in cats. These incidents apparently occurred as a result of treatment of pets with products normally used on humans. "In dogs and, especially, cats, primary signs included seizures, tremors, and sometimes emesis. Ataxia or lethargy occasionally occurred." Symptoms reported for cats by the National Animal Poison Control Center included increased salivation, tremors, vomiting, ataxia/incoordination and depression.

According to the Toxicology Branch one-liners, symptoms in rats following dosage with a product containing 22.95% DEET (also with dimethyl phthalate, 15.3%; Di-n-propyl isocinchomeronate, 1%; and N-octyl bicycloheptene dicarboximide 1%) included hypoactivity, ataxia, salivation, prostration and loss of righting reflexes. The oral LD₅₀ for males was 4550 (3434-6029) mg/kg, and for females was 5450 (3759-7903) mg/kg.

5. After taking into account the data indicated above, as well as the considerable number of reported adverse incidences involving cats (109, with 5 deaths) following exposure to Blockade as reported to the National Animal Poison Control Center from March 10 through July 17, 1987, the Toxicology Branch is of the opinion that there is an insufficient safety factor associated with normal (following

label directions) use of EPA Reg. No. 2596-114 (Hartz Blockade for Cats).

6. The reported incidents involving dogs are also of considerable concern, although these appear to be less frequent and usually less severe than those involving cats. However, a considerable number of deficiencies are evident on examination of the label for 2596-115 (Hartz Blockade for Dogs). These include the following:

- i) Sick and debilitated dogs are not excluded from treatment, as well as puppies and possibly toy breeds with large body surface to volume ratios (a death was reported in a 4 lb 8-yr old Yorkshire Terrier in Texas on 4/16 according to information from the National Animal Poison Control Center).
- ii) There is no limitation on the dosage applied (such as spraying no more than so many seconds, or applying until the coat is only so moist). The exact wording of this should have been based on information from the registrant as to what constitutes an effective but safe dose and should have been correlated with actual dosage values (gms/kg) of product applied to dogs in studies.
- iii) There is no limitation specified as to the frequency of treatments.

7. Toxicity studies on dogs were conducted. However, the maximum exposure was as a 1X (use-direction) spray applied on a once-a-week basis over a period of 4 weeks. Adverse effects ("mild emesis" occurring 2 hours after exposure) were noted for two (out of 40) dogs in one of these studies. It is noted that a considerable number of dogs were used in more than one of these studies, that the only information provided regarding the individual dogs was breed, weight and hair coat (nothing as to age; 2 individuals in one study are, however, reported as "nursing puppies").

The dog toxicity studies (as well as the cat efficacy studies) were conducted by a laboratory [REDACTED] for which the address is given (in one document) [REDACTED]. None of these studies has a quality assurance statement, and there is no indication that this facility follows GLP regulations.

8. The Toxicology Branch has no record that any subchronic or chronic toxicity studies on DEET have been conducted on dogs. There is some concern regarding possible kidney and liver effects.

9. It is noteworthy that diarrhea is reported as a symptom in some incidents involving dogs. While no deaths were reported in the acute dermal rabbit LD₅₀ study conducted (Leberco Testing, Inc.) on the concentrate, diarrhea (associated with weight loss) was reported from several animals, so that toxicity due to dermal absorption of the active cannot be ruled out. The only individual whose name appears on these reports is [REDACTED]

10. A search through the available literature on DEET has failed to turn up any antidotal information, or anything other than "supportive treatment" for poisoning by this compound. This has made it difficult for the Toxicology Branch to respond to inquiries from veterinarians as to the appropriate procedure to follow.

11. The Toxicology Branch expresses reservations that additional toxicity testing - as outlined in the draft review from IRB/TSS - will expeditiously resolve the problems associated with these products.

