

US EPA ARCHIVE DOCUMENT



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

OFFICE OF CHEMICAL SAFETY  
AND POLLUTION PREVENTION

October 5, 2010

*CA - Dog  
pharmacokinetics*

**MEMORANDUM**

Subject: Name of Pesticide Product: CERTIFECT FOR DOGS  
EPA Reg. No. /File Symbol: 65331-T  
DP Barcode: DP 375363  
Decision No.: 423378  
Action Code: R320  
PC Codes: 129121 (Fipronil); 105402 (S-Methoprene); 106201 (Amitraz)

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

*Byron T. Backus  
Oct - 5 - 2010  
M. H. Ashur*

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

Registrant: Merial Limited

FORMULATION FROM LABEL:

Side A

<u>Active Ingredient(s):</u>	<u>By wt.</u>
129121 Fipronil	9.8%
105402 (S)-Methoprene	8.8%
<u>Other Ingredient(s):</u>	<u>81.4%</u>
TOTAL	100.00%

Side B

<u>Active Ingredient(s):</u>	<u>By wt.</u>
106201 Amitraz	22.1%
<u>Other Ingredient(s):</u>	<u>77.9%</u>
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.”

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**ACTION REQUESTED:** The Risk Manager requests:

“...Please review the following data submission for the newly proposed spot-on for dogs. The formulation is made up of half a currently registered product and half a new product with a new ai, however, the two are separated within the container. The new data submitted does test the entire combined product. Please see the company’s cover letter for more information...”

**BACKGROUND:**

The material received includes a non-guideline study (in MRID 47914238) titled: “A Study to Determine the Pharmacokinetic Profile and Interaction Potential of Three Active Pharmaceutical Ingredients When Topically Administered Alone or in Combinations to Dogs.”

**COMMENTS AND RECOMMENDATIONS:**

1. An Agency contractor, Oak Ridge National Laboratory, conducted the primary review of the non-guideline study in MRID 47914238. TRB and HED conducted the secondary review and made changes as necessary.
2. This study has been classified as **Not Classifiable/Non-Guideline**. It is not necessary for the registrant to address the deficiencies, as this study is not needed to support the registration of 65331-T.

DATA EVALUATION RECORD

FRONTLINE PLUS® (FIPRONIL + S-METHOPRENE) AND AMITRAZ

STUDY TYPE: PHARMACOKINETICS – DOG  
(NONGUIDELINE)  
MRID 47914238

Prepared for

Registration Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
One Potomac Yard  
2777 S. Crystal Drive  
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group  
Environmental Sciences Division  
Oak Ridge National Laboratory  
Oak Ridge, TN 37831

Primary Reviewer:  
Tom C. Marshall, Ph.D., D.A.B.T.

Signature: Robert H. Ross  
for Tom Marshall  
Date: JUL 20 2010

Secondary Reviewers:  
H.T.Borges, Ph.D., MT (ASCP), D.A.B.T.

Signature: Tina Borges  
Date: JUL 20 2010

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross  
Date: JUL 20 2010

Quality Assurance:  
LeeAnn Wilson, M.A.

Signature: L.A. Wilson  
Date: JUL 20 2010

Disclaimer

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

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Secondary Reviewer: Byron T. Backus, Ph.D.  
Technical Review Branch, Registration Division (7505P)

Signature: Byron T. Backus  
Date: Oct - 5 - 2010

EPA Tertiary Reviewer: Kit Farwell, D.V.M.  
Risk Assessment Branch VII, HED (7509P)

Signature: Kit Farwell  
Date: Oct 5 - 2010

Template version 02/06

**DATA EVALUATION RECORD**

**STUDY TYPE:** Pharmacokinetics - Dog; Nonguideline.

**PC CODE:** 105402; 106201; 129121

**DP BARCODE:** 375363

**TEST MATERIAL (PURITY):** Frontline Plus (10% w/v fipronil, 9% w/v S-methoprene), and amitraz (20% w/v)

**SYNONYMS:** Certifect (Frontline Plus combined with amitraz)  
Frontline Plus (ML-2,095,988509T = 10% w/v fipronil, 9% w/v S-methoprene)  
fipronil (ML-2,095,988)  
S-methoprene (ML3,335,716)  
amitraz (ML-3,948,906)

**CITATION:** Letendre, L., J. Blair, J. Prullage (2009). A study to determine the pharmacokinetic profile and interaction potential of three active pharmaceutical ingredients when topically administered alone or in combinations to dogs. Merial Limited, Missouri Research Center, Fulton MO 65251. Project No. 0185901. MRID 47914238. Unpublished.

