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

OFFICE OF PRE

AND TOXIC SUBSTANCES

Date: August 2, 2005

MEMORANDUM

Subject: EPA File Symbol: 2596-RLL - HARTZ REFERENCE 123
DP Barcode: D318727
Decision No.: 358347
PC Code: 044312 DINOTEFURAN (CAS #165252-70-0)

From: Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

To: Rita Kumar/Daniel Kenny RM 01
Insecticide-Rodenticide Branch
Registration Division (7505C)

Applicant: The Hartz Mountain Corporation

FORMULATION DECLARATION FROM LABEL:

	% by wt
Active Ingredient(s):	
Dinotefuran (CAS #165252-70-0)	14.85%
Other Ingredients:	85.15%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

"Please review companion animal safety study for this new cat spot-on product. This is a new use for Dinotefuran. MRID No. 46581607. This will be an expedited review as asked by Lois Rossi..."

BACKGROUND:

This package includes a companion animal safety study (cats and kittens) in MRID 46581607.

COMMENTS AND RECOMMENDATIONS:

1. While the number of kittens/dose (2/sex) in this study was somewhat below what Agency reviewers would prefer, nothing of toxicological significance was observed in the kittens at even a 5X (x 1.2 mL) dosage rate. The companion animal safety study in MRID 46581607 is acceptable in support of all proposed label uses for this product except application at 2.0 mL for kittens weighing more than 4.0 kg. As there were no kittens in this study weighing $\geq$4.0 kg, labeling should specify an application rate of 1.2 mL for all kittens from the age of 12 weeks to 6 months of age. If the registrant wishes to have a claim for a 2.0 mL application rate on kittens weighing $\geq$ 4.0 kg, appropriate additional companion animal data should be generated and submitted.

2. Some additional material necessary for this review was received by fax from the registrant. This material consisted of observational data from the laboratory relating to effects at the site of application, and corrected pages 238-254 (as originally received by the Agency the lower third of these pages was blank). The study in MRID 46581607 should be resubmitted to the Agency incorporating the observational data and corrected pages, and will be assigned a new MRID number.

3. The following is the executive summary for the DER prepared for this study:

   In a companion animal safety study (MRID 46581607) with European mixed-breed cats, 4 groups, each with 8 (4/sex) adult (age: 12-28 months) cats (source: Charles River Laboratories BioLabs Europe's colony at Glenamoy, Ireland; Males: 3.1-4.0 kg; Females: 2.3-3.9 kg) and 4 (2/sex) approximately 12-week old kittens (source: Charles River Laboratories BioLabs Europe's SPF colony at Carrentrila, Ireland; Males: 1.3-1.5 kg; Females: 1.2-1.4 kg) were treated at 0X (5 applications of 1.2 mL of the control item); 1X (1 application each of 1.2 or 2.0 mL, according to the cat's weight, of the test material); 3X (3 applications of 1.2 or 2.0 mL, according to the cat's weight, of the test material); and 5X (Five 1.2 mL applications of the test material). The 1.2 mL applications were made to adult cats and kittens weighing $\leq$ 4.0 kg; the 2.0 mL applications were made to adult cats weighing > 4.0 kg (only 2 adults weighed more than 4.0 kg, male 08010 in the 1X Group, and male 27099 in the 3X group; none of the kittens weighed more than 4.0 kg) somewhat consistent with label directions specifying a single application of 1.2 mL to cats or kittens weighing 9 lbs or less and 2.0 mL to cats or kittens weighing 9 lbs or more. For convenience in dosing, each dose group was subdivided into Sets 1 and 2, with 4

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were primarily erythema, scabbing and/or alopecia, and, in at least some cases, were probably due to the cat scratching the site. Cosmetic effects were observed in all cats and kittens, and included matting, spiking, clumping, greasy appearance, discoloration and deposits. The cosmetic effects were gone from all adult cats and 3/4 kittens of the 1X group by Study Day 4, but were more persistent in the other 3 groups (including controls), persisting in some individuals through Day 14.

Overall, adult cats had minor weight changes from preexposure Day -1 or -2 to Day 14 (ranging from a loss of about 0.1 kg to a gain of 0.3 kg), with no indication of any dose-related trend. All kittens showed weight gains (from 0.1 to 0.5 kg during the same interval) with no indication of any dose-related trend or effects.

There was no indication of an effect on any of the hematology or clinical chemistry parameters, and there were no symptoms or other indications of systemic toxicity.

TRB concludes that this companion animal safety study (OPPTS 870.7200) demonstrates an adequate margin of safety (at least 5X) between the exposure associated with most of the proposed use levels for this formulation (1.2 mL for cats weighing $\leq$ 4.0 kg and 2.0 mL for cats weighing $\geq$ 4.0 kg; 1.2 mL for kittens <u>of all weights</u>) and that at which <u>significant</u> systemic effects may occur. It does not support a dose level of 2.0 mL for kittens (which can be considered to be animals of under 6 months of age) $\geq$ 4.0 kg, as kittens of this body weight were not included in this study. Labeling should be revised to specify a dose level of no more than 1.2 mL for kittens of up to 6 months of age.

EPA Primary Reviewer: Byron T. Backus, Ph.D. Signature: _____
Technical Review Branch, Registration Division (7505C) Date_____
EPA Secondary Reviewer: William Dykstra, Ph.D. Signature: _____
Health Effects Division (7509C) Date_____
EPA Tertiary Reviewer: Kit Farwell, DVM, DABT Signature: _____
Health Effects Division (7509C) Date _____

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety - Cats and 12-Week Old Kittens OPPTS 870.7200
PC CODES: 044312 (Dinotefuran)
DP BARCODE: D318727 **RISK MANAGER: (EPA): 01** **DECISION NO.: 358347**

PRODUCT AND TEST MATERIAL: S1638 (15%) (TS # 12560); a colorless liquid containing 15.46% of the active S-1638, consistent with the proposed product [Hartz Reference 123] label declaration of 14.85% Dinotefuran (CAS #165252-70-0) as sole active, and other ingredients at 85.15%.

CITATION: Doherty, P. (2005) Tolerance of an Experimental Flea Dermal Treatment when Topically Administered to Adult Cats and 12 Week Old Kittens at 1 X, 3 X and 5 X the Recommended Dose. Study No. USA004\05-001; Hartz Test #1781. Unpublished study prepared by Charles River Laboratories BioLabs Europe, Ireland. Study Completion Date: 7 June 2005; MRID 46581607.