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED

HARTZ[®] BLOCKADE[™]

CAT FLEA & TICK REPELLENT

- repels fleas
- repels ticks
- keeps your cat free of fleas and ticks for up to 21 days

ACTIVE INGREDIENTS:
N,N-Diethyl-m-tolamide 8.55%
Other Isomers 0.45%
Cyano (3-phenoxypheyl)
methyl-4-chloro-alpha-
(1-methylethyl)
benzenesulfate 0.09%
INERT INGREDIENTS 90.91%
100.00%

Net Wt.
7 oz 198 g

EPA Est. 2596-NJ-1 EPA Reg. No. 2596-114

Keep out of reach of children.

CAUTION: See back panel for additional precautionary statements.

HARTZ BLOCKADE CAT FLEA AND TICK REPELLENT

- repels fleas • kills fleas • kills ticks • repels mosquitoes
- keeps your pet flea and tick free for up to 21 days • repels insects which reduces incidence of itching and scratching

Hartz Blockade Flea and Tick Repellent prevents these pests from actually inhabiting your cat. In laboratory and field tests, animals treated with this spray repelled fleas and ticks for up to 21 days. The spray may also be used on pets infested with fleas or ticks in order to kill these parasites and prevent additional ones from inhabiting the pet.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

To repel fleas and ticks, thereby reducing incidence of itching and scratching, hold container 6 to 10 inches from animal and spray over entire body. Be sure to cover feet and tail. Do not spray in eyes. For best penetration of spray to the skin, direct spray against the natural lay of the fur to cause fluffing of the coat. Under normal circumstances, repeat spray every 21 days. In areas or periods of heavy infestation it may be necessary to treat the cat more frequently. Under such circumstances, an occasional flea or tick may be seen on the animal. For more prolonged flea and tick control, the animal's bedding, quarters, and surrounding area should also be sprayed lightly until damp to help prevent reinfestation. Complete control can be obtained by affixing a Hartz 2 in 1 Reflecting Collar to the pet in addition to use of this spray.

Storage and Disposal
Replace cap, wrap empty container and put in trash.

PRECAUTIONARY STATEMENTS

Hazards to Humans & Domestic Animals

CAUTION: Avoid inhalation of spray. Avoid spraying in eyes. It is good practice to wash hands after use. Do not contaminate water or food.

Physical or Chemical Hazards

Contents under pressure. Do not use or store near heat or open flame. Do not puncture or incinerate container. Exposure to temperatures above 130°F may cause bursting.

STATEMENT OF PRACTICAL TREATMENT

If in eyes: Rinse eyes with plenty of water. Call a physician if irritation persists.

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Harrison, N.J. 07029-9987
and St. Thomas, Ontario
NSP 3W7, Canada

Made and printed in U.S.A.

NOT REVIEWED

In Accordance with PR Notice 82-2:

Based on Draft Labeling Dated 5-12-86

123
Exhibit C 3/20/87 ACC

...ary problem of gastroin-
mes hemolysis. Paradichlo-
ess frequent but may be
ataxia, and seizures.

icides. Amitraz (Mitaban,
nded for dogs less than 3
s occasionally serious, or
isonings. Signs of serious
/ occur in younger or very
lude weakness, salivation,
coma, and death. It is not
ire to cause mild weakness
arger dogs, and most such
recover.

an Cyanamid), which con-
a heavily used fire ant
action is poorly under-
dro is low, and toxicoses
requent than exposures.
it is present in Combat
merican Cyanamid).

1 apparent effort to avoid
ulations, crude citrus oil
sted as "pet dips" that
small print, followed by)
large print) without ac-
cticidal. Such products

, and ataxia, depression,
ilted even when label
lowed. Some such for-
rawn from the market.

not, however, be con-
ng D-limonene (such as
emicals, Inc.). Our ex-
lips in cats suggest that

commended concentra-
: exposure, toxic effects
on, hypothermia, and
ts last minutes to sev-
age. In addition, scro-

massive overexposure
sient signs sometimes
d concentration.

l in origin, rotenone is
fish but also to mam-
ly affected than dogs.

e a result of topical
ing dips or powders.
in both dogs and cats

osis or suspected tox-
ariable but often in-
ors, and dyspnea.

gone). Each year the
egarding pennyroyal
ised as an insecticide

ived in 1984 regard-
osis consistently in-
described panting,
hial sounds. These

are compatible with reports of pennyroyal oil toxi-
cosis in humans, the effects of which may also
include disseminated intravascular coagulation, he-
patic necrosis, abortion, and death.