**SPONSOR:** Merial Limited, 3239 Satellite Blvd., Duluth, GA, USA

**EXECUTIVE SUMMARY:** In a pharmacokinetic study (MRID 47914238), Frontline Plus [10% w/v fipronil, 9% w/v S-methoprene (Batch No. D62705AR)] and/or amitraz [20% w/v (ID No. ML-3,948,909 500 A 001)] were administered topically to groups of six male Beagle dogs (three castrated, three intact) as follows: Group 1) amitraz (8.27 mg/kg body weight); Group 2) Frontline Plus [combination product of the active ingredients fipronil (6.85 mg/kg) and S-methoprene (6.17 mg/kg)]; and Group 3) Frontline Plus [fipronil (6.86 mg/kg); S-methoprene (6.18 mg/kg)] combined with amitraz (8.20 mg/kg). The objective of the study was to determine the pharmacokinetic (P-K) profile and interaction potential of the active ingredients in the three treatments. Blood samples were collected prior to treatment, at 5 and 10 hours post-treatment on day 0, and on days 1, 2, 4, 5, 6, 8, 10, 14, 21, 28, 35, and 42. Urine, feces and expired air were not collected. Plasma concentrations for fipronil, S-methoprene, amitraz and the active metabolite, fipronil sulfone, were determined by HPLC/mass spectrometry. The area under the plasma concentration vs. time curve from time 0 ( $T_0$ ) to the last quantifiable time point ( $AUC_{0-t_{last}}$ ) and terminal plasma half-life ( $T_{1/2}$ ) were calculated for each animal. Maximum plasma

concentration ( $C_{\max}$ ) and time to that observation ( $T_{\max}$ ) were taken as the actual measured peak concentration and its associated sampling time point. The P-K parameters were evaluated by treatment group, and tested for any significant differences.

There were no toxic effects observed in the treated dogs during the study. Amitraz was not detected (LOQ = 1 ng/mL) in most of the plasma samples of Groups 1 and 3, so it was not feasible to produce meaningful statistics on any of the amitraz data. Similarly, plasma concentrations for S-methoprene were below the LOQ (5 ng/mL) for all samples. Dose levels were insufficient to meet the full objectives of the study. The only chemical analytical data usable for P-K analyses were those on fipronil and fipronil sulfone. The P-K parameters for Frontline Plus in Groups 2 and 3, as determined by fipronil concentrations, implied slow absorption and elimination processes with a  $T_{\max}$  of about 5 days for both groups. The  $T_{\max}$  for the metabolite fipronil sulfone was about 21 and 13 days for Groups 2 and 3, respectively.

Fipronil sulfone  $AUC_{0-t_{\text{last}}}$  values were 899 and 946 ngBday/mL in Groups 2 and 3, respectively, while the respective values for fipronil were 351 and 255 ngBday/mL, showing that exposure to fipronil sulfone was about three-fold higher than to fipronil. The  $AUC_{0-t_{\text{last}}}$  data indicate that fipronil was readily metabolized to fipronil sulfone upon absorption and/or was eliminated more slowly. The variability of all P-K parameters was high as indicated by standard deviations that ranged from about 30% to as much as 80% of the mean values. No statistically significant difference was observed between Groups 2 and 3 for any of the P-K parameters, giving the impression that the combination of amitraz with Frontline Plus does not statistically affect the kinetics of fipronil.

The data show no statistically significant effect on the P-K parameters of fipronil when Frontline Plus is combined with amitraz and administered topically to dogs. The data suggest that the simultaneous administration of Frontline Plus and amitraz does not markedly facilitate the absorption of amitraz. However, the absorption of amitraz may be inhibited by Frontline Plus as 5/6 dogs from Group 1 (administered amitraz alone) had one or two quantifiable concentrations of amitraz, while only 1/6 dogs from Group 3 (administered amitraz and Frontline Plus) had a quantifiable concentration of amitraz. In both cases the data are inconclusive due to sparseness.