SPONSOR: The Hartz Mountain Corporation

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 46581607) with European mixed-breed cats, 4 groups, each with 8 (4/sex) adult (age: 12-28 months) cats (source: Charles River Laboratories BioLabs Europe's colony at Glenamoy, Ireland; Males: 3.1-4.0 kg; Females: 2.3-3.9 kg) and 4 (2/sex) approximately 12-week old kittens (source: Charles River Laboratories BioLabs Europe's SPF colony at Carrentrila, Ireland; Males: 1.3-1.5 kg; Females: 1.2-1.4 kg) were treated at 0X (5 applications of 1.2 mL of the control item); 1X (1 application each of 1.2 or 2.0 mL, according to the cat's weight, of the test material); 3X (3 applications of 1.2 or 2.0 mL, according to the cat's weight, of the test material); and 5X (Five 1.2 mL applications of the test material). The 1.2 mL applications were made to adult cats and kittens weighing $\leq$ 4.0 kg; the 2.0 mL applications were made to adult cats weighing > 4.0 kg (only 2 adults weighed more than 4.0 kg, male 08010 in the 1X Group, and male 27099 in the 3X group; none of the kittens weighed more than 4.0 kg) somewhat consistent with label directions specifying a single application of 1.2 mL to cats or kittens weighing 9 lbs or less and 2.0 mL to cats or kittens weighing 9 lbs or more. For convenience in dosing, each dose group was subdivided into Sets 1 and 2, with 4 adults (2M, 2F) and 2 kittens (1M, 1F) in each set of each dose group. Set 1 animals were dosed 24 hours before those of Set 2.

The test material was a colorless liquid containing 15.46% S-1638 (Dinotefuran).
Cats receiving more than 1 application had treatments at 1 hour ($\pm$ 5 minutes) intervals. The 1.2 or 2.0 mL dose of test material was applied dorsally to a spot at the base (on the back) of each animal's head using a syringe. Once the control or test item was applied, the

cat was held in an upright position for at least 2 minutes to prevent any potential loss (run-off?).

Clinical assessments were carried out on each cat or kitten prior to the first treatment, and at approximately 1, 2, 3 and 4 hours following the last application. Cats receiving more than one application treatment were also evaluated 10 minutes before each treatment.

According to proposed label directions the product would be applied to one spot along the cat's (kitten's) back. This should be revised to state that application should be made at the back of the neck.

Individual body weights were measured on Days -15, -1 (Set 1)/-2 (Set 2), 0, 7 and 14. Individual food consumption was measured on a daily basis for Days -7, -6, -4 and then daily thereafter through Day 14 (values represented the amount of food consumed during the previous 24 hours). Blood samples were taken once pretest (Day -14), 1, 7 and (for WBC counts) on Days 8 or 9 following an overnight fast (except for blood taken for WBC counts).

There was no mortality. Clinical observations seen in one or more groups included abnormal (loose) feces, pruritis, abnormal (excessive?) salivation (seen only in 3 adult cats at the 3X dose level 1-3 hrs after 3 applications), abnormal site of spot-on application and vomiting. The pruritus, salivation, and effects observed at the site of application can be considered as effects of the test material and/or solvent.

For adult cats of all groups there were reductions in mean food consumption on Days 0 and 1. There was also a reduction for Day 7 (associated with fasting prior to blood taking). The reduction in mean consumption on Day 0 involved cats of Set 1 only, and was probably due to a deviation from the study plan in which diet was erroneously withdrawn on Study Day -1 from these animals. On Day 1 adult cats in the 5X group had a slightly (not statistically significant) lower mean food consumption than adult cats in the other 3 groups (Males: controls: 89.1 g; 1X: 99.8 g; 3 X: 89.4 g; 5X: 53.8 g; Females: controls: 25.2 g; 1X: 30.9 g; 3X: 29.4 g; 5X: 18.2 g).

The site of application was observed to be "abnormal" on a number of occasions for adult cats in the control, 3X and 5X (but not 1X groups), with the following reported incidences: Controls: 3/8; 1X: 0/8; 3X: 2/8; 5X: 3/8. Only one kitten (in the 5X group group) showed a similar effect (from Day 10 to 12). Effects at the site of application were primarily erythema, scabbing and/or alopecia, and, in at least some cases, were probably due to the cat scratching the site. Cosmetic effects were observed in all cats and kittens, and included matting, spiking, clumping, greasy appearance, discoloration and deposits. The cosmetic effects were gone from all adult cats and 3/4 kittens of the 1X group by Study Day 4, but were more persistent in the other 3 groups (including controls), persisting in some individuals through Day 14.

Overall, adult cats had minor weight changes from preexposure Day -1 or -2 to Day 14 (ranging from a loss of about 0.1 kg to a gain of 0.3 kg), with no indication of any dose-related trend. All kittens showed weight gains (from 0.1 to 0.5 kg during the same interval) with no indication of any dose-related trend or effects.

There was no indication of an effect on any of the hematology or clinical chemistry parameters, and there were no symptoms or other indications of systemic toxicity.

TRB concludes that this companion animal safety study (OPPTS 870.7200) demonstrates an adequate margin of safety (at least 5X) between the exposure associated with most of the proposed use levels for this formulation (1.2 mL for cats weighing ≤ 4.0 kg and 2.0 mL for cats weighing ≥ 4.0 kg; 1.2 mL for kittens of all weights) and that at which significant systemic effects may occur. It does not support a dose level of 2.0 mL for kittens (which can be considered to be animals of under 6 months of age) ≥ 4.0 kg, as kittens of this body weight were not included in this study. Labeling should be revised to specify a dose level of no more than 1.2 mL for kittens of up to 6 months of age.

COMPLIANCE: Signed and dated Quality Assurance (p. 4), [No] Data Confidentiality (p. 2), and Good Laboratory Practice Compliance (p. 3) Statements were present.

I. MATERIALS

A. MATERIALS

1. Test material: S1638 (15%) (TS # 12560), described (p. 188 of MRID 46581607) as a colorless liquid containing 15.46% active.
   Description: A colorless liquid with a density of 1.078 g/mL
   Batch No.: 12560; manufacturing date: Dec 04 [2004?]
   Storage: Between 15°C and 20°C in the dark.

   Placebo: S1638 (Blank) (TS#12559). A colorless liquid not containing any active ingredient.
   Description: A liquid
   Batch No.: 12559: Dec 04 [2004?]
   Storage: Between 15°C and 20°C.

2. Administration: Topical (spot-on) on Day 0.

3. Test animals
   Species: Cat (Felis catus)
   Breed: European mixed breed
   Ages and weights at study initiation (Day 0): Adults: Males: 12 - 28 months; 3.1-4.0 kg; Females: 16-28 months; 2.3-3.9 kg; Kittens: Males: 84-86 days; 1.3- 1.5 kg; Females: 84-87 days; 1.2-1.4 kg.
   Source: Adults: Charles River Laboratories BioLabs Europe; Glenamoy, Ireland; Kittens: Charles River Laboratories BioLabs Europe SPF colony at Carrentrila, Ireland.
   Housing: Individually housed in steel and/or mesh cages.
   Diet: Adults: Standard commercially available cat food ["Gilpa Umami"] at the recommended rate of approximately 100 g/cat/day. Kittens: Standard commercially available kitten food ["Whiskas Kitten Food"] at the recommended rate of approximately 400 g/kitten/day. Diet was withdrawn from all animals between 16:00 and 17:00 on Study Days -15, 0 and 6 for fasting prior to blood sampling.

