

US EPA ARCHIVE DOCUMENT



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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

29/DEC/2004

MEMORANDUM

Subject: Name of Pesticide Product: Promeris Spot On for Dogs
EPA Reg. No. /File Symbol: 80490-E
DP Barcode: D311471
Decision No: 351841
PC Codes: 106201, 281251/281250

From: Eugenia McAndrew, Biologist *EM*
Technical Review Branch
Registration Division (7505C)

To: Ann Hanger, RM Team 07
Insecticide-Rodenticide Branch
Registration Division (7505C)

Applicant: Fort Dodge Animal Health
P.O. Box 5366
Princeton, NJ 08543-5366

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>		<u>% by wt.</u>
106201	Amitraz	14.34
281250/281251	Metaflumizone	14.34
<u>Inert Ingredient(s):</u>		<u>71.32</u>
Total:		100.00%

ACTION REQUESTED: RM requests review of acute toxicity data for Promeris Spot On for Dogs, EPA File Symbol 80490-E.

BACKGROUND: Fort Dodge Animal Health has submitted a six pack of acute toxicity studies in support of registration of a new flea and tick end use product, Promeris Spot On for Dogs, EPA File Symbol 80490-E. The studies were conducted at MB Research Laboratories, Spinnerstown, PA with assigned MRID numbers 463958-05 to -10.

RECOMMENDATIONS: The six studies have been reviewed and classified as acceptable.

The acute toxicity profile for Promeris Spot On for Dogs, EPA File Symbol 80490-E, is as follows:

acute oral toxicity ^a	III	Acceptable	MRID 46395805
acute dermal toxicity	IV	Acceptable	MRID 46395806
acute inhalation toxicity	III	Acceptable	MRID 46395807
primary eye irritation	IV	Acceptable	MRID 46395808
primary skin irritation	IV	Acceptable	MRID 46395809
dermal sensitization	Positive	Acceptable	MRID 46395810

^a The incorrect protocol (OECD 401: Acute Oral LD₅₀) was used for this test. Although we accepted the study in this case, our guidance is that OECD 401 is an unacceptable protocol. Please inform the Registrant that the preferred protocol is OECD 425: Acute Oral Toxicity Up and Down Procedure.

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

PRODUCT ID #: 080490-00002

PRODUCT NAME: Promeris Spot On for Dogs

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: CAUTION

Harmful if inhaled. Harmful if swallowed. Avoid breathing spray mist. Remove and wash contaminated clothing before reuse. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

First Aid:

If inhaled:

-Move the person to fresh air.

-If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.

-Call a poison control center or doctor for further treatment advice.

If swallowed:

- Call a poison control center or doctor immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to by a poison control center or doctor.
- Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Acute Oral Toxicity - S-D Rat; OPPTS 870.1100; OECD 401

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Cerven, D. 15% w/v R-28153/15% w/v amitraz spot-on. Acute Oral Toxicity/LD₅₀ in Rats. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.01. February 18, 2004. MRID 46395805. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46395805), five/sex Wistar young adult albino rats (226-266 g males and 200-222 g females) were given a single oral dose of 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid) at an initial dose of 5000 mg/kg. Based on the results of the initial dose, an additional group of five males and five females were dosed at 500 mg/kg. Animals were then observed for 14 days.

Oral LD₅₀ Males = > 500 and < 5000 mg/kg
Oral LD₅₀ Females = > 500 and < 5000 mg/kg
Oral LD₅₀ Combined = > 500 and < 5000 mg/kg

All animals survived the 500 mg/kg dose and gained weight. Clinical signs noted included lethargy, chromorrhinorrhea, sagging eyelids, wet anogenital area, hunched posture and red staining of nose/mouth area. The animals recovered from these symptoms by day 4. Necropsy results were normal. Seven animals died by day 3 at the 5000 mg/kg dose. Toxic signs noted prior to death included lethargy, sagging eyelids, prostration, few feces, flaccid muscle tone, ataxia, coma, excess lacrimation and red staining of the nose/mouth area. The surviving animals exhibited lethargy, few feces, emaciated appearance, sagging eyelids, chromodaccryorrhea, soiled anogenital area, vocalization when handled, excess lacrimation and red staining of the nose/mouth area. The three survivors gained weight by the end of the study. Necropsy results were normal.

Toxicity based on the lack of death at the limit dose of 500 mg/kg. EPA Toxicity Category III.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 401) in the rat.

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

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	2/5	5/5	7/10
500	0/5	0/5	0/10

A. Mortality - as noted in table.

B. Clinical observations - All animals survived the 500 mg/kg dose and gained weight. Clinical signs noted included lethargy, chromorhinorrhea, sagging eyelids, wet anogenital area, hunched posture and red staining of nose/mouth area. The animals recovered from these symptoms by day 4. Necropsy results were normal. Seven animals died by day 3 at the 5000 mg/kg dose. Toxic signs noted prior to death included lethargy, sagging eyelids, prostration, few feces, flaccid muscle tone, ataxia, coma, excess lacrimation and red staining of the nose/mouth area. The surviving animals exhibited lethargy, few feces, emaciated appearance, sagging eyelids, chromodaccryorrhea, soiled anogenital area, vocalization when handled, excess lacrimation and red staining of the nose/mouth area. The three survivors gained weight by the end of the study.

C. Gross Necropsy - Necropsy results for the animals dosed at 500 mg/kg and for the survivors dosed at 5000 mg/kg were normal. Necropsy of the decedents dosed at 5000 mg/kg revealed abnormalities of the lungs, thymus, liver, urinary bladder and gastrontestinal tract.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Acute Dermal Toxicity - S-D Rabbit; OPPTS 870.1200; OECD 402

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Cerven, D. 15% w/v R-28153/15% w/v amitraz spot-on. Acute Dermal Toxicity/LD₅₀ in Rats. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.02. February 18, 2004. MRID 46395806. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46395806), five/sex of New Zealand White young adult rabbits (Source: Millbrook Breeding Labs, Amherst, MA; 2.1-2.7 kg males and 2.1-2.5 kg females) were dermally exposed to 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid) applied to approximately 10% of body surface area at a dose of 5000 mg/kg. Test sites were covered with a gauze patch and wrapped with plastic sheeting in a semi-occlusive manner and secured with tape for a 24 hours period. Animals were then observed for 14 days.

Dermal LD₅₀ Males => 5000 mg/kg
Dermal LD₅₀ Females => 5000 mg/kg
Dermal LD₅₀ Combined => 5000 mg/kg

One female died on day 4. Toxic signs noted prior to death were lethargy and few feces. Clinical signs noted in the other nine animals included few feces, lethargy, ataxia, sagging eyelids, flaccid muscle tone, diarrhea and emaciation. Very slight erythema was noted at three test sites at the 24 hour observation. Body weight changes were normal in 6/9 survivors. Necropsy results of the decedent revealed abnormalities of the lungs, treated skin, liver, intestines, spleen and kidneys, excess fluid in the pleural cavity, red fluid from the nose/mouth area, stomach distended with gas and soiling of the anogenital area. Necropsy results were normal in the survivors.

Toxicity based on one death at the limit dose. EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rabbit.

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

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	1/5	1/10

A. Mortality - as noted in table.

B. Clinical observations - One female died on day 4. Toxic signs noted prior to death were lethargy and few feces. Clinical signs noted in the other nine animals included few feces, lethargy, ataxia, sagging eyelids, flaccid muscle tone, diarrhea and emaciation. Very slight erythema was noted at three sites at the 24 hour observation. Body weight changes were normal in 6/9 survivors.

C. Gross Necropsy - Necropsy results of the decedent revealed abnormalities of the lungs, treated skin, liver, intestines, spleen and kidneys, excess fluid in the pleural cavity, red fluid from the nose/mouth area, stomach distended with gas and soiling of the anogenital area. Necropsy results were normal in the survivors.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Acute Inhalation Toxicity -S-D rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Cerven, D. 15% w/v R-28153/15% w/v amitraz spot-on. Acute Inhalation Toxicity/LC₅₀ in Rats. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.05. February 18, 2004. MRID 46395807. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46395807), five/sex of Wistar young adult albino rats (Source: Ace Animals, Inc., Boyertown, PA; 274-384 g males and 203-239 g females) were exposed nose only via the inhalation route to 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid) for 4 hours at a concentration of 2.32 mg/L. Based on the results of the first dose, an additional group of five male and five female rats were exposed to a concentration of 0.57 mg/L. Animals were then observed for up to 20 days.

LC₅₀ Males = > 0.57 and < 2.32 mg/L
LC₅₀ Females = > 0.57 and < 2.32 mg/L
LC₅₀ Combined = > 0.57 and < 2.32 mg/L

All animals survived at 0.57 mg/L. Clinical signs noted during the exposure included dyspnea, sagging eyelids, closed eyes, wetness of the nose/mouth area, hunched posture, coating of the fur with test article and abnormal licking. Lethargy, sagging eyelids, few feces, chromorrhinorrhea, soiling of the anogenital area, chromodacryorrhea, wetness of the anogenital area, red staining of the abdomen, emaciation, dyspnea, piloerection, tremors, tachypnea, red staining of the nose/mouth area, piloerection, excess lacrimation, crusting around the eye, unkempt appearance, ocular discharge and crusting, hunched posture, brown staining of the nose/mouth area, vocalization when handled and localized alopecia. Some animals lost weight during the first 14 days but all animals gained weight by day 14. Necropsy results were normal in 7/10 animals. Localized alopecia and/or soiling of the anogenital area were noted in three animals. At the 2.32 mg/L dose, 8/10 animals died by day 3. Toxic signs noted prior to death included dyspnea, lethargy, sagging eyelids, chromodacryorrhea, flaccid muscle tone, prostration, few feces, negative righting reflex, ataxia, tremors, wet and soiled anogenital area, closed eyes, wetness and red staining of the nose/mouth area, coating of the fur with test article, excess lacrimation and crusting around the eye, unkempt appearance, abnormal licking, hunched posture, opaque eyes and wetness of the body. Necropsy revealed abnormalities of the lungs, thymus, eyes, liver, urinary bladder and gastrointestinal tract, chromodacryorrhea, red staining of the nose/mouth area, brown staining of the anogenital area and soiling of the anogenital area. Clinical signs noted in the surviving animals included dyspnea, lethargy, sagging eyelids, wet and soiled anogenital area, chromodacryorrhea,

chromorhinorrhea, closed eyes, red staining and wetness of the nose/mouth area, unkempt appearance, fur coated with test article, appears to be licking inside of mouth, red staining of front paws, vocalization and abnormal response when handled. The surviving animals lost weight during the first 14 days. The observations were extended to day 20 at which time the survivors gained weight. Necropsy results of the survivors were normal. The gravimetric concentrations were 0.57 mg/L and 2.32 mg/L. The mass median aerodynamic diameter was 1.03-1.05 μ with a geometric standard deviation of 2.09 - 2.97.

Toxicity based lack of deaths at the limit dose of 0.57 mg/L. EPA Toxicity Category III.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

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

RESULTS and DISCUSSION:

Nominal Concentration (mg/L)	Gravimetric Concentration (mg/L)	MMAD μm	GSD μm	Mortality/Number Tested		
				Males	Females	Combined
not reported	0.57	1.03	2.97	0/5	0/5	0/10
not reported	2.32	1.05	2.09	3/5	5/5	8/10

Test Atmosphere / Chamber Description:

Chamber 57 L
Volume:
Airflow: 18 LPM
Temperature: 20-23°C
Relative 29-59%
Humidity:
Time to not reported
Equilibrium:

A. Mortality - as noted in table.

B. Clinical observations - All animals survived at 0.57 mg/L. Clinical signs noted during the exposure included dyspnea, sagging eyelids, closed eyes, wetness of the nose/mouth area, hunched posture, coating of the fur with test article and abnormal licking. Lethargy, sagging eyelids, few feces, chromorhinorrhea, soiling of the anogenital area, chromodacryorrhea, wetness of the anogenital area, red staining of the abdomen, emaciation, dyspnea, piloerection, tremors, tachypnea, red staining of the nose/mouth area, piloerection, excess lacrimation, crusting around the eye, unkempt appearance, ocular discharge and crusting, hunched posture, brown staining of the nose/mouth area, vocalization when handled and localized alopecia. Some animals lost weight during the first 14 days but all animals gained weight by day 14. At the 2.32 mg/L dose, 8/10 animals died by day 3. Toxic signs noted prior to death included dyspnea, lethargy, sagging eyelids, chromodacryorrhea, flaccid muscle tone, prostration, few feces, negative righting reflex, ataxia, tremors, wet and soiled anogenital area, closed eyes, wetness and red staining of the nose/mouth area, coating of the fur with test article, excess lacrimation and crusting around the eye, unkempt appearance, abnormal licking, hunched posture, opaque eyes and wetness of the body. Clinical signs noted in the surviving animals included dyspnea, lethargy, sagging eyelids, wet and soiled anogenital area, chromodacryorrhea, chromorhinorrhea, closed eyes, red staining and wetness of the nose/mouth area, unkempt appearance, fur coated with test article, appears to be licking inside of mouth, red staining of front paws, vocalization and abnormal response when handled. The surviving animals lost weight during the first 14 days. The observations were extended to day 20 at which time the survivors gained weight.

C. Gross Necropsy - At the 0.57 mg/L dose, necropsy results were normal in 7/10 animals. Localized alopecia and/or soiling of the anogenital area were noted in three animals. At the 2.32 mg/L dose, necropsy results of the survivors were normal. Necropsy of the decedents revealed abnormalities of the lungs, thymus, eyes, liver, urinary bladder and gastrointestinal tract, chromodacryorrhea, red staining of the nose/mouth area, brown staining of the anogenital area and soiling of the anogenital area.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Primary Eye Irritation - NW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Cerven, D. 15% w/v R-28153/15% w/v amitraz spot-on. Acute Eye Irritation in Rabbits. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.04. February 18, 2004. MRID 46395808. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46395808), 0.1 mL of 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid) was instilled into the conjunctival sac of the right eye of three young adult New Zealand albino rabbits (2 male and 1 female; Source: Millbrook Breeding Labs, Amherst, MA). Animals were then observed at 1, 24, 48, and 72 hours and on day 7 post-instillation. Irritation was scored by the method of Draize.

In this study, formulation is slightly irritating to the eye. EPA Toxicity Category IV.

Iritis was noted in 2/3 eyes and conjunctivitis was noted in 3/3 eyes at the one hour observation. No positive scores were noted at 24 hours.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

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

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested				
	Hours				Days
	1	24	48	72	7
Corneal Opacity	0/3	0/3	0/3	0/3	0/3
Iritis	2/3	0/3	0/3	0/3	0/3
Conjunctivae:					
Redness	0/3	0/3	0/3	0/3	0/3
Chemosis	3/3	0/3	0/3	0/3	0/3
Discharge	3/3	0/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

A. Observations - Iritis was noted in 2/3 eyes and conjunctivitis was noted in 3/3 eyes at the one hour observation. No positive scores were noted at 24 hours.

B. Reviewer's Conclusions: Agree with study author

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Primary Dermal Irritation - NW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Hoff, T. 15% w/v R-28153/15% w/v amitraz spot-on. Acute Dermal Irritation in Rabbits. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.03. February 18, 2004. MRID 46395809. Unpublished

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46395809), three young adult New Zealand White rabbits (1 male and 2 female; Source: Millbrook Breeding Labs, Amherst, MA) were dermally exposed to 0.5 mL of 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid). The test substance was applied to one dose site on the dorsal area of each animal. Test sites were covered with a 2.5 cm x 2.5 cm gauze patch, secured with tape and wrapped with plastic in a semi-occlusive manner for a 4 hour period. Animals were then observed at 1, 24, 48 and 72 hours and on day 7 after patch removal. Irritation was scored by the method of Draize.

In this study, the formulation is a mild irritant. EPA Toxicity Category IV.

Primary Dermal Irritation Index (PDII) - 0.6 No dermal irritation was noted at the one hour, 24 hour or 48 observations. At 72 hours, very slight to well defined erythema was noted at all three sites and very slight edema at two sites. All sites were free of dermal irritation by day 7.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

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

RESULTS and DISCUSSION:

A. Observations - No dermal irritation was noted at the one hour, 24 hour or 48 observations. At 72 hours, very slight to well defined erythema was noted at all three sites and very slight edema at two sites. All sites were free of dermal irritation by day 7.

B. Results - PDII - 0.6

C. Reviewer's Conclusions - Agree with study author

Reviewer: Eugenia McAndrew
Risk Manager: 07

December 29, 2004

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

CITATION: Hall, D. 15% w/v R-28153/15% w/v amitraz spot-on. Delayed Contact Dermal Sensitization Test - Buehler Method. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11648.06. February 18, 2004. MRID 46395810. Unpublished

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46395810) with 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid), 30 young adult Hartley albino guinea pigs (Source: Elm Hill Breeding Labs, Chelmsford, MA; 289-355 g males and 283-394 g females) were tested using the Buehler method. The procedures were validated using dinitrochlorobenzene (DNCB) as the positive control substance.

Once each week for three weeks, 0.4 mL of undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. The animals rested for two weeks. Fourteen days after the last induction, 0.4 mL of undiluted test substance (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Ten naive control guinea pigs were treated with the undiluted test substance at challenge only. Readings were made 24 and 48 hours after each induction application and after the challenge application.

In this study, the formulation is a dermal sensitizer.

Very faint to moderate erythema (0.5 -2) was noted at all test animal sites during the induction phase. Following the challenge, a sensitizing response (1 or greater) was noted at 6/20 test sites at 24 hours and at 8/20 sites at 48 hours. In the naive control group, very faint erythema (0.5) was noted at two sites at 24 hours and at one site at 48 hours. No sensitizing responses were noted. The results of the DNCB positive control study were appropriate to validate test procedures.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the Guinea pig .

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

I. PROCEDURE

A. Induction - Once each week for three weeks, 0.4 mL of the undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. The animals rested for two weeks. Readings were made 24 and 48 hours after each induction application.

B. Challenge - Fourteen days after the last induction, 0.4 mL of undiluted test substance (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Readings were made 24 and 48 hours after the challenge application.

C. Naive Controls - Ten naive control guinea pigs were treated with the undiluted test substance at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Very faint to moderate erythema (0.5 -2) was noted at all test animal sites during the induction phase. Following the challenge, a sensitizing response (1 or greater) was noted at 6/20 test sites at 24 hours and at 8/20 sites at 48 hours. In the naive control group, very faint erythema (0.5) was noted at two sites at 24 hours and at one site at 48 hours. No sensitizing responses were noted.

B. Positive control - The results of the DNCB positive control study were appropriate to validate test procedures.

C. Reviewer's Conclusions: Agree with study author

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D311471
2. **PC CODES:** 106201, 281251/281250
3. **CURRENT DATE:** 29/DEC/2004
4. **TEST MATERIAL:** 15% w/v R-28153/15% w/v amitraz spot-on (Lot/Batch # 0381702; 14.65% amitraz and 14.70% metaflumizone; yellow liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat MB Research Laboratories MB 03-11648.01/2-18-04	46395805	LD ₅₀ > 500 and < 5000 mg/kg (males, females combined)	III	A
Acute dermal toxicity/rabbit MB Research Laboratories MB 03-11648.02/2-18-04	46395806	LD ₅₀ > 5000 mg/kg (males, females combined)	IV	A
Acute inhalation toxicity/rat MB Research Laboratories MB 03-11648.05/2-18-04	46395807	LC ₅₀ > 0.57 mg/L and < 2.32 mg/L (males, females combined)	III	A
Primary eye irritation/rabbit MB Research Laboratories MB 03-11648.04/2-18-04	46395808	Iritis and conjunctivitis at one hour. No positive scores at 24 hours.	IV	A
Primary dermal irritation/rabbit MB Research Laboratories MB 03-11648.03/2-18-04	46395809	PDII = 0.6 Slight irritant	IV	A
Dermal sensitization/guinea pig MB Research Laboratories MB 03-11648.06/2-18-04	46395810	A sensitizer	-	A

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