This pharmacokinetic study is classified **Not Classifiable/Non-guideline**. It is not necessary for the registrant to address the deficiencies, as this study is not needed to support the registration of 65331-T.

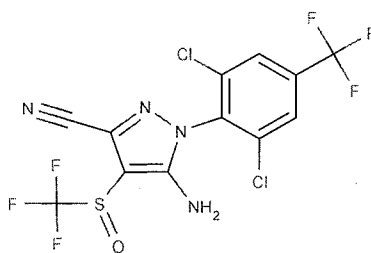
**COMPLIANCE:** Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

## I. MATERIALS AND METHODS

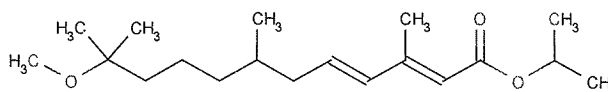
A. MATERIALS:1. Test compound:

Radiolabeled test material: None  
 Radiochemical purity:  
 Specific activity:  
 Lot/batch #:

Non-Radiolabeled test material: Frontline Plus  
 Description: Not described  
 Lot/batch #: D62705AR  
 Purity: 10% w/v fipronil, 9% w/v S-methoprene  
 Contaminants: Not reported  
 CAS # of TGAI: See below  
 Structure:

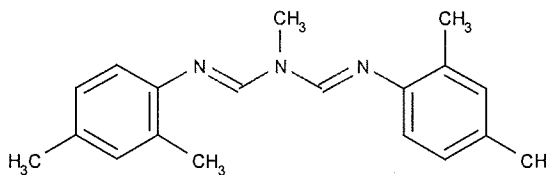


fipronil (CAS# 120068-37-3)



S-methoprene (CAS# 65733-16-6)

Non-Radiolabeled test material: Amitraz  
 Description: Not described  
 Lot/batch #: Not reported  
 Purity: 20% w/v  
 Contaminants: Not reported  
 CAS # of TGAI: 33089-61-1  
 Structure:



2. **Vehicle:** Not provided

3. **Test animals:**

<b>Species:</b>	Dog	
<b>Strain:</b>	Beagle	
<b>Age/weight at study initiation:</b>	22.4 – 119.6 months/8 - 20 kg	
<b>Source:</b>	MRC colony	
<b>Housing:</b>	Individually in stainless steel cages (0.83 M <sup>2</sup> ) that allowed for rear-flush excreta collection	
<b>Diet:</b>	Science Diet Active Adult, 150 – 200 g/day	
<b>Water:</b>	On-site well, <i>ad libitum</i>	
<b>Environmental conditions:</b>	<b>Temperature:</b>	Not reported
	<b>Humidity:</b>	Not reported
	<b>Air changes:</b>	Not reported
	<b>Photoperiod:</b>	Not reported
<b>Acclimation period:</b>	>7 days	

4. **Preparation of dosing solutions:** The formulations were prepared by the Sponsor, shipped to the Merial Limited Missouri Research Center, and stored at room temperature. The amitraz sample "expired" in April 2009, about 4 months prior to dosing on September 4, 2009. The test substances were assayed for concentration by the Sponsor and Certificates of Analysis provided to the laboratory, where the results were considered "acceptable" but no details were provided. The Certificates of Analysis were not provided in the Study Report.

**B. STUDY DESIGN AND METHODS:**

1. **Study Objective:** The objective of the study was to determine the pharmacokinetic (P-K) profile and interaction potential of the active ingredients of Certifect, which are fipronil, S-methoprene, and amitraz. The active metabolite of fipronil, fipronil sulfone, was also evaluated. Potential pharmacokinetic interactions were assessed by comparing the plasma concentrations and/or P-K parameters from three topical treatments in dogs: 1) Frontline Plus (combination product of the active ingredients fipronil and S-methoprene); 2) amitraz; and 3) Frontline Plus combined with amitraz.
  
2. **Group arrangements:** Animals were assigned to the test groups noted in Table 1 using a randomized block design based upon body weight. Body weight on day -10 ranged from 9.8 to 17.6 kg, but body weight "rounded to the nearest whole kg" on day 0 ranged from 8 to 20 kg. These values imply a marked weight shift of ±2 kg over a 10-day period prior to dosing which was unexplained. Individual animal weights for day 0 were not given by dog identification numbers (a discrepancy of Study Report Table 2) to determine how many and which dogs were affected by this body weight change. No body weights were provided for the end of the 42-day experimental period. The average age of the castrated males was 28.2 months, while for the intact males the average was 92.6, a three-fold difference.