   Water: "potable water," *ad libitum*
   Environmental conditions:
   Temperature: 17-22°C
   Humidity: 36-56%
   Air changes: Not specified.

TABLE 1. Study design						
		Number of Animals	Number of Applica-tions	Total Amount Applied to Each Animal	Mean Cat or Kitten Wt ± S.D. on Day 0	Mean Dose Dinotefuran mg/kg
Placebo Control (1)	Adult Males	4	5	6.0 mL[a]	3.825 ± 0.222	0
	Adult Females	4	5	6.0 mL[a]	2.675 ± 0.287	0
	Kittens (2M & 2F)	4	5	6.0 mL[a]	1.375 ± 0.096	0
Group 2 (1X)	Adult Males	4	1	1.2 or 2.0 mL[c]	3.700 ± 0.497	63
	Adult Females	4	1	1.2 mL	2.575 ± 0.206	78
	Kittens (2M & 2F)	4	1	1.2 mL[c]	1.300 ± 0.115	154
Group 3 (3X)	Adult Males	4	3	3.6 or 6.0 mL[c]	3.950 ± 0.342	176
	Adult Females	4	3	3.6 mL[c,d]	2.575 ± 0.263	233
	Kittens (2M & 2F)	4	3	3.6 mL[c]	1.375 ± 0.096	436
Group 4 (5X)	Adult Males	4	5	6.0 mL[c]	3.700 ± 0.141	270
	Adult Females	4	5	6.0 mL[c]	2.950 ± 0.733	339
	Kittens (2M & 2F)	4	5	6.0 mL[c]	1.300 ± 0.141	769

Individual body weights given on p. 49 of MRID 46581607; the means (with standard deviations) were calculated by this reviewer from these data.

[a] Placebo

[b] Based on a specific gravity of 1.078 g/mL

[c] Test material (with active); amount delivered.

[d] One adult male in Group 3 weighing 4.1 kg on Study Day 0 was dosed at 1.2 mLs based on its Study Day -1 bodyweight of 4.0 kg (see p. 38 of MRID 46581607).

C. DOSE SELECTION RATIONALE

From p. 28 of MRID 46581607: "The route of administration (topical) is the proposed route of administration for normal use of the final product. The dose levels used were the normal recommended dose for this product on adult cats/kittens weighing 4kg or less and for adult cats weighing greater than 4 kg, three times the normal recommended dose and five times the normal recommended dose as per the health effects test guidelines (OPPTS 870.7200)."

According to the proposed label this product will consist of either 0.04 fl. oz. (1.2 mL) or 0.06 fl. oz. (2.0 mL) single applications. The smaller amount would be for cats/kittens weighing 9 lbs or less and the larger would be for cats/kittens weighing 9 lbs or more. "Outer packaging may contain up to 150 units." The product claim is that it "Kills 100% of the fleas on cats within 24 hours and continues to prevent infestation for four weeks." The precautionary statements includes the following: "Do not apply more than once every 30 days."

D. EXPERIMENTAL DESIGN

From p. 31 of MRID 46581607: "Each adult cat and kitten was examined by a Veterinary Surgeon on Study Day -15 and on Study Day -1 (Set 1)/ -2 (Set 2). Only healthy adult cats and kittens as assessed by these veterinary examinations were included in the study... General health observations were carried out on each adult cat and kitten twice daily (morning and afternoon) from Study Day -14 to Study Day -1, with at least 4 hours between each observation. No general health observations were performed from Study Day 0 to...14 inclusive, as clinical assessments were performed..."

"Clinical assessments were carried out on all adult cats and kittens prior to the first treatment and at 1 hour (± 5 minutes), 2 hours (± 10 minutes), 3 hours (± 10 minutes) and 4 hours (± 10 minutes), after the final treatment on Study Day 0, by a veterinary surgeon. For adult cats and kittens assigned to Groups 1, 3 and 4, clinical assessments were also carried out by a veterinary surgeon within 10 minutes prior to the second, third, fourth and fifth dosings, where relevant. No adverse reactions were observed at the final clinical assessment on Study Day 0, which were considered by the examining veterinary surgeon to warrant further investigation in any group.

"Where adverse reactions, such as erythema at the site of spot on, were observed prior to the +4 (± 10 minutes) assessment and had not worsened in their intensity and were considered by the examining veterinary surgeon unlikely to deteriorate by the Study Day 1 (am) assessment, then hourly assessments were not performed."

"In addition, clinical assessments were performed by a veterinary surgeon twice daily on all adult cats and kittens assigned to Groups 1, 2, 3 and 4 from Study Day 1 to Study Day 14 inclusive, once in the morning and once in the afternoon, with at least 4 hours between assessments." Each animal was observed for at least 1 minute for the presence (score of 1) or absence (score of zero) for the following parameters:

"Lethargy, ataxia, recumbency, paralysis, coma, pruritus, hyperactivity, tremors, convulsions, abnormal mydriasis, abnormal miosis, corneal opacity, dyspnoea, tachypnoea, coughing, abnormal salivation, vomiting, abnormal mucous membranes, ocular discharge, nasal discharge, cardiovascular changes, abnormal faeces (if present), abnormal urine (if present), abnormal coat condition, abnormal site of spot-on application. For every parameter given a score of "1", a brief comment, if applicable, was made to describe the abnormal assessment 9e.g. abnormalities at the site of spot-on application may include oedema, erythema, alopecia, pruritus)."

"...Where the site of spot-on application showed any cosmetic effect after treatment, this was considered clinically normal. Cosmetic effects included any discolouration, stiffness causing the hair to stand up (spiking), stiffness with the hair sticking together (clumping), tangling of the hair (matting), greasy appearance or any deposits. Any cosmetic effects present were recorded."

"Each animal was weighed, before feeding, on Study Days -15, -1 (Set 1)/-2 (Set 2), 0, 7 and 14."

From p. 22: "...Adult cats and kittens were fed once daily in the afternoon between 12:00 and 15:00. The quantity of diet offered was weighed and recorded daily from Study Day -14 to Study Day 13 inclusive. Between Study Day -13 and Study Day 14 diet not consumed from the previous day was removed from each cat's cage between 10:00 and 12:00 and subsequently weighed, with the following exceptions. Diet was withdrawn from all animals, between 16:00 and 17:00 on Study Days -15, 0 and 6 in order to facilitate fasting prior to blood sampling. The weight of the diet withdrawn was recorded as diet not consumed for the following day."

