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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

January 4, 2011

MEMORANDUM

Subject: Acute Toxicity, Response to Second Rebuttal for Dermal Sensitization
Name of Pesticide Product: CERTIFECT FOR DOGS
EPA Reg. No. /File Symbol: 65331-T
DP Barcode: DP 384819
Decision No.: 423378
Action Code: R320
PC Codes: 129121 (Fipronil: 9.8%)
105402 (S-Methoprene: 8.8%)
106201 (Amitraz: 22.1%)

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

Byron T. Backus
01/04/2011

M Hawkins
Team Leader/Tox

To: Autumn Metzger/John Hebert RM 07
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: MERIAL LIMITED

FORMULATION FROM LABEL:

Side A

Active Ingredient(s):		By wt.
129121 Fipronil		9.8%
105402 (S)-Methoprene		8.8%
Other Ingredient(s):		81.4%
	TOTAL	100.0%

Side B

Active Ingredient(s):		By wt.
106201 Amitraz		22.1%
Other Ingredient(s):		77.9%
	TOTAL	100.0%

"The amount of active ingredients in the total volume is equivalent to 6.4% Fipronil, 5.8% (S)-Methoprene, and 7.6% Amitraz."

ACTION REQUESTED: The Risk Manager requests:

"Please review the following second rebuttal submission addressing acute tox issues for this new spot on product for dogs. The submission should address concerns for it coming up positive as a skin sensitizer

"Please review the submission to determine if this product will be a skin sensitizer on dogs and if the product should be registered.

"Included in this submission are:

-requested efficacy (lab) studies previously cited in first rebuttal (PR&D 0200201 & 0200301)
-field trial studies conducted in EU as previously cited in first rebuttal
-cover letter for field trial studies

"No MRIDs have been provided as of yet. Please review and they will be added after getting through 86-5.

"Please let RD know if they have proved to the Agency that this product will NOT be a skin sensitizer on dogs."

BACKGROUND:

The material received for review includes a 33 page document titled "Analysis of Laboratory and Field Data for Assessing the Dermal Sensitization Potential of CERTIFECT™ for Dogs" which has not yet been assigned an MRID number. As indicated on p. 3 the purpose of this document is to provide a response to EPA's memorandum dated 01 September 10 which included the following statement:

"TRB has serious health concerns for both animals and humans because of the positive dermal sensitization study (MRID 47914233) for this formulation, and the exposure that would be associated with the proposed use (spot-on for dogs). TRB recommends against this registration due to these concerns."

The 33 page document cites three additional documents which are also included in this package (PR&D 0200201: A Study to Evaluate ML-3,481,564 in the Prevention of the Transmission of *Ehrichia canis* (Dumler et al., 2001) from Infected *Rhipicephalus sanguineus* (Latreille, 1806; Acari: Ixopdidae) to Dogs Under Natural Conditions; PR&D 0200301: A Study to Evaluate ML-3,481,564 in the Prevention of the Transmission of *Babesia canis* (Piana & Galli-Valerio, 1895) from Infected *Dermacentor reticulatus* (Fabricius, 1794) to Dogs under Natural Conditions; and PR&D 0196901-12, 14-15: Acceptability of Monthly Topical Treatments with ML-3,481,564 When Administered to Dogs under Field Conditions in the Prevention and/or Treatment of Flea and/or Tick Infestations, which has been assigned MRID# 48321001).

COMMENTS AND RECOMMENDATIONS:

1. The two cited efficacy studies (PR&D 0200201 and PR&D 0200301), while indicating that health observations were conducted following treatments, do not state whether or not these included dermal effect observations. In addition, there is nothing in the reports (including data from individual dogs) relating to the potential (or lack thereof) for dermal sensitization effects.

2. Field trial data (MRID 48321001) indicate there is an acceptably low dermal sensitization risk (maximum of 18/368 [=4.9%] treated dogs showing equivocal but possible dermal sensitization effects following three or fewer treatments). A summarization of Local Tolerance [presumably relating to application site effects] indicates 91.58% of the 368 [or 337/368] had excellent tolerance, 6.52% [24/368] had good tolerance, while 1.90% [7/368] had poor tolerance, but these percentages take into account all dermal effects, and not just those possibly associated with sensitization.

3. TRB concludes that the registrant has adequately addressed the issue of dermal sensitization for this product. However, the registrant should provide information regarding the Treatment Group 2 dog which died (refer to p. 33 of MRID 48321001) in the field conditions study.

Reviewer: Byron T. Backus **Date:** January 3, 2011
Risk Manager (EPA): 10

STUDY TYPE: Companion Animal (Dog) Field Trial [Non-guideline]

TEST MATERIAL: ML-3,481,564 (ML-2,095,988 509T, ML-3,335,716 and ML-3,948,906), formulated as a topical spot-on solution;

CITATION: Dumont, P. & Denton, D.R. (2010). Acceptability of Monthly Topical Treatments with ML-3,481,564 When Administered to Dogs under Field Conditions in the Prevention and/or Treatment of Flea and/or Tick Infestations. Study Numbers PR&D 0196901-12, 14-15. 14 Study Locations in France. 10 December 2010. 36 p. with an additional 14 page appendix. MRID 48321001.