Test group	Dose of material (mg/kg)	Number/sex	Remarks
Group 1: Amitraz	8.27	3 intact males 3 castrated males	Blood collected at 5 and 10 hours following topical administration on day 0 and on days 1, 2, 4, 5, 6, 8, 10, 14, 21, 28, 35, 42. Animals were not sacrificed
Group 2: Frontline Plus <sup>b</sup>	Fipronil: 6.85 S-methoprene: 6.17	3 intact males 3 castrated males	Blood collected at 5 and 10 hours following topical administration on day 0 and on days 1, 2, 4, 5, 6, 8, 10, 14, 21, 28, 35, 42. Animals were not sacrificed
Group 3: Amitraz & Frontline Plus <sup>b</sup>	Fipronil: 6.86 S-methoprene: 6.18 Amitraz: 8.20	3 intact males 3 castrated males	Blood collected at 5 and 10 hours following topical administration on day 0 and on days 1, 2, 4, 5, 6, 8, 10, 14, 21, 28, 35, 42. Animals were not sacrificed

<sup>a</sup> Information taken from Table 2, p.20, in MRID 47914238.

<sup>b</sup> Frontline Plus is a mixture of 10% w/v fipronil, 9% w/v S-methoprene.

3. **Dosing and sample collection:** Frontline Plus (10% w/v fipronil, 9% w/v S-methoprene) and/or amitraz (20% w/v) were administered topically to three intact male Beagle dogs and three castrated male Beagle dogs per experimental group as shown in Table 1. The dosing formulations were used exactly as supplied by the Sponsor. The sample volumes ranged from 0.40 to 1.21 mL/kg body weight. Doses were administered by parting the hair and applying a single dose of the appropriate treatment directly onto the skin using a 1 mL tuberculin syringe. All treatments were divided into two equal volumes and applied to two separate spots on the dorsal midline of the neck. Blood samples were collected in heparinized tubes from the jugular vein.
- Pharmacokinetic studies:** Blood samples were collected in heparinized tubes from the jugular vein prior to treatment (day -10), at 5 and 10 hours post-treatment on day 0, and on days 1, 2, 4, 5, 6, 8, 10, 14, 21, 28, 35, and 42. The samples were centrifuged and the plasma frozen until analyzed. Urine, feces and expired air were not collected, and neither were the animals terminated or tissues collected.
  - Metabolite characterization studies:** The active metabolite of fipronil, fipronil sulfone, was quantified in plasma as described below. No other metabolite characterization was performed.
  - Analytical techniques:** Plasma concentrations for fipronil, S-methoprene, amitraz and the active metabolite, fipronil sulfone, were determined by reverse-phase HPLC with tandem mass spectrometry detection. The method was validated for biological media and reported separately (MRID 47914239). The lower limit of quantitation was 1 ng/mL for fipronil and amitraz, and 5 ng/mL for S-methoprene.
4. **Data Analysis and Statistics:** The area under the plasma concentration vs. time curve from time 0 ( $T_0$ ) to the last quantifiable time point ( $AUC_{0-t_{last}}$ ) was determined for each animal and

each active ingredient administered using the log down trapezoid method. The AUC was extrapolated to infinity ( $AUC_{0-\infty}$ ) using the first order rate constant ( $\lambda_z$ ) associated with the log-linear portion of the curve. The terminal plasma half-life ( $T_{1/2}$ ) for each animal was calculated ( $\ln 2/\lambda_z$ ), but  $C_{max}$  and  $T_{max}$  were taken as the actual measured peak concentration and its associated sampling time point. The P-K parameters were averaged by treatment. A two-sided Student's T-test was used to determine if a significant difference was observed between each P-K parameter among the treatment groups. This test was adequate for the design of the study.