E. PATHOLOGICAL PARAMETERS

Blood samples were collected from each animal at the following Study Days: -14, +1, and 7. Because of an instrument malfunction (see p. 38 of MRID 46581607) , the Set 1 Study Day 7 WBC counts had to be redone on Study Day 9; in addition, insufficient analytical reagent was available for 3 kittens in Set 2 on Day 7 so these were done on Study Day 8.

The CHECKED (X) parameters were examined:

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count	X	Absolute reticulocytes
	Blood clotting measurements	X	Percent reticulocytes
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time [PT])*		
X	(Activated partial thromboplastin time [APTT])*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin (Alb)*
X	Chloride*	X	Blood creatinine (Crea)*
	Magnesium	X	Blood urea nitrogen (BUN)*
X	Phosphorus*	X	Urea
X	Potassium*		Total Cholesterol
X	Sodium*	X	Globulin (Glob)*
		X	Glucose (Gluc)*
	ENZYMES	X	Total bilirubin (T Bil)*
X	Alkaline phosphatase(ALPor ALK)*	X	Direct bilirubin (D Bil)*
	Cholinesterase(ChE)	X	Total serum protein (TP)*
	Creatine kinase		Triglycerides
	Lactic acid dehydrogenase(LDH)		Serum protein electrophoresis
X	Serum alanine aminotransferase (ALT or SGPT)*		Albumin/Globulin (A/G) ratio
X	Serum aspartate aminotransferase(AST or SGOT)*		Lipase
	Gamma glutamyl transferase(GGT)		
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. STATISTICS

A statistical summary report is found in Appendix 5, running from pages 189 to 294 of MRID 46581607.

From p. 173: "Statistical analysis will be performed separately for adult cats and for kittens. A combined analysis of adult cats and kittens will also be performed. Clinical chemistry and haematology, diet consumption and bodyweight data will be analysed using a mixed model repeated measures analysis of covariance including set and its interaction with day as random effects, and sex, treatment, sampling day, and interaction of sex and treatment with day as fixed effects. The covariate for each variable will be the applicable baseline measurement. The average value, or the final pre-treatment value, will be used for more than one baseline measurement. For each analysis, the appropriate variance-covariance matrix structure will be selected from among compound symmetry, first-order autoregressive, heterogeneous first-order autoregressive, and unstructure based on Akaike Information Criterion."

"If the overall treatment by time interaction is significant at alpha = 0.05, then the pairwise comparison of each dose group mean for adult cats, kittens and for adult cats and kittens combined against the control group mean at each evaluation point will be tested. These pairwise comparisons will be obtained from linear contrasts on the time by treatment group interaction. These interactions will be tested at '=0.05 '. If one or more of the interactions is significant, the treatment means will be graphed over time and 95% confidence intervals will be constructed based on the standard error of the difference between the treated groups and the control group at each time point..."

"If the overall treatment by time interaction is not significant, the treatment main effect will be evaluated. If this term is significant, treatment contrasts comparing control to each dosage level will be tested at the 5% significance level."

"...All data will be subjected to a data review before analysis. This will include a check for missing data, and may include a check for potential outliers and exploratory plots, at the discretion of the Statistician..."

G. DISPOSITION OF ANIMALS

Not stated. According to the OPPTS 870.7200 Guidelines: "Routine sacrifice or necropsy is not required for surviving animals." No animals died in the course of this study.

H. COMPLIANCE

Signed and dated Quality Assurance [p. 4], [No] Data Confidentiality [p. 2], and Good Laboratory Practice (GLP) Compliance [p. 3] Statements were present.

III. RESULTS

A. EXPOSURE LEVELS

The mean doses of dinotefuran were the following: 1X (Group 2): adult males: 63 mg/kg; adult females: 78 mg/kg; kittens (both sexes): 154 mg/kg; 3X (Group 3): adult males: 176 mg/kg; adult females: 233 mg/kg; kittens (both sexes): 436 mg/kg; 5X (Group 4): adult males: 270 mg/kg; adult females: 339 mg/kg; kittens (both sexes): 769 mg/kg.

B. MORTALITY

None of the animals died.

C. CLINICAL SIGNS

From p. 11: "Vomiting, pruritus, abnormal salivation, lethargy, abnormal site of spot-on application and abnormal faeces were the only adverse events observed..."

"There was no evidence of vomiting observed in any of the kittens assigned to any of the groups at any timepoint. Vomiting was observed in one out of eight adult cats assigned to Group 1 (control), three out of eight adult cats assigned to Group 2 (1X), five out of eight adult cats assigned to Group 3 (3X) and three out of eight adult cats assigned to Group 4 (5X)."

"Abnormal faeces were observed in one out of four kittens assigned to Group 1 (control), three out of four kittens assigned to Group 2 (1X), one out of four kittens assigned to Group 3 (3X) and three out of four kittens assigned to Group 4 (5X). Abnormal faeces were observed in four out of eight adult cats assigned to Group 1 (control), six out of eight adult cats assigned to Group 2 (1X), five out of eight adult cats assigned to Group 3 (3X) and three out of eight adult cats assigned to Group 4 (5X)."

From information on p. 51-52 of MRID 46581607 pruritus was observed in only two animals (a 1X kitten and a 5X adult male), one time for each animal, on the day of application. Most subsequent (Day 1 - 14) observations of pruritus occurred in control cats (4/8 adults and 3/4 kittens), although it also was noted in 1/8 adult cats in Group 2 (1X), 1/8 adult cats in Group 3 (3X) and 1/8 adult cats in Group 4 (5X). Pruritus was not observed in kittens in the 1X, 3X or 5X groups in the period from Day 1 to 14. Most observations of pruritus were sporadic one-time occurrences.

From p. 53-54: Vomiting was not observed in any cat or kitten on the day of application, or on Days 1-2. Vomiting was noted for one 5X adult female on Day 3 (A.M. observation), with two occurrences in one adult female in the 1X group on Days 5 and 6 (both were at the P.M. observations). The remaining 6 occurrences involved a female in the control group on Day 13, a male in the 1X group on Day 12, a female in the 1X group on Day 10, two events for a male in the 3X group on Days 10 and 11, and a male in the 5X group on Day 12. These occurrences can be considered to be unrelated to exposure to the test material, as there was no indication of a dose response and there was no occurrence in the period during or immediately following application of the test material.

From p. 55-56: Abnormal salivation was noted in one adult female in the 3X group at 1 hour after the final (third) application and in two adult males in the same group at 3 hours following the final application. It was also observed in one kitten in the control group just before the third treatment. It was not observed in any animal at any time during the subsequent 14-day observation period. While not dose- related, this abnormal salivation must be considered as related to exposure; it may have occurred in response to incidental ingestion (from grooming) or because of the smell of the solvent.

From p. 68: One adult male in the 3X group showed lethargy at the A.M. observation on Day 12.