REPELLENTS. Diethyltoluamide (DEET), found
in many insect repellent products (such as Off,
Deep Woods Off, Cutter Insect Repellent, and
others [S. C. Johnson and Son and Cutter]), was
associated with seven suspected cases of toxicosis
or toxicosis calls in cats and four such calls in dogs.
Naturally these occur during warm months and are
a result of owner treatment of their pets. In dogs
and, especially, cats, primary signs included sei-
zures, tremors, and sometimes emesis. Ataxia or
lethargy occasionally occurred.

RODENTICIDES. The rodenticide class is the sec-
ond most prevalent category of agents associated
with calls to the NAPCC for two reasons: (1) Ro-
denticides are often placed in areas in which both
rodents and pet animals are present, and (2) the
NAPCC has an agreement with the manufacturers
of brodifacoum so that the NAPCC telephone num-
ber is on packages containing this common antico-
agulant (Talon and Havoc [ICI Americas and oth-
ers]). Naturally, this causes us to receive a
disproportionate number of calls concerning brodi-
facoum.

Anticoagulant Rodenticides. The vast majority of
anticoagulant rodenticide calls, regardless of the
agent involved, were for exposure only. In the case
of brodifacoum, the number of clinically serious
poisonings resulting from exposure was undoubt-
edly minimized by virtue of access to appropriate
antidotal information. It appears that dogs are more
sensitive than cats to brodifacoum.

Owing to the extremely wide availability of anti-
coagulants, a significant number of toxicoses result
from their use. Baits that contain bromadiolone,
chlorophacinone, pindone, diphacinone, and others
are occasionally consumed by small animals. Of
these, it appears that diphacinone may cause the
greatest number of poisonings (see page 159).

Strychnine. The convulsant strychnine continues
to cause toxicosis, but the prevalence of this poison-
ing may be declining. Nevertheless, strychnine-
containing baits are still available over the counter.
During 1984, 26 calls pertaining to accidental and
malicious poisonings of dogs were received. Only
two such calls pertained to cats.

Fluoroacetate (Compound 1080). Fluoroacetate
toxicosis is comparatively infrequent at the present
time. This is a result of restrictions placed on the
use of fluoroacetate-containing baits. Currently,
fluoroacetate may be used as a rodenticide only by
licensed exterminators. Depending on the outcome
of legal battles continuing at the time of this writing,
fluoroacetate may eventually be encountered as a
result of its use in coyote control in the form of
"single lethal dose baits" and less often in toxic

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APR 7 1985

PESTICIDE
ENFORCEMENT

CORE Grade/

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Day/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/Doc. No.
Primary eye irritation - rabbit; Dept. of Army; #75-51-0034-81; 1/1981	TECH 100%		PIS = 4.7 at 72 hrs (washed eye) PIS = 0.0 at 7 days (washed eye) Corneal opacity present at day 3, cleared by day 7 for both washed and unwashed eyes.	II	Minimum 000825
Primary eye irritation - rabbit; Dept. of Army; #75-51-0031-81; 1/1981	75% solution DEET in denatured EtOH		PIS = 0.8 at 72 hrs (unwashed) PIS = 0.0 at 7 days (unwashed) PIS = 8.0 at 72 hrs (unwashed eyes) PIS = 0.0 at 7 days (unwashed eyes) Corneal opacity present at day 3, but cleared by day 7 for both washed and unwashed.	II	Minimum 000825
Primary eye irritation - rabbit; Dept. of Army; #75-51-0034-81; 1/1981	50% solution DEET in denatured Ethanol		PIS = 4.6 at 72 hrs (washed eye) PIS = 0.0 at 7 day (washed eye) PIS = 13.8 at 72 hrs (unwashed eye) PIS = 1.1 at 14 days (unwashed eye) Corneal opacity present at day 14 for both washed and unwashed eyes.	I	Minimum 000825
Primary eye irritation - rabbit; Dept. of Army; #75-51-0034-81; 1/1981	Federal Specification (0-I-503 b) Insect Repellent 71.25% - DEET 25.0% - denatured Ethanol 3.25% - Other diethyl tolalides		PIS = 4.2 at 72 hrs (washed eye) PIS = 0.5 at 14 days (washed eye) PIS = 10.6 at 72 hrs (unwashed eye) PIS = 0.0 at 7 days (unwashed eye) Corneal opacity present at 72 hrs but cleared by day 7.	II	Minimum 000825