SPONSOR: Merial Limited, 3239 Satellite Blvd., Duluth, GA 30096-4640

EXECUTIVE SUMMARY: For the purposes of this review the emphasis is on dermal effects that were observed, particularly those that suggest or indicate the test material can cause dermal sensitization in dogs.

The study was conducted at 15 sites in France, but data from one site [number 13] was not incorporated into the final report due to lack of investigator compliance and data errors. For the remaining 14 sites, there were 467 [Table 1 on p. 13 indicates 462 dogs] client-owned dogs enrolled, ranging from 9 weeks to 16 years of age and weighing 2.7 to 81.0 kg. On Day 0 dogs were randomly allocated to either Treatment Group 1 or 2 based on order of enrollment and a randomization list; 94 [Table 2 indicates 95] dogs were assigned to Group 1 (Frontline Combo, treatment with ≥6.70 mg fipronil/kg and ≥6.03 mg (S)-methoprene/kg body weight) and 373 [Table 1 on p. 13 indicates 368; Table 2 on pp. 17-31 indicates 376, but some of these were removed from the study] were assigned to Group 2 (ML-3,481,564; treatment ≥6.70 mg fipronil/kg, ≥6.03 mg (S)-methoprene/kg and ≥8.00 mg amitraz/kg body weight). Most dogs received 3 monthly treatments, with a total of 282 [= 3 x 94] treatments for Group 1 and 1096 [slightly less than 3 x 368 = 1104] for Group 2.

Five dogs (all in Group 2) were removed from the study, three by their owners following the second treatment because they were showing application site pruritus, and two 14-year old dogs by the investigator "for age related considerations." It is noted on p. 3 of the report that: "Two cases were incorrectly enrolled, but were excluded from the study before treatment on Day 0" (From p. 25 #2833, a 14-year old dog was removed from the study 4 days after the third treatment; from p. 27 #3022, a 14-year old dog was removed from the study after the second treatment; from p. 21 there is no indication that #2421 or #2434, 14-year old dogs, were removed from the study; from p. 24 there is no indication that #2715, a 14-year old dog, was removed from the study; from p. 29 there is no indication that #3220 or #3228, 14-year old dogs, were removed from the study).

In Treatment Group 1, 52 abnormal health observations were recorded in the course of the study in 32 of 94 dogs and 64 clinical signs were VeDDRA [Veterinary Dictionary for Drug

Regulatory Activities] coded. For Treatment Group 2 there were 255 abnormal health observations in 141 of 368 dogs and 342 clinical signs were VeDDRA coded.

The most common signs in Group 1 were pruritus (2.13%), application site pruritus (1.77%), cough (1.77%), otitis (1.77%), cardiac disorder (1.42%), arthrosis (1.06%), dermatitis and eczema (1.06%), erythema (1.06%), and musculoskeletal disorder (1.06%). The most common signs in Group 2 were lethargy (5.11%), application site pruritus (3.19%), pruritus (3.01%), diarrhea (1.46%) and emesis (1.09%). These percentages were calculated based on the number of documented treatments applied (282 for Group 1 and 1096 for Group 2). Based on these percentages, there were 56 cases of lethargy, 35 cases of application site pruritis, and 33 cases of pruritus in Group 2 animals following 1096 applications [each one of these symptoms may have occurred up to 3 times in any one animal].

One Group 2 dog died (from Table 4, p. 33). No additional details are provided in this report.

A summarization [Table 6, p. 36] of Local Tolerance [presumably relating to application site effects] Scores in Table 6 indicates that for Group 1 95.74% of the 94 [or 90/94] dogs had excellent tolerance, 4.26% [4/90] had good tolerance, and 0.00% [0/94] had poor tolerance. For Group 2 91.58% of the 368 [or 337/368] had excellent tolerance, 6.52% [24/368] had good tolerance, while 1.90% [7/368] had poor tolerance. For systemic tolerance [Table 7, p. 36] 93.62% [88/94] Group 1 dogs had excellent tolerance, 6.38% [6/94] had good tolerance, and 0.00% [0/94] had poor tolerance. For Group 2 86.65% [318/367] had excellent tolerance, 10.35% [38/367] had good tolerance, while 3.00% [11/367] had poor tolerance. It is noted that the basis of the scoring is not provided except (from p. 12): "When investigators reviewed with pet Owners/Designees the tolerance of the products, the following information was consolidated…"

MATERIALS AND METHODS

A. MATERIALS:

1. Test material: ML-3,481,564, containing [from the proposed label] ~6.4% ML-2,095,988 (Fipronil); ~5.8% ML-3,335,716 (S-Methoprene); and ~7.6% ML-3,948,906 (Amitraz).

Batch #: Not stated

Dosages (based on information on p. 13 of MRID 48321001 and from proposed label dated 11/13/09 [taken from review for DP 372058 dated September 22, 2010].