From p. 75-76: An "abnormal site of spot-on application" was observed in three adult cats in the control group (one of these cats, #16563, a male, showed this effect continuously from pretreatment No. 5 on Day 0 through the P.M. observation on Day 14; a second male, #49264, showed this effect from the A.M. observation on Day 2 through the P.M. observation on Day 5, then again at both observations on Day 7; the third cat, a female, #35587, showed an effect only at the P.M. observation on Day 10), in none of the adult cats in the 1X group, in two of the adult cats in the 3X group, and in 3 adult cats in the 5X group. Only a single kitten (a male in the 5X group) showed this effect (from day 10 through 13).

In response to a request by this reviewer Hartz faxed additional information (copies of daily observations) regarding the effects seen in "abnormal site of spot-on application." This information is summarized in Table 3, below.

TABLE 3. Effects Seen in "Abnormal Site of Spot-On Application."		
Group & Animal #	Days observed	Described Effect in Log
Control adult male #16563	0-14	erythema (sometimes described as "slight" or "mild") at spot- on site days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12; scabs present days 7, 10, 11, alopecia present days 8, 9, 10, 11, 12
Control adult male #49264	2-5; 7	erythema days 2, 3, 4, 5, 7; slight pruritus day 2
Control adult female #35587	10	slight pruritus day 10
3X adult male #80091	3-5; 7	erythema days 3, 4, 5, 7+ some alopecia on day 3
3X adult male #41818	5-8; 10-12	some scabs days 5, 6, 7, 8, 10, 11,12
5X adult male #59859	2-7	slight hair loss or alopecia days 2, 3, 4, 5, 6, 7
5X adult male #19365	3-7	erythema days 3, 4, 5, 6, 7; slight alopecia day 3
5X adult female #57324	8-14	alopecia days 8, 9, 10, 11, 12, 13
5X kitten male #02042	10-12	skin thickened days 10,11, 12

From data p. 75-76 of MRID 46581607.

Control adult female #35587 is reported (p. 76) as having had an abnormal site of spot-on application at the P.M. observation on Day 10. However, the log indicates just slight pruritus (consistent with information on p. 52). Some of the log pages (for days 13-14) are missing, but this is not essential information. Overall, the effects seen are minimal, and are consistent with the cats scratching themselves at the application site.

From p. 97-98: Abnormal faeces ("Loose faeces present") were observed in one adult female at 1X, one adult male at 3X, two adult males at 5X and one kitten at 5X immediately before the first application of test material. They were then observed sporadically in all four groups during the subsequent 14-day observation period, with no indication of a dose-related pattern.

D. BODY WEIGHT AND WEIGHT GAIN

From p. 192: "There was no significant interaction of sex and treatment or sex , treatment and post-treatment day, no significant interaction of treatment and day, and no significant overall treatment effect for kittens, adults or the combined age groups; accordingly, no pairwise comparisons were done." From information on p. 49 all kittens gained or maintained weight in the period from Day 0 to Day 7, and all (except male #95626 at 5X) gained or maintained weight in the period from Day 7 to 14. Male #95626 at 5X gained 0.3 kg in the period from Day 0 to 7, and then lost 0.1 kg from Day 7 to 14. Among adults, a few (female #26878 in the controls, male #80091 at 3X, male #27099 at 3X, female #67379 at 3X, female #02259 at 5X) had slight (0.1-0.2 kg) weight losses in the period from Day 0 to 7.

E. FOOD CONSUMPTION

From information on p. 117, a number of cats showed reduced food consumption values on Day 0. From information on p. 49 these cats were in Set #1; according to p. 39: "...diet was withdrawn in error on Study Day -1 from Set #1 animals." Although cats and kittens of all groups showed reduced food consumption values on Day 1 (which would cover the period from Day 0 to 1) diet had been withdrawn from

Photoperiod: Not specified.
Acclimation period: 15 days.

II. STUDY DESIGN

A. IN LIFE DATES

Start of Dosing: 1 March 2005 (Set 1); 2 March 2005 (Set 2); Last Observational Day: 15 March 2005 (Set 1); 16 March 2005 (Set 2).

B. ANIMAL ASSIGNMENT/ DOSAGE AND ADMINISTRATION

There were a total of 8 (4 males & 4 females) adult cats and 4 kittens (2 males & 2 females) per dosage group. On treatment Day 0 each adult cat or kitten in the [Placebo] Control group (Group 1) was treated with five 1.2 mL applications (spaced at one hour intervals) of the placebo formulation (containing the same "inert" ingredients but lacking the active - Dinotefuran - present in the test substance formulation). Most (weighing $\leq$ 4.0 kg) adult cats and all kittens in the 1X group (Group 2) were treated with a single application of 1.2 mL of the test material containing 15.46% Dinotefuran; one adult male weighing 4.1 kg was treated with a single application of 2.0 mL of the test material. Most ($\leq$ 4.0 kg) cats and all kittens at 3X (Group 3) were treated with 3 applications (spaced at one-hour intervals) of 1.2 mL test material; one adult male weighing 4.3 kg was treated with 3 applications of 2.0 mL. All cats and kittens at 5X (Group 4) were treated with 5 applications (spaced at one-hour intervals) of 1.2 mL test material. The maximum use-application rate of 2.0 mL would involve dosage with 333 mg of the active Dinotefuran.

The site of application was on the mid back area between the shoulders.

these animals between 16:00 and 17:00 on Study Day 0 for fasting purposes prior to blood taking. Similarly reduced food consumption values were observed for Day 7, as diet had been withdrawn from animals on Study Day 6 prior to blood taking on Day 7. No significant or biologically relevant differences were observed between dose groups with respect to food consumption.

TABLE 4. Mean Food Consumption Values (g/animal) for Certain Study Days

Group	g ± S.D.				
	Day -1	Day 0	Day 1	Day 2	Day 7
Control Adult Males	91.5 ± 17.7	76.0 ± 45.4	89.1 ± 14.8	101.8 ± 1.05	87.4 ± 16.6
Control Adult Females	79.8 ± 15.4	53.1 ± 35.6	25.2 ± 11.3	82.8 ± 15.5	51.6 ± 36.6
Control Kittens	330.6 ± 69.4	205.5 ± 151.7	135.4 ± 57.1	389.2 ± 24.8	123.6 ± 101.9
1X Adult Males	99.8 ± 1.7	100.8 ± 1.9	99.8 ± 0.5	102.1 ± 0.9	84.9 ± 32.9
1X Adult Females	70.3 ± 5.3	53.6 ± 33.8	30.9 ± 12.7	79.8 ± 3.5	33.2 ± 18.0
1X Kittens	300.2 ± 41.1	130.9 ± 135.7	84.8 ± 46.4	379.0 ± 25.8	143.5 ± 127.7
3X Adult Males	92.5 ± 13.0	82.3 ± 28.1	89.4 ± 14.8	98.8 ± 6.6	100.5 ± 0.6
3X Adult Females	60.4 ± 31.6	34.5 ± 22.4	29.4 ± 8.8	69.1 ± 23.4	40.6 ± 28.5
3X Kittens	354.7 ± 49.2	219.4 ± 135.1	134.8 ± 40.0	401.3 ± 1.2	176.1 ± 179.2
5X Adult Males	94.5 ± 13.0	84.5 ± 26.3	53.8 ± 31.6	101.9 ± 1.03	87.2 ± 16.7
5X Adult Females	68.1 ± 19.8	36.4 ± 27.9	18.2 ± 23.9	84.9 ± 22.6	49.3 ± 34.5
5X Kittens	333.6 ± 63.7	228.0 ± 190.7	121.6 ± 27.9	402.0 ± 1.2	176.5 ± 85.3

Values calculated from data on p. 117-118 of MRID 46581607

F. HEMATOLOGY

There were no indications of any dose-related effects involving White Blood Cell (WBC) counts [refer to p. 195-197], Red Blood Cell (RBC) counts [refer to p. 197-199], or Hemoglobin (HGB) concentrations [p. 199-202].

For Hematocrit (HCT) percentages [p. 202-204] there appeared to be a statistically significant ($p < 0.05$) overall treatment effect involving lower HCT percentages in the 1X and 5X (but not 3X) adult cat dose groups. Examination of individual HCT data for Study Days 1 and 7 (p. 106 & 107) shows that two female adults at 1X had lower-than-normal HCT values on Day 7 only [#57849: 28.2%; #26517: 27.1%; both also had lower-than-normal RBC counts]; all HCT values for 5X cats on Study Days 1 and 7 were within the reported normal reference range for adults of 29.1- 53.3% [5X: Day 1: 33.2%-44.;9%; Day 7: 31.7%-41,8%]. As all HCT percentages for 5X adult cats (both males and females) on Days 1 and 7 were within the normal range, it is concluded that exposure to the test material had no significant effect on this parameter. There was also no indication of an effect on HCT in the kittens (see p. 109-110; reported normal reference range: 21.6%-35.3%) for either Study Day 1 or 7 (Study Day 1: Control range: 29.1%-32.8%; 1X: 29.9%-34.4%; 3X: 28.7%-36.6%; 5X: 29.5%-31.6%; Study Day 7: Controls: 29.6%-32.2%; 1X: 29.4%- 32.1%; 3X: 28.0%-32.1%; 5X: 27.1%-31.2%).

There were no indications of any dose-related effects involving Mean Corpuscular Volume (MCV) [refer to p. 204-207], or Mean Corpuscular Hemoglobin (MCH) [refer to p. 207-209].

For Mean Corpuscular Hemoglobin Concentration (MCHC) the initial statistical tests

appeared to show a significant overall treatment effect for adult cats alone and for adult cats and kittens combined (but not for kittens alone), but, as noted on p. 209, pairwise comparisons showed no significant effect. Examination of individual adult cat MCHC data for postexposure Study Days 1 and 7 (p. 106 & 107) shows that all animals on both dates from the control and 5X groups were within the laboratory's normal reference range of 30.9-36.3 g/dL; one female in the 1X group had a slightly elevated (38.1 g/dL) value on Day 1 and this female and another in the 1X group had elevated levels (40.5 and 44.4 g/dL) on Day 7. It is concluded that exposure to the test material had no significant effect on this parameter.

There were no indications of any dose-related effects involving percentage of Mature Neutrophils (MN), Band Neutrophil (BN) counts, Lymphocyte (LC) counts, or percentage Monocytes (MC). Refer to p. 212-229 of the report.

For Eosinophils (EP) initial statistical tests appeared to show a significant interaction of treatment, day and sex for kittens. However, pairwise comparisons did not show a dose-related effect (see p. 232-234). An examination of individual data (p. 108-110) indicates most (11/16) of the kittens across all test groups showed elevated EP counts at preexposure (Study Day -14), and the two male kittens of the control group showed elevated levels on both Days 1 and 7. It is concluded that there was no dose-related effect involving this parameter.

For Basophil (BP) counts there was no indication of any dose-related effect (p. 234-237).

For Prothrombin Time (PT) initial statistical tests appeared to show a significant effect of treatment for kittens and adult cats combined (p. 239: "There was a significant ($p<0.05$) effect of treatment for kittens and adult cats combined; the combined age groups treated at 1X and 3X use level had significantly ($p<0.05$) higher Prothrombin time than the controls."). However, pairwise comparisons (Table 120, p. 239) showed no statistically significant effect. From p. 106 and 107, values for all adult cats in the control and 5X groups were within the laboratory's reference range of 9-15 seconds for Study Days 1 and 7; one female adult in the 1X and one female adult in the 3X groups had a slightly elevated PT (16 seconds in both cases) on Day 7. The PT values for all kittens (in all 4 groups) were also within the normal reference range on these dates. It is concluded that there was no dose-related effect involving this parameter.

For Activated Partial Thromboplastin Time (APTT) it is stated (p. 240) that: "There was a significant interaction of sex and treatment, and also a significant overall treatment effect for kittens... There was no other significant interaction of sex and treatment or sex, treatment and post-treatment day, no significant interaction of treatment and day, and no significant overall treatment effect for adults or the combined age groups..." An examination of individual kitten post-treatment APTT values (p. 109-110) shows that except for one kitten (male #16857 in the 3X group) all (including all 4 kittens in the control and 5X groups) had APTT values within the normal range of 12-22 seconds. It is concluded then that there was no dose- related effect involving this parameter.

G. CLINICAL CHEMISTRY

There were no indications of any dose-related effects involving values (IU/L) for

Alanine Aminotransferase (ALT; p. 243-245); values (IU/L) for Aspartate Aminotransferase (AST; p. 245-247); values (mmol/L) for Urea (p. 247-250); values (mg/dL) for Blood Urea Nitrogen (BUN; p. 250-252); values (µmol/L) for Creatinine (CREAT; p. 252-254); values (g/L) for Total Protein (T.PROT; p. 254-257); values (g/L) for Albumin (ALB; p. 257-259); or values (g/L) for Globulin (GL; p. 259-261).

For values (µmol/L) of Total Bilirubin (T.BIL) it is stated (p. 261) that: "There was a significant interaction of sex and treatment for the combined age groups..." However, for pairwise comparisons (see Table 183, p. 264) it is stated: "...however, none of the pairwise comparisons of medicated groups to controls of the same sex were significant ($p>0.05$)." An examination of post-exposure individual data for adult cats (p. 112-113) shows that, with the exception of male #20636 in the 1X group on Day 7, all values were within the laboratory's normal reference range (0-7 µmol/L) on Days 1 and 7. Post-exposure values for kittens (p. 114-115) were, with the exception of male #38377 in the 1X group on Study Day 1, all within the laboratory's normal reference range (0-6 µmol/L). It is concluded that exposure to the test material had no significant effect involving this parameter.

For values (mmol/L) of Glucose (GLU) it is stated (p. 264) that: "There was a significant interaction of sex and treatment of kittens..." Examination of individual kitten data for Days 1 and 7 (p. 115-116) shows that on these dates none of the kittens in any of the 4 groups had a glucose level outside the laboratory's reference range of 4.61 to 10.73 mmol/L; examination of the adult data (p. 112-113) for these dates shows that on Day 1 one male and one female in the 1X group had elevated glucose levels, as did one male in the 3X group (the laboratory's normal reference range for adults is given as 3.25 to 7.09 mmol/L); one male at 1X had an elevated glucose level on Day 7. It is concluded then that exposure to the test material had no significant effect involving glucose levels.

There were no indications of any dose-related effects involving values (mmol/L) for Sodium (Na; p. 267-270).

For values (mmol/L) of Potassium (K) it is stated (p. 270) that: "There was an overall effect of treatment for the combined age groups..." However, for pairwise comparisons (Table 203, p. 272) a dose-response was not evident, although "...animals treated at 3X use level had significantly ($p<0.05$) higher Potassium than the controls, averaged over sex and post-treatment days." Examination of individual adult data for Days 1 and 7 shows that all animals in all 4 groups were within the laboratory's normal reference range of 2.99 to 6.26 mmol/L (the range for Day 1 was 3.56 to 5.13 mmol/L, and for Day 7 was 3.32 to 4.81 mmol/L); for kittens the laboratory's normal reference range is given as 3.56 to 6.91 mmol/L (kitten range for Day 1 was 4.26 to 6.15 mmol/L., and for Day 7 it was 3.67 to 6.46 mmol/L). It is concluded that there were no indications of any biologically relevant effects involving serum potassium levels as a result of treatment/exposure to the test material.

For values (mmol/L) of Chloride (Cl) it is stated (p. 272) that: "There was a significant interaction of sex and treatment for adult cats and the combined age groups..." From p. 275: "Males treated at 1X use level had significantly ($p<0.05$) lower Chloride (mmol/L) than the controls; for females, none of the pairwise comparisons of female medicated groups to the females were significant ($p>0.05$). There was a significant ($p<0.05$) sex-by-treatment interaction for the combined age groups; however, none of the pairwise comparisons of medicated groups to the

controls of the same sex were significant ($p>0.05$)." Examination of individual adult data for Days 1 and 7 shows that, with the exception of a lower value for a 1X male on Day 7, all adults had values that were within the laboratory's normal reference range of 112-127 mmol/L. It is concluded that there were no indications for any biologically relevant effects involving serum Chloride levels as a result of treatment/exposure to the test material.

There were no indications of any dose-related effects involving values (mmol/L) for Calcium (Ca; p. 275-278).

For values (mmol/L) of Phosphorus it is stated (p. 278) that: "There was a significant interaction of sex and treatment, and treatment and day, for the combined age groups..." On p. 280 it is stated: "...however, none of the pairwise comparisons of medicated groups to the controls of the same sex were significant ($p>0.05$). There was a significant ($p<0.05$) treatment-by-day interaction for the combined age groups. Animals treated at 3X use level had significantly ($p<0.05$) lower Phosphorus (mmol/L) on Day than controls; on Day 7, none of the pairwise comparisons of medicated groups to the controls of the same sex were significant ($p>0.05$)." Examination of individual data for adults for Study Days 1 and 7 (p. 112-113) indicates that all values for Phosphorus were within the laboratory's reference range of 0.65-2.69 mmol/L on both occasions. Examination of individual data for kittens for Study Days 1 and 7 (p. 115-116) indicates that all values for serum Phosphorus were within the laboratory's reference range of 1.50-3.52 mmol/L on both occasions. It is concluded that there were no indications for any biologically relevant effects involving serum Phosphorus levels as a result of treatment/exposure to the test material.

For values (IU/L) of Alkaline Phosphatase it is stated (p. 281) that: "There was a significant interaction of treatment and day for kittens... There was a significant overall treatment effect for adult cats..." On p. 283 it is stated: "There was a significant ($p<0.05$) treatment-by-day interaction for kittens; however, none of the pairwise comparisons of medicated groups to controls [on] the same day were significant ($p>0.05$) within day. There was a significant ($p<0.05$) overall treatment effect for adult cats; adult cats treated at 3X use level had significantly ($p<0.05$) lower Alkaline Phosphatase (IU/L) than the controls, averaged over sex and post-treatment day." Examination of individual data for adults for Study Days 1 and 7 (p. 112-113) indicates that all values for Alkaline Phosphatase were within the laboratory's reference range of 10-133 IU/L on both occasions. Examination of individual data for kittens for Study Days 1 and 7 (p. 115-116) indicates that all values for serum Alkaline Phosphatase were within the laboratory's reference range of 36-213 IU/L on both occasions, and there were no marked changes. It is concluded that there were no indications for any biologically relevant effects involving serum Alkaline Phosphatase levels as a result of treatment/exposure to the test material.

There were no indications of any dose-related effects involving values (µmol/L) for Direct Bilirubin (D.BIL; p. 283-284).

H. NECROPSY FINDINGS

As there were no mortalities, no necropsies were necessary.

IV. DISCUSSION

In a companion animal safety study (MRID 46581607) with European mixed-breed cats, 4 groups, each with 8 (4/sex) adult (age: 12-28 months) cats (source: Charles River Laboratories BioLabs Europe's colony at Glenamoy, Ireland; Males: 3.1-4.0 kg; Females: 2.3-3.9 kg) and 4 (2/sex) approximately 12-week old kittens (source: Charles River Laboratories BioLabs Europe's SPF colony at Carrentrila, Ireland; Males: 1.3-1.5 kg; Females: 1.2-1.4 kg) were treated at 0X (5 applications of 1.2 mL of the control item); 1X (1 application each of 1.2 or 2.0 mL, according to the cat's weight, of the test material); 3X (3 applications of 1.2 or 2.0 mL, according to the cat's weight, of the test material); and 5X (Five 1.2 mL applications of the test material). The 1.2 mL applications were made to adult cats and kittens weighing $\leq$ 4.0 kg; the 2.0 mL applications were made to adult cats weighing > 4.0 kg (only 2 adults weighed more than 4.0 kg, male 08010 in the 1X Group, and male 27099 in the 3X group; none of the kittens weighed more than 4.0 kg) somewhat consistent with label directions specifying a single application of 1.2 mL to cats or kittens weighing 9 lbs or less and 2.0 mL to cats or kittens weighing 9 lbs or more. For convenience in dosing, each dose group was subdivided into Sets 1 and 2, with 4 adults (2M, 2F) and 2 kittens (1M, 1F) in each set of each dose group. Set 1 animals were dosed 24 hours before those of Set 2.

The test material was a colorless liquid containing 15.46% S-1638 (Dinotefuran).

Cats receiving more than 1 application had treatments at 1 hour ($\pm$ 5 minutes) intervals. The 1.2 or 2.0 mL dose of test material was applied dorsally to a spot at the base (on the back) of each animal's head using a syringe. Once the control or test item was applied, the cat was held in an upright position for at least 2 minutes to prevent any potential loss (run-off?).
Clinical assessments were carried out on each cat or kitten prior to the first treatment, and at approximately 1, 2, 3 and 4 hours following the last application. Cats receiving more than one application treatment were also evaluated 10 minutes before each treatment.

According to proposed label directions the product would be applied to one spot along the cat's (kitten's) back. This should be revised to state that application should be made at the back of the neck.

Individual body weights were measured on Days -15, -1 (Set 1)/-2 (Set 2), 0, 7 and 14. Individual food consumption was measured on a daily basis for Days -7, -6, -4 and then daily thereafter through Day 14 (values represented the amount of food consumed during the previous 24 hours). Blood samples were taken once pretest (Day -14), 1, 7 and (for WBC counts) on Days 8 or 9 following an overnight fast (except for blood taken for WBC counts).

There was no mortality. Clinical observations seen in one or more groups included abnormal (loose) feces, pruritis, abnormal (excessive?) salivation (seen only in 3 adult cats at the 3X dose level 1-3 hrs after 3 applications), abnormal site of spot-on application and vomiting. The pruritus, salivation, and effects observed at the site of application can be considered as effects of exposure to the test material and/or solvent.

For adult cats of all groups there were reductions in mean food consumption on Days 0 and 1. There was also a reduction for Day 7 (associated with fasting prior to blood taking). The reduction in mean consumption on Day 0 involved cats of Set 1 only, and was probably due to a deviation from the study plan in which diet was erroneously withdrawn on Study Day -1

from these animals. On Day 1 adult cats in the 5X group had a slightly (not statistically significant) lower mean food consumption than adult cats in the other 3 groups (Males: controls: 89.1 g; 1X: 99.8 g; 3 X: 89.4 g; 5X: 53.8 g; Females: controls: 25.2 g; 1X: 30.9 g; 3X: 29.4 g; 5X: 18.2 g).

The site of application was observed to be "abnormal" on a number of occasions for adult cats in the control, 3X and 5X (but not 1X groups), with the following reported incidences: Controls: 3/8; 1X: 0/8; 3X: 2/8; 5X: 3/8. Only one kitten (in the 5X group group) showed a similar effect (from Day 10 to 12). Effects at the site of application were primarily erythema, scabbing and/or alopecia. Cosmetic effects were observed in all cats and kittens, and included matting, spiking, clumping, greasy appearance, discoloration and deposits. The cosmetic effects were gone from all adult cats and 3/4 kittens of the 1X group by Study Day 4, but were more persistent in the other 3 groups (including controls), persisting in some individuals through Day 14.

Overall, adult cats had minor weight changes from preexposure Day -1 or -2 to Day 14 (ranging from a loss of about 0.1 kg to a gain of 0.3 kg), with no indication of any dose-related trend. All kittens showed weight gains (from 0.1 to 0.5 kg during the same interval) with no indication of any dose-related trend or effects.

There was no indication of an effect on any of the hematology or clinical chemistry parameters, and there were no symptoms or other indications of systemic toxicity.

TRB concludes that this companion animal safety study (OPPTS 870.7200) demonstrates an adequate margin of safety (at least 5X) between the exposure associated with most of the proposed use levels for this formulation (1.2 mL for cats weighing $\leq$ 4.0 kg and 2.0 mL for cats weighing $\geq$ 4.0 kg; 1.2 mL for kittens <u>of all weights</u>) and that at which <u>significant</u> systemic effects may occur. It does not support a dose level of 2.0 mL for kittens (which can be considered to be animals of under 6 months of age) $\geq$ 4.0 kg, as kittens of this body weight were not included in this study. Labeling should be revised to specify a dose level of no more than 1.2 mL for kittens of up to 6 months of age.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D318727
2. **PC CODE:** 044312 (Dinotefuran)
3. **CURRENT DATE:** July 22, 2005
4. **TEST MATERIAL:** S1638 (15%) (TS # 12560); a colorless liquid containing 15.46% of the active S-1638, consistent with the proposed product [Hartz Reference 123] with a label declaration of 14.85% Dinotefuran (CAS #165252-70-0) as sole active, and other ingredients at 85.15%.

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion animal/European mixed-breed cats/Charles River BioLabs Europe, Ireland/Study No. USA004\05-001; Hartz Test #1781/7 June 2005	46581607	4 groups of mixed breed European adult cats (8; 4/sex) and 12-week old kittens (4; 2/sex) were treated at 0X (5 1.2 mL applications of formulation without active), 1X (1 application of 1.2 or 2.0 mL - depending on cat's weight - of proposed product), 3X (3 applications of 1.2 or 2.0 mL proposed product) or 5X (5 1.2-mL applications of proposed product). 1.2-mL applications were made to adult cats and kittens weighing ≤4.0 kg; 2.0-mL applications were made to cats ≥4.0 kg (no kittens weighed ≥4.0 kg). Cats/kittens receiving more than one application got them at 1-hr intervals. Application was to a spot at the back of the neck. There was a 14-day post-exposure observation period. There was no mortality. On Day 1 adult cats at 5X had a slightly (not statistically significant)lower mean food consumption than adults in the other 3 groups (control males: 89.1 g; 5X males: 53.8 g; control females: 25.2 g; 5X females: 18.2 g). Clinical observations which can be considered as effects of test material or solvent included pruritus, salivation and effects observed at site of application. Abnormal salivation was seen in one adult female at 3X at 1 hr after the final (3rd) application in two adult males at 3X at 3 hrs after the final application. Effects at application site (erythema, scabbing and/or alopecia) were seen in adult cats with following incidences: 0X: 3/8; 1X: 0/8; 3X: 2/8; 5X: 3/8. Only one 5X kitten showed minor effects at site of application. Adult cats had minor weight changes (from -0.1 kg to +0.3 kg) with no indication of dose-related trend; all kittens showed weight gains (+0.1 to +0.5 kg) in the same interval. There was no indication of an effect on any of the hematology or clinical chemistry parameters, and there were no symptoms of systemic toxicity. Study demonstrates 5X margin of safety for 1.2 mL application to kittens (all weights) and for 1.2 mL and 2.0 mL to cats ≤4.0 kg and ≥4.0 kg respectively.	N/A	Acceptable

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**