## II. RESULTS:

### A. PHARMACOKINETIC STUDIES:

1. **Preliminary experiment:** None reported.
2. **Plasma pharmacokinetics:** There were no toxic effects observed in the treated dogs during the course of the study. Pharmacokinetic parameters for plasma concentrations of amitraz (Group 1), Frontline Plus (Group 2), and Frontline Plus combined with amitraz (Group 3) following a single topical administration are shown in Table 2. The analogous parameters for fipronil sulfone are shown in Table 3. Amitraz was not detected (LOQ = 1 ng/mL) in most of the plasma samples of Groups 1 and 3, so it was not feasible to produce meaningful statistics on any of the amitraz data. Four of six dogs from Group 1 had quantifiable concentrations of amitraz in the two samples taken on Day 0 (of 42), and only the very first sample was quantifiable in one of six dogs from Group 3. The study design was insufficient to meet the study objectives related to any effect on the kinetics of amitraz. Apparently amitraz is not readily absorbed or its chemical integrity is altered on the skin prior to absorption. Similarly, plasma concentrations for S-methoprene, one component of Frontline Plus, were below the LOQ (5 ng/mL) for all samples in Groups 2 and 3. Therefore, the only chemical analytical data in the study usable for P-K analyses were those on fipronil and fipronil sulfone.

The P-K parameters for Frontline Plus in Groups 2 and 3, as determined by fipronil plasma concentrations, imply slow absorption and elimination processes with a  $T_{max}$  of about 5 days for both groups (Table 2). The  $T_{max}$  for the metabolite fipronil sulfone was about 21 and 13 days for Groups 2 and 3, respectively. Exposure to fipronil sulfone was about three-fold higher than fipronil as demonstrated by fipronil sulfone  $AUC_{0-tlast}$  values of 899 and 946 ngBday/mL in Groups 2 and 3, respectively, compared to  $AUC_{0-tlast}$  values of 351 and 255 ngBday/mL for fipronil. The data indicate that fipronil is readily metabolized to fipronil sulphone upon absorption and/or is eliminated more slowly. The variability of all P-K parameters was high as indicated by standard deviations that ranged from about 30% to as much as 80% of the mean values. More variability is expected with topical administration and small treatment groups. No statistically significant difference was observed between Groups 2 and 3 for any of the P-K parameters. The data indicate that the combination of amitraz with Frontline Plus does not statistically affect the kinetics of fipronil. No conclusions can be drawn on a potential effect of amitraz on S-methoprene PK parameters, or any potential effect of Frontline Plus on the kinetics of amitraz. Oddly, plasma samples from five dogs in Group 1 (amitraz only) had quantifiable concentrations of fipronil ranging from

1.0 to 1.6 ng/mL (three dogs on day 8, one on day 14, one on day 21). The sporadic nature of this problem suggests some form of exposure or instrument cross-contamination which raises uncertainty regarding the quality of all measured fipronil concentrations.

Test group	C <sub>max</sub> <sup>b</sup> (ng/mL)	T <sub>max</sub> <sup>b</sup> (days)	Terminal T <sub>1/2</sub> (days)	AUC <sub>0-tlast</sub> (ngBday/mL)	AUC <sub>0-∞</sub> (ngBday/mL)
Group 1: Amitraz	ND	ND	ND	ND	ND
Group 2: Frontline Plus <sup>c</sup>	23.8±8.3	5.1±2.3	8.7±3.7	351±112	372±119
Group 3: Amitraz + Frontline Plus <sup>c</sup>	19.3±9.1	5.0±2.8	11.3±8.4	255±110	281±110

<sup>a</sup> Data are the mean and standard deviation taken from Table 3, pp.21, MRID 47914238.

<sup>b</sup> C<sub>max</sub> and T<sub>max</sub> are the actual measured peak concentration and its associated sampling time point, respectively.

<sup>c</sup> Values are fipronil data only, as S-methoprene and amitraz were below the level of quantitation.

ND = Not determined since most plasma concentrations were below the level of quantitation.

Test group	C <sub>max</sub> <sup>b</sup> (ng/mL)	T <sub>max</sub> (days)	Terminal T <sub>1/2</sub> (days)	AUC <sub>0-tlast</sub> (ngBday/mL)
Group 2: Frontline Plus <sup>b</sup>	31.2±14.9	20.8±12.8	41.4±33.3	899±493
Group 3: Amitraz + Frontline Plus <sup>b</sup>	37.7±14.3	13.0±6.3	31.3±11.9	946±254

<sup>a</sup> Data are the mean and standard deviation taken from Table 4, pp.22, MRID 47914238.

<sup>b</sup> Values are fipronil data only, as S-methoprene and amitraz were below the level of quantitation.

## **B. METABOLITE CHARACTERIZATION STUDIES:**

The active metabolite of fipronil, fipronil sulfone, was quantified in plasma as discussed above. No other metabolite characterization was performed.

## **III. DISCUSSION AND CONCLUSIONS:**

**A. INVESTIGATORS' CONCLUSIONS:** The investigators' concluded that the P-K parameters of all the active pharmaceutical ingredients were not altered by simultaneous topical administration to dogs.

**B. REVIEWER COMMENTS:** An all-encompassing conclusion that the P-K parameters of all the active pharmaceutical ingredients were not altered by their simultaneous topical administration cannot be reached because the only analytical data from the study that were sufficient for P-K analyses were those on fipronil and its active metabolite fipronil sulfone. Plasma concentrations of the other active ingredients were measureable in only 9/168 samples obtained from amitraz-treated dogs and 0/168 samples obtained from S-methoprene-treated dogs. The data show no statistically significant effect on the P-K parameters of fipronil when Frontline Plus is combined with amitraz and administered topically to dogs. The data suggest that the simultaneous administration of Frontline Plus and amitraz does not markedly facilitate the absorption of amitraz. However, the absorption of amitraz may be inhibited by Frontline Plus as 5/6 dogs from Group 1 (administered amitraz alone) had one or

two quantifiable concentrations of amitraz, while only 1/6 dogs from Group 3 (administered amitraz and Frontline Plus) had a quantifiable concentration of amitraz. In both cases the data are inconclusive due to sparseness.

This pharmacokinetic study is classified **Not Classifiable/Non-guideline**. It is not necessary for the registrant to address the deficiencies indicated below, as this study is not needed to support the registration of 65331-T.

**C. STUDY DEFICIENCIES:** The following deficiencies were identified.

1. The use of radiolabeled test materials would have been helpful.
2. Exposure and/or instrument cross-contamination of plasma from Group 1 dogs treated only with amitraz raises uncertainty regarding the quality of all measured fipronil concentrations.
3. The amitraz sample was labeled "expired April 2009", about 4 months prior to dosing on September 4, 2009. Certificates of Analysis should correct this deficiency, if the detailed findings of the analyses are provided. Otherwise, the reviewer is unable to validate the acceptability of the batch used in this study.
4. Reference to other P-K/metabolism studies would likely support conclusions regarding absorption of the active ingredients.
5. Product recovery data from treated skin, if available, would likely support conclusions regarding absorption of the active ingredients.
6. The body weight discrepancy between Study Report Table 2 and the Appendix 2 table needs to be corrected.
7. Table 2 needs to have the body weight on day 0, not day-10, and the dose calculations corrected, if necessary, depending on the resolution of Item 8.
8. The vehicle in the dosing preparations was not identified. The active ingredients were a minor percentage of the material applied and the vehicle(s) could have had an effect upon the PK parameters.

1. **DP BARCODE:** DP 375363
2. **PC CODES:** 129121 (Fipronil); 105402 (S-Methoprene); 106201 (Amitraz)
3. **CURRENT DATE:** October 5, 2010
4. **TEST MATERIAL:** CERTIFECT<sup>®</sup> for Dogs: 62.6% by weight ML-2,095,988 509T [a clear, colorless liquid, specific gravity = 1.019 g/mL, assaying 9.99% (w/v) Fipronil and 8.97% (w/v) S-Methoprene] and 37.4% by weight ML-3,948,906 [a pale yellow liquid, specific gravity = 0.9044 g/mL, assaying 22.12-22.67% Amitraz].

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Pharmacokinetic profile and interaction potential of Fipronil, S-Methoprene combination with Amitraz/adult dog  Merial Limited Missouri Research Center, Fulton MO 65251  Study No. PR&D 0185901 / June 4 2009	47914238	Topical administration to male beagles: no toxic effects observed. Only chemical data usable for P-K analyses were those on fipronil and fipronil sulfone. There was slow absorption and elimination processes, with a T <sub>max</sub> of about 5 days for both groups. Data indicated fipronil was readily metabolized to fipronil sulfone upon absorption and/or was eliminated more slowly. No conclusions can be drawn on the potential of amitraz to affect S-methoprene P-K parameters, or for Frontline Plus to affect the kinetics of amitraz.	N/A	Not Classifiable

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