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Study/Lab/Study #/Date	Material	Accession No.	Results:		TOX Category	CORE Grade/Doc. No.
			LD50, LC50, PIS, NOEL, LEL			
Acute oral LD50 - rat; Miles Laboratories; Report #28; 12/20/83	DEET.....22.95% Dimethyl phthalate.....15.30% Di-n-propyl isocinchomeronate.....1.275% N-Octyl bicycloheptene dicarboximide.1.275%	254183	LD50 (male) = 4550(3434-6029) mg/kg LD50 (female)=5450(3759-7903).mg/kg Symptoms: hypoactivity, ptosis, ataxia, salivation, prostration, loss of righting reflex, bradypnea.	III	Minimum 003891	
Acute dermal LD50 - rabbit; Miles Laboratories; Report #31; 12/20/83	DEET.....22.95% Dimethyl phthalate.....15.30% Di-n-propyl isocinchomeronate.....1.275% N-Octyl bicycloheptene dicarboximide.1.275%	254183	Three accidental deaths occurred at 2 g/kg (only dose tested).	(III)	Supplementary 003891	
Acute inhalation LC50 - rat; Bio-Research Lab. Ltd; Project No. 81774; 12/27/83	DEET.....22.95% Dimethyl phthalate.....15.30% Di-n-propyl isocinchomeronate.....1.275% N-Octyl bicycloheptene dicarboximide.1.275%	254183	10% mortality at 5.3 mg/L (actual concentration; only level tested); Nominal concentration = 39.1 mg/L; (4-hr exposure). Mass median diameter = 3.1 um, with 94% of particles < 9 um in diameter. Symptoms: ataxia, lethargy, salivation, respiratory distress. Inhalation LC50 (both sexes) > 5.3 mg/L (4-hr exposure; actual concentration).	IV	Minimum 003891	

EPA		Accession		Results:		TOX	CORE Grade/ Doc. No.
Study/Lab/Study #/Date	Material	No.	LD50, LC50, PIS, NOEL, LEL	Category	Doc. No.		
Primary dermal irritation - rabbit; Miles Laboratories; Report #27; 12/20/83	DEET.....22.95% Dimethyl phthalate.....15.30% Di-n-propyl isocinchomeronate.....1.275% N-Octyl bicycloheptene dicarboximide.1.275%	254183	PDIS =0.21 (24-hr occluded exposure) with all sites clear at 72 hrs.	IV	Minimum 003891		
Primary eye irritation - rabbit; Miles Laboratories; Report #18; 11/18/83	DEET.....22.95% Dimethyl phthalate.....15.30% Di-n-propyl isocinchomeronate.....1.275% N-Octyl bicycloheptene dicarboximide.1.275%	254183	All eyes (washed and unwashed) had some irritation. Some eyes had corneal involvement. All eyes were clear by day 7.	III	Minimum 003891		
Primary eye irritation - rabbit; Medical College of Wisconsin; 1983	Deet..... 100%	252568	Serious inconsistencies in the reported data.		INVALID 001743		
Primary eye irritation - rabbit; Medical College of Wisconsin; 1983	Deet..... 20% Ethanol.. 80%	252568	Serious inconsistencies in the reported data.		INVALID 001743		