(S=1.07 mL) for dogs up to 10 kg
(M=2.14 mL) for dogs 10.1-20 kg
(L=4.28 mL) for dogs 20.1-40 kg
(XL=6.42 mL) for dogs 40.1-60 kg
(XL+S=6.42 mL+1.07 mL=7.49 mL) for dogs 60.1-70 kg
(XL+M=6.42 mL+2.14 mL=8.56 mL) for dogs 70.1-80 kg
(XL+L=6.42 mL+4.28 mL=10.70 mL) for dogs 80.1-100 kg

2. **Control:** Frontline Combo, treatment with ≥6.70 mg fipronil/kg and ≥6.03 mg (S)-methoprene/kg body weight.

3. **Test animals:**

Species:	Dog
Numbers of Purebreds and Mixed (Group 1)	Purebreds: 69; Mixed: 25; Total: 94
Numbers of Purebreds and Mixed (Group 2)	Purebreds: 275; Mixed: 98; Total: 373
Most Common Purebreds (Group 1):	Shih Tzu: 7; Labrador Retriever: 5; French Bulldog: 5; Beauceron Shepherd: 4; Brittany: 4; Poodle: 3
Most Common Purebreds (Group 2):	Labrador Retriever: 29; French Bulldog: 18; Golden Retriever: 14; Beauceron Shepherd: 13; German Shepherd: 12; Yorkshire Terrier: 12; German Boxer: 10; Wirehaired Dachsund: 10; Jack Russel Terrier: 10; Brittany: 9; Rottweiler: 9
Age/weight at study initiation (Group 1):	0.31-16.0 years [mean: 5.1 years] / 3.5-62.0 kg [mean: 23.0 kg]
Age/weight at study initiation (Group 2):	0.17-16.0 years [mean: 5.2 years] / 2.7-81.0 kg [mean: 22.0 kg]
Source:	Varied (individual owners)

RESULTS AND DISCUSSION:

A. **Mortality:** One Group 2 dog died (from Table 4, p. 33). No additional details are provided in the report.

B. **Dermal observations:** Dermal incidents are reported on pp. 21-33 of the document "Analysis of Laboratory and Field Data for Assessing the Dermal Sensitization Potential of CERTIFECT™ for Dogs" [No MRID assigned as of January 4, 2011]. The most common finding (see table on p. 22) that could be ascribed to the formulation was pruritus at the application site, with 42 occurrences and 23 dogs involved [from the table on pages 23-24 there were 40 occurrences; and 3 of these dogs and 8 occurrences were from site #13 for which data was not incorporated into the final report; interestingly, an additional dog from site #13 had application site serous discharge following treatment #1 and was removed from the study, although it is not clear whether this followed treatment #1 or whether it followed a treatment #2 which did not cause a response]. Eighteen dogs [none from site #13] met the criteria for showing possible dermal sensitization (from p. 14: 11 dogs were observed with dermal findings only after the 3rd dose; 3 dogs had findings only after the 2nd dose and did not receive a 3rd dose; 3 dogs had findings after both the 2nd and 3rd dose; and one dog's reaction was more severe following the 2nd and 3rd dose than after the first dose).

   Other findings reported as being associated with the application site included hair change (6 occurrences, involving 4 dogs), application site lesion (4 occurrences, 2 dogs), and application site dandruff (6 occurrences, 2 dogs). These occurred at low incidences, and are, at most, of minor toxicological significance.

C. **Reviewer's conclusions:** The field trial data (MRID 48321001) indicate there is an acceptably low dermal sensitization risk (maximum of 18/368 [=4.9%] treated dogs showing a possible but equivocal dermal sensitization response following three or fewer treatments). A summarization of Local Tolerance [presumably relating to application site effects]

indicates 91.58% of the 368 [or 337/368] had excellent tolerance, 6.52% [24/368] had good tolerance, while 1.90% [7/368] had poor tolerance. The registrant has adequately addressed the issue of dermal sensitization.

1. **DP BARCODE:** DP 384819
2. **PC CODES:** 129121 (Fipronil); 105402 (S-Methoprene); 106201 (Amitraz)
3. **CURRENT DATE:** January 3, 2011
4. **TEST MATERIAL:** CERTIFECT™ FOR DOGS (65331-T; Fipronil: 6.4%; (S)-Methoprene: 5.8%; Amitraz: 7.6%) [Percentages based on total volume].

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Field Trial / Dog / 14 sites in France / PR&D 0196901-12, 14-15 / Dec. 10 2010	48321001	~368 dogs received 3 treatments at 1X at one month intervals. Most common signs were lethargy (5.11%), application site pruritus (3.19%), pruritus (3.01%), diarrhea (1.46%) and emesis (1.09%). Eighteen (4.9%) of ~368 dogs met the criteria for showing a possible (but equivocal) dermal sensitization response. 1.90% (7/368) had poor tolerance for local effects. Data indicate there is an acceptably low dermal sensitization risk in dogs associated with use exposure to this product.		S

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived