



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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: June 10, 2005

MEMORANDUM

Subject: EPA File Symbol: 80490-G PROMERIS SPOT-ON FOR CATS
DP Barcode: D314411
Decision No.: 354816
PC Code: 281250 (Metaflumizone, R-28153, BAS 320 I)

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

Byron T. Backus
6/10/2005
E. M. Linder

To: Ann Hanger/John Hebert, RM 7
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: FORT DODGE ANIMAL HEALTH

FORMULATION DECLARATION FROM LABEL:

<u>Active Ingredient(s):</u>	% by wt
Metaflumizone (CAS 35037-73-1).....	18.53%
<u>Inert Ingredients:</u>	81.47%
Total:	100.00%

ACTION REQUESTED:

The Risk Manager requests:

"Please review the acute tox studies (MRIDs 46437603 through 46437608) submitted for this 18.53% metaflumizone (aka BAS 320 I) end-use product..."

BACKGROUND: This product is proposed as a spot-on (application rate: once a month) for control of fleas on cats and kittens over 8 weeks of age.

This package includes acute oral LD₅₀ (MRID 46437603), acute dermal LD₅₀ (MRID 46437604), acute inhalation LC₅₀ (MRID 46437605), primary eye irritation (MRID 46437606), primary dermal irritation (MRID 46437607) and dermal sensitization (MRID 46437608) studies.

COMMENTS AND RECOMMENDATIONS:

1. The six acute studies have been reviewed and have all been classified as acceptable.
2. Based on the results of the acute toxicity studies the following is the acute toxicity profile for EPA File Symbol 80490-G PROMERIS SPOT-ON FOR CATS:

<u>Study Type</u>	<u>Tox. Cat.</u>	<u>Classification & MRID #</u>
Oral LD ₅₀ (rat)	Tox. Cat. IV	Acceptable (MRID 46437603)
Dermal LD ₅₀ (rabbit)	Tox. Cat. IV	Acceptable (MRID 46437604)
Inhalation LC ₅₀ (rat)	Tox. Cat. IV	Acceptable (MRID 46437605)
Eye Irritation (rabbit)	Tox. Cat. III	Acceptable (MRID 46437606)
Dermal Irritation (rabbit)	Tox. Cat. IV	Acceptable (MRID 46437607)
Dermal Sensitization	Not a Sensitizer	Acceptable (MRID 46437608)

3. Based on the acute toxicity profile indicated above, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: 080490-00003

PRODUCT NAME: PROMERIS SPOT-ON FOR CATS

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and

[R-28153 20%]

EPA File Symbol 80490-G: PROMERIS SPOT-ON FOR CATS

water after handling.

First Aid:

If in eyes:

- Hold eye open and rinse slowly and gently with water for 15-20 minutes.
- Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
- Call a poison control center or doctor for treatment advice.

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: Byron T. Backus, Ph.D.
Risk Manager (EPA): 07

Date: June 2, 2005
DP Barcode: D314411

STUDY TYPE: Acute Oral Toxicity Up and Down Procedure - Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153, a clear liquid with a specific gravity of 1.13 (p. 5 of MRID 46437603) or 1.0783 (p. 13).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, with a label declaration of 18.53% Metaflumizone (R-28153)

CITATION: Cerven, D.R. (2004) Acute Oral Toxicity - Up and Down Procedure (UDP): 20% w/v R-28153 Spot-on, Lot/batch #0481702. Amended Final Report. Project No. MB 04-12416.01. Unpublished study prepared by MB Research Laboratories, Spinnerstown, 14 p. Study Completion Date: 24 September, 2004. MRID 46437603.

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

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46437603), ostensibly conducted using the up-and-down procedure, undiluted 20% w/v R-28153 Spot-On, Lot/batch #0481702, a clear yellow liquid with a density of 1.13 (p. 5) or 1.0783 g/cm³ (p. 13), was administered to a single female Wistar rat at a dose of 5000 mg/kg. When this rat survived, an additional two female Wistar rats were also dosed at 5000 mg/kg. Rats (source: Ace Animals, Boyertown, PA) weighed 195-217 g, and were about 9 weeks old).

On the day of dosage rats were observed 4 times (0.5, 1, 2 and 4 hrs postdose) for mortality and signs of toxicity. They were then observed at least once a day for the remainder of the 14-day observation period. Individual body weights were recorded just prior to dosing (Day 0) and on days 7 and 14.

There were no mortalities or signs of toxicity, although the report states that an additional (fourth) rat was dosed incorrectly and died with evidence of intratracheal installation. The other 3 rats all gained weight in the period from day 0 to day 7 and again from day 7 to 14. Post-sacrifice necropsies were normal.

Estimated Oral LD₅₀ in female rats > 5000 mg/kg.

The test material, 20% w/v R-28153 Spot-On, Lot/batch #0481702 (20.43% R-28153), a clear yellow liquid with a density of 1.13 (p. 5) or 1.0783 g/cm³ (p. 13) is in EPA Toxicity Category IV in terms of oral toxicity based on the results of this study.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 12), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Friday, June 03, 2005, 3:12:50 PM

Data file name: promeriscat.dat

Last modified: 6/3/2005 3:08:38 PM

Test/Substance: Promeris for cats

Test type: Limit Test

Limit dose (mg/kg): 2000

Assumed LD50 (mg/kg): Default

Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
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1	2	5000	O	O
2	3	5000	O	O
3	4	5000	O	O

(X = Died, O = Survived)

Dose Recommendation: Dose an additional animal at 2000 mg/kg.

WARNING:

Please review the data for accuracy.

At least one dose is well above the limit dose.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
5000	3	0	3
All Doses	3	0	3

[R-28153 20%]

EPA File Symbol 80490-G: PROMERIS SPOT-ON FOR CATS

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	-	0/3	-

Statistics - Not necessary to compute the oral LD₅₀.

A. Mortality - None, as noted in the table above. However, the statement is made in the report (p. 7) that: "One animal was dosed incorrectly and died with evidence of intratracheal instillation. This animal was subsequently replaced."

B. Clinical observations - No abnormal physical signs were noted during the observation period.

C. Gross Necropsy - Necropsy results were normal.

D. Reviewer's Conclusions: The study is acceptable. EPA File Symbol 80490-G, with a label declaration of 18.53% Metaflumizone (R-28153) is in EPA Toxicity Category IV in terms of oral toxicity based on the observed LD₅₀ (>5000 mg/kg in female rats) of this study.

E. Deficiencies - Study protocol did not adhere to up-and-down procedure (more of a limit test). The specific gravity of the test material is reported as 1.13 (p. 5 of MRID 46437603) and as 1.0783 g/cm³ (p. 13).

Reviewer: Byron T. Backus, Ph.D.

Risk Manager (EPA): 07

Date: June 6, 2005

DP Barcode: D314411

STUDY TYPE: Acute Dermal Toxicity - New Zealand white rabbits - OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153, a clear liquid with a specific gravity of 1.13 (p. 5 of MRID 46437604) or 1.0783 (p. 14).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, with a label declaration of 18.53% Metaflumizone (R-28153)

CITATION: Gilotti, A. (2004) Acute Dermal Toxicity/LD 50 in Rabbits: 20% w/v R-28153 Spot-On. Project No. MB/04/12416/02, 1100/02, 0817/T/US/20/04. . Unpublished study prepared by MB Research Laboratories, Spinnerstown, PA 18968. 15 p. Study Completion Date: 4 October 2004. MRID 46437604.

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

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID #46437604) a group (5M & 5F) of New Zealand White rabbits (source: Millbrook Breeding Labs, Amherst, MA; age: approximately 15 weeks; Males: 2.6-3.3 kg; Females: 2.9-3.3 kg) were dermally exposed (approximately 10% of body surface) for 24 hrs to 5000 mg undiluted 20% w/v R-28153 Spot-On, Lot/batch #0481702, a clear yellow liquid with a density of 1.13 (p. 5) or 1.0783 g/cm³ (p. 14), with 24 hour semiocluded exposure.

Rabbits were observed 3 times (1, 2 and 4 hours postdose) on the day of application (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing (day 0) and on days 7 and 14.

There was no mortality. One male had diarrhea at 4 hours postdose; one male had few feces on Day 1 and from Days 10 through 13; one female had few feces from Day 10 through Day 12. One male had minimal (grade 1) erythema at 24 hours; all other dermal irritation scores at 24 hours were zero. All dermal irritation scores on Days 7 and 14 were zero. All rabbits gained or maintained weight in the period from Day 0 to 7, and 9/10 gained weight from Day 7 to 14 (the remaining rabbit maintained weight).

Post-sacrifice necropsy results were normal.

Dermal LD₅₀ Males > 5000 mg/kg (0/5 died)
Females > 5000 mg/kg (0/5 died)
Combined > 5000 mg/kg (0/10 died)

20% w/v R-28153 Spot-On, Lot/batch #0481702, a clear yellow liquid with a density of 1.13 (p. 5) or 1.0783 g/cm³ (p. 14) is in EPA toxicity category IV in terms of dermal toxicity based on the results of this study.

This acute dermal study is classified as 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 Compliance (p. 3), Quality Assurance (p. 13), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

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

Statistics - Not necessary to compute the dermal LD₅₀.

A. Mortality - None, as noted in the table above.

B. Clinical observations - One male had diarrhea at 4 hours postdose; one male had few feces on Day 1 and from Days 10 through 13; one female had few feces from Day 10 through Day 12. One male had minimal (grade 1) erythema at 24 hours; all other dermal irritation scores at 24 hours were zero. All dermal irritation scores on Days 7 and 14 were zero. All rabbits gained or maintained weight in the period from Day 0 to 7, and 9/10 gained weight from Day 7 to 14 (the remaining rabbit maintained weight).

C. Gross Necropsy - No gross abnormalities were observed at post-sacrifice necropsy.

D. Reviewer's Conclusions: The study is acceptable. 20% w/v R-28153 Spot-On, Lot/batch #0481702, a clear yellow liquid with a density of 1.13 (p. 5) or 1.0783 g/cm³ (p. 14) is in EPA toxicity category IV in terms of dermal toxicity with a rabbit LD₅₀ > 5000 mg/kg.

E. Deficiencies - Two different density measurements [1.13 (p. 5) and 1.0783 g/cm³ (p. 14)] are reported

Reviewer: Byron T. Backus, Ph.D.
Risk Manager (EPA): 07

Date: June 8, 2005
DP Barcode: D314411

STUDY TYPE: Acute Inhalation Toxicity - Wistar albino rat; OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153, a clear liquid with a specific gravity of 1.13 (p. 5 of MRID 46437603) or 1.0783 (p. 24 of MRID 46437605).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, Promeris Spot-On for Cats, with a label declaration of 18.53% Metaflumizone (R-28153)

CITATION: Gilotti, A. (2004) Acute Inhalation Toxicity/LC 50 in Rats: 20% w/v R-28153 Spot-On. Project No. MB/04/12416/05, 1300/02, 0817/T/US/23/04. . Unpublished study prepared by MB Research Laboratories, Spinnerstown, PA 18968. 25 p. Study Completion Date: 4 October 2004. MRID 46437605.

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

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46437605), a group (5/sex) of Wistar albino rats (source: Ace Animals, Boyertown, PA; age: young adult 7-8 weeks at start of study; weight: males: 255-257 g; females: 173-193 g) were exposed (whole body) to an aerosol obtained from a 20% w/v R-28153 Spot-on, Lot/batch #0481702, described as a clear (p. 5 of MRID 46437605) or clear yellow liquid (p. 24). The rats were exposed to a mean gravimetrically determined concentration of 2.02 ± 0.29 mg/L test material during the 4-hr exposure period. The MMAD was 1.37 μ m, and the GSD was 2.07.

Rats were monitored during exposure, one hour after exposure, and once daily then for 14 days for toxicity and pharmacological effects. Rats were observed twice daily for mortality.

During exposure all rats showed sagging eyelids and/or closed eyes, and fur coated with test material. Several rats also had a wet snout/mouth area. Following exposure, several rats showed wetness or soiling of the anogenital area (one female still showed soiling of the anogenital region and an unkempt appearance at termination on Day 14). 4/5 females also showed few feces starting on Day 4-7, followed by emaciation, which persisted through Day 12 in all four of these females.

All males gained weight in the period from day 0 to 7 and again from day 7 to 14; 4/5 females lost weight in the period from day 0 to 7, but all females gained weight from day 7 to 14 (and from day 0 to 14).

Necropsy results are reported as normal for 5/5 males and 2/5 females; red areas in the lungs were found in 2/5 females and pale areas of the liver in 1/5 females.

LC₅₀ Males >2.02 mg/L (0/5M died following 4-hr exposure).

LC₅₀ Females >2.02 mg/L (0/5F died following 4-hr exposure).

20% w/v R-28153 Spot-On, Lot/batch #0481702, a clear (or clear yellow) liquid with a density of 1.0783 g/mL is in EPA toxicity category IV in terms of inhalation toxicity based on the results of this study.

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 (p. 3), Quality Assurance (p. 23), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Actual Mean Conc. $\pm$ S.D. (Gravimetric; mg/L)	MMAD μ m	GSD μ m	Mortality/Number Tested		
				Males	Females	Combined
Not reported	2.02 $\pm$ 0.29	1.37	1.42	0/5	0/5	0/10

Test Atmosphere / Chamber Description:

Chamber Volume: 57 L
Airflow: 12 LPM
Temperature: 22.4-23.2°C
Relative Humidity: 51-56 %
Time to 99% Equilibrium: not stated

Test atmosphere concentration: analyzed 5 times during exposure (times not stated). Values were 2.07, 2.47, 1.93, 1.68, and 1.95 mg/L [Mean: 2.02 mg/L with SD = 0.29 mg/L].

Particle size determination: This was measured 3 times. In general, >99.99% of the particles had an effective cut-off diameter of 5.8 μ m; >79.79% had an effective cut-off diameter of 3.3 μ m, and >47.01% had an effective cut-off diameter of 1.1 μ m. MMADs were 1.20, 1.35, and 1.55 μ m, and the respective GSDs were 2.11, 2.16 and 1.95.

Statistics - Statistical calculations were not necessary to determine the LC₅₀ value.

A. Mortality - None, as noted in the table.

B. Clinical observations - During exposure all rats showed sagging eyelids and/or closed eyes, and fur coated with test material. Several rats also had a wet snout/mouth area. Following exposure, several rats showed wetness or soiling of the anogenital area (one female).

still showed soiling of the anogenital region and an unkempt appearance at termination on Day 14). 4/5 females also showed few feces starting on Day 4-7, followed by emaciation, which persisted through Day 12 in all four of these females.

C. **Gross Necropsy** - Necropsy results are reported as normal for 5/5 males and 2/5 females; red areas in the lungs were found in 2/5 females and pale areas of the liver in 1/5 females.

D. **Reviewer's Conclusions:** The study results (4-hr LC_{50} >2.02 mg/L) define a toxicity category IV hazard potential by the inhalation exposure route.

Reviewer: Byron T. Backus, Ph.D.
Risk Manager (EPA): 07

Date: June 9, 2005
DP Barcode: D314411

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

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153, a clear liquid with a specific gravity of 1.0783 (p. 11 of MRID 46437606).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, Promeris Spot-On for Cats, with a label declaration of 18.53% Metaflumizone (R-28153)

CITATION: Cerven, D. (2004) Acute Eye Irritation in Rabbits: 20% w/v R-28153 Spot-On. Project No. MB/04/12416/04, 1200/02, 0817/T/US/22/04. Unpublished study prepared by MB Research Laboratories, Spinnerstown, PA 18968. 12 p. Study Completion Date: 24 September 2004; Amended Report: 4 October 2004. MRID 46437606.

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

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46437606), 0.1 mL of undiluted 20% w/v R-28153 Spot-on, Lot/batch #0481702, described as a clear (p. 5 of MRID 46437606) or clear yellow liquid (p. 11) was instilled into the conjunctival sac of one eye of each of 3 adult New Zealand White Rabbits (weights: 2.9-3.4 kg; age: about 15 weeks at testing; source: Millbrook Breeding Labs, Amherst, MA), with observations and scoring at 1, 24, 48 and 72 hours and day 7 after instillation. Sodium fluorescein dye was used at the 24, 48 and 72 hours evaluations.

No corneal opacity was observed. However, positive sodium fluorescein readings (scores of "1" or "2") were observed in 3/3 eyes at 24 hrs and in 2/3 at 48 hrs. Sodium fluorescein scores were zero at 72 hrs. Iridial irritation (score of "1") was observed in 2/3 eyes at 1 hour, but had cleared by 24 hours. All three eyes were positive for conjunctival irritation effects (scores of 1-2 for redness and 2-3 for chemosis) at 1 and 24 hrs; but the maximum score for redness and/or chemosis at 48 and 72 hrs was 1. All scores were zero on Day 7.

R-28153 Spot-on, Lot/batch #0481702 (Promeris Spot-On for Cats) is in EPA Toxicity Category III for eye irritation, based on the presence of eye irritation effects at 24 hours with clearing by Day 7.

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 Compliance (p. 3), Quality Assurance (p. 10), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested				
	1 hr	24 hrs ²	48 hrs	72 hrs	7 days
Corneal Opacity	0/3	0 ^a /3	0 ^b /3	0/3	0/3
Iritis	3/3	0/3	0/3	0/3	0/3
Conjunctivae:					
Redness ¹	0/3	1/3	0/3	0/3	0/3
Chemosis ¹	3/3	3/3	0/3	0/3	0/3
Discharge ¹	3/3	2/3	0/3	0/3	0/3

¹Score of 2 or more considered positive²Fluorescein staining was used to verify the absence of corneal opacity; any corneas which exhibited fluorescein staining were also evaluated at subsequent readings until staining no longer occurred.^aAll 3 eyes were positive at 24 hours under UV following sodium fluorescein treatment.^b2/3 eyes were positive at 48 hours under UV following sodium fluorescein treatment.

A. Observations - No systemic effects were observed. No corneal opacity was observed. However, positive sodium fluorescein readings (scores of "1" or "2") were observed in 3/3 eyes at 24 hrs and in 2/3 at 48 hrs. Sodium fluorescein scores were zero at 72 hrs. Iridial irritation (score of "1") was observed in 2/3 eyes at 1 hour, but had cleared by 24 hours. All three eyes were positive for conjunctival irritation effects (scores of 1-2 for redness and 2-3 for chemosis) at 1 and 24 hrs; but the maximum score for redness and/or chemosis at 48 and 72 hrs was 1. All scores were zero on Day 7.

B. Reviewer's Conclusions: The study adequately defines a Toxicity Category III hazard potential for eye irritation for R-28153 Spot-on, Lot/batch #0481702 (Promeris Spot-On for Cats) based on the presence of positive eye irritation effects at 24 hours with clearing by Day 7.

C. Deficiencies - None

[R-28153 20%]

EPA File Symbol 80490-G: PROMERIS SPOT-ON FOR CATS

Reviewer: Byron T. Backus, Ph.D.
Risk Manager (EPA): 07

Date: June 9, 2005
DP Barcode: D314411

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

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153, a clear liquid with a specific gravity of 1.0783 (p. 11 of MRID 46437607).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, Promeris Spot-On for Cats, with a label declaration of 18.53% Metaflumizone (R-28153; BAS 320 I)

CITATION: Hoff, T. (2004) Acute Dermal Irritation in Rabbits: 20% w/v R-28153 Spot-On: Amended Final Report. Project No. MB/04/12416/03, 1130/02, 0817/T/US/21/04. Unpublished study prepared by MB Research Laboratories, Spinnerstown, PA 18968. 12 p. Study Completion Date: 24 September 2004; Amended Report: 5 October 2004. MRID 46437607.

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

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46437607), 0.5 mL aliquots of undiluted 20% w/v R-28153 Spot-on for Cats (active ingredient: R-28153 at 20.43%), Lot/batch #0481702, were applied to single dermal sites on each of 3 male adult New Zealand White albino rabbits (weights: 2.9-3.3 kg; age: about 13-15 weeks at testing; source: Millbrook Breeding Labs, Amherst, MA) with 4-hour semioccluded exposure.

After 4 hours, the gauze patch, plastic covering and holding tape were removed. The test sites were scored (Draize) at 1, 24, 48 and 72 hrs.

No edema and no erythema were observed (all scores were zero). The PII (average of scores at 1, 24, 48 & 72 hrs) = 0.00

20% w/v R-28153 Spot-on for Cats (active ingredient: R-28153 at 20.43%), Lot/batch #0481702 is in EPA Toxicity Category IV for dermal irritation effects, based on the lack of dermal irritation (PII = 0.00) following 4-hr semi-occluded exposure.

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 Compliance (p. 3), Quality Assurance (p. 10), and [No] Data Confidentiality (p. 2) statements were provided.

RESULTS and DISCUSSION:

A. Observations - No edema and no erythema were observed.

B. Results - The PII (average of scores at 1, 24, 48 & 72 hrs) = 0.00

C. Reviewer's Conclusions - 20% w/v R-28153 Promeris Spot-on for Cats (active ingredient: R-28153 at 20.43%), Lot/batch #0481702 is in EPA Toxicity Category IV in terms of dermal irritation based on the lack of irritation (PII = 0.00) following 4-hr semiocluded dermal exposure.

D. Deficiencies - None

Reviewer: Byron T. Backus, Ph.D.
Product Manager (EPA): 07

Date: June 10, 2005
DP Barcode: D314411

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

TEST MATERIAL (% a.i.): 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I), a clear liquid with a specific gravity of 1.0783 (p. 42 of MRID 46437608).

SYNONYMS: The test material description is consistent with the proposed product EPA File Symbol 80490-G, Promeris Spot-On for Cats, with a label declaration of 18.53% Metaflumizone (R-28153; BAS 320 I)

CITATION: Hall, D. (2004) Delayed Contact Dermal Sensitization Test (in Guinea Pigs) - Buehler Method: 20% w/v R-28153 Spot-on, Lot/batch #0481702. Amended Final Report. Project No. MB/04/12416/06, 1160/02, 0817/T/US/24/04. Unpublished study prepared by MB Research Laboratories, Spinnerstown, PA 18968. 43 p. Study Completion Date: 27 September 2004; Amended Report: 6 October 2004. MRID 46437608.

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

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46437608) with 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I), a group of 10M and 10F Hartley albino guinea pigs (young adult; Males: 293-355 g; Females: 307-336 g; source: Elm Hill Breeding Labs, Chelmsford, MA) were each dermally exposed (6 hours) to a 0.4 mL aliquot of undiluted (100%) 20% w/v R-28153 Spot-on (containing 20.43% Metaflumizone, also known as R-28153 and BAS 320 I) on a once-a-week basis for 3 consecutive weeks. After a two week rest period each was dermally challenged with 0.4 mL of undiluted mixture of the test material at a previously unexposed site. An additional 10 (5M, 5F) previously unexposed guinea pigs were similarly treated at this time. Challenge sites on all 30 guinea pigs were evaluated and scored for erythema at 24 and 48 hours after the application.

Following challenge, the maximum score observed for erythema at 24 and/or 48 hours was 0.5, seen in 3 (1M, 2F) previously exposed guinea pigs. The remaining 17 guinea pigs scored zero. The maximum score observed in the naive controls was 0.5, seen in one male at 24 hours only. All other scores in the naive group were zero.

The report includes results from a positive control study (Project No. MB 04-12037.06) which was conducted with 0.2% DNCB. The experimental start date for the positive control study was 2/24/04; the experimental start date for the study on 20% w/v R-28153 Spot-on was 7/06/04, so the two studies were conducted within 6 months of each other. In the positive control study 7/10 male and 8/10 female previously exposed guinea pigs showed a sensitization response (score of "1" or more at 24 and/or 48 hours); 0/5 male and 0/5 female naive guinea pigs showed such a response.

In this study there were no indications that 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I) is a dermal sensitizer.

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 Compliance (p. 3), Quality Assurance (p. 25), and [No] Data Confidentiality (p. 2) statements were provided.

I. PROCEDURE

A. Induction - Each of 10M and 10F Hartley albino guinea pigs was treated once a week for 3 consecutive weeks to a 6-hour exposure to 0.4 mL undiluted 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I).

B. Challenge - Fourteen days after the last induction exposure 0.4 mL undiluted 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I) was applied to a naive (previously unexposed) dermal site on each guinea pig. These sites were evaluated and scored for erythema at 24 and 48 hours after the challenge application.

C. Naive Controls - At the time the 20 previously induced guinea pigs were challenged, 10 (5M and 5F) previously unexposed (negative control) guinea pigs were similarly challenged.

II. RESULTS and DISCUSSION:

A. Reactions and duration - Following challenge, the maximum score observed for erythema at 24 and/or 48 hours was 0.5, seen in 3 (1M, 2F) previously exposed guinea pigs. The remaining 17 guinea pigs scored zero. The maximum score observed in the naive controls was 0.5, seen in one male at 24 hours only. All other scores in the naive group were zero.

B. Positive control -The report includes results from a positive control study (Project No. MB 04-12037.06) which was conducted with 0.2% DNCB. The experimental start date for the positive control study was 2/24/04; the experimental start date for the study on 20% w/v R-28153 Spot-on was 7/06/04, so the two studies were conducted within 6 months of each other. In the positive control study 7/10 male and 8/10 female previously exposed guinea pigs showed a sensitization response (score of "1" or more at 24 and/or 48 hours); 0/5 male and 0/5 female naive guinea pigs showed such a response. These results are acceptable for a positive control study.

C. Reviewer's Conclusions: Based on the results of this study 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone, BAS 320 I) is not a dermal sensitizer.

D. Deficiencies - None

ACUTE TOX ONE-LINERS

1. DP BARCODE: D314411
2. PC CODE: 281250 (Metaflumizone, R-28153, BAS 320 I)
3. CURRENT DATE: June 10, 2005
4. TEST MATERIAL: 20% w/v R-28153 Spot-on, Lot/batch #0481702; containing 20.43% R-28153 (Metaflumizone; BAS 320 I), a clear (or clear yellow) liquid with a specific gravity of 1.13 (p. 5 of MRID 46437603) or 1.0783 (p. 13 of MRID 46437603).

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat	Core Grade
Acute oral toxicity/rat/MB Research Laboratories/MB 04- 12416.01/Amended report date OCT-04-2004	46437603	LD ₅₀ >5000 mg/kg. Test animals: female Wistar albino rats. Ostensibly up and down method, but actually limit test (no mortalities among 3 females dosed at 5000 mg/kg). No signs of toxicity, although report states an additional fourth rat was dosed incorrectly and died with evidence of intratracheal installation. All rats gained weight from day 0 to 7 and again from day 7 to 14. Post-sacrifice necropsies were normal.	IV	A
Acute dermal toxicity/rabbit/MB Research Laboratories/MB 04- 12416.02/OCT-04-2004	46437604	LD ₅₀ > 5000 mg/kg. 5M & 5F NZ white rabbits were dermally exposed to 5000 mg/kg for 24 hrs; no mortality. One male had diarrhea at 4 hours postdose; one male had few feces on day 1 and from day 10 to 13; one female had few feces from day 10 to 12. One male had minimal (grade 1) erythema at 24 hrs; all other dermal irritation scores (at 24 hrs and subsequently) were zero. All rabbits maintained or gained wt from day 0 to 7; 9/10 gained wt from day 7 to 14 and 1/10 maintained wt. Post-sacrifice necropsy results were normal.	IV	A
Acute Inhalation Toxicity/rat/MB Research Laboratories/MB 04- 12416.05/OCT-04-2004	46437605	5/sex Wistar-derived albino rats were exposed (whole body) for 4 hrs to 2.02 mg/L; MMAD = 1.37 µm and GSD = 2.07. No mortality. During exposure all rats showed sagging eyelids and/or closed eyes and fur coated with test material. Several rats also had a wet snout/mouth area. After exposure, several rats showed wetness or soiling of the anogenital area (one female still showed this on day 14). 4/5 females showed few feces starting on day 4-7, followed by emaciation, which persisted through day 12 in all 4 of these females. Males gained wt from day 0 to 7 and again from 7-14; 4/5 females lost wt from day 0 to 7, but all females gained wt from day 7 to 14 (and from day 0 to 14). Necropsy results normal for 5/5 males and 2/5 females; red areas in lungs of 2/5 females and pale areas of the liver in 1/5 females.	IV	A

Primary eye irritation/rabbit/ MB Research Laboratories/MB 04-12416.04/OCT-04-2004	46437606	No corneal opacity was observed, but positive fluorescein readings of 1 or 2 were observed in 3/3 eyes at 24 hrs and 2/3 at 48 hrs. Iridial irritation (score of 1) was seen in 2/3 eyes at 1 hr but was clear by 24 hrs. All 3 eyes were positive for conjunctival irritation effects at 1 and 24 hrs, but scores were 0 or 1 (not considered positive) at 48 & 72 hrs. All scores were zero by day 7.	III	A
Primary dermal irritation/rabbit/ MB Research Laboratories/MB 04-12416.03/OCT-04-2004	46437607	No edema & no erythema. The PII (average of scores at 1, 24, 48 & 72 hrs) = 0.00	IV	A
Dermal sensitization/guinea pig/ MB Research Laboratories/MB 04-12416.06/OCT-06-2004	46437608	Modified Buehler: Once a week induction treatments with undiluted test material for 3 weeks, followed by challenge with undiluted test material two weeks after last induction. At challenge maximum score for erythema was 0.5, seen in 3 (1M, 2F) of the 20 previously exposed guinea pigs. 1/10 naive guinea pigs showed a score of 0.5; all other scores were zero. Positive control study was acceptable and was conducted less than 6 months before this study.	Not a sensitizer	A

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