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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

March 9, 2009

MEMORANDUM

Subject:	Name of Pesticide Product:	SPAH 1.0
	EPA Reg. No. /File Symbol:	773-OG
	DP Barcode:	DP 353336
	Decision No.:	393685
	Action Code:	R260
	PC Codes:	067710 (Indoxacarb)

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

Byron T. Backus 3-9-2009 E McAnchen

To: Julie Chao/John Hebert, RM 07
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: SCHERING-PLOUGH ANIMAL HEALTH CORPORATION

FORMULATION FROM LABEL:

Active Ingredient(s):		% by wt.
067710 Indoxacarb		19.53%
Other Ingredient(s):		80.47%
	TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"Please review the attached acute toxicology data, submitted in support of 773-OG, an indoxacarb spot-on flea control product for cats and kittens. Copies of the cover letter, CSF, and proposed label are included..."

BACKGROUND:

The material received for review includes (MRIDs 47424502, 47424503, 47424505, 47424506 and 47424507) five acute toxicity studies, along with a request for an inhalation study waiver (MRID 47424504).

In addition this package includes a copy of the label (with a declaration of 19.53% Indoxacarb as the sole active and the proposed signal word CAUTION) and a CSF dated 4-7-08.

COMMENTS AND RECOMMENDATIONS:

1. The 5 acute toxicity studies (conducted at Calvert Laboratories, Olyphant, PA) have all been classified as acceptable. These studies adequately define the acute toxicity by these exposure routes of the formulation that was tested.

2. TRB concludes that an inhalation toxicity study waiver is appropriate, based on the use pattern.

3. However, TRB has reservations regarding the applicability of the 5 acute toxicity studies to the formulation in the CSF dated 4-7-08. The material that was tested in the 5 acute toxicity studies is reported as having a specific gravity of 1.12 g/mL, while the CSF indicates a formulation with a specific gravity of ~1.0 g/mL. In addition, the inert composition of the test material used in the cat and kitten companion animal safety studies (refer to p. 550 of MRID 47424508 and p. 539 of MRID 47424509) is not consistent with the CSF dated 4-7-08.

4. Based on the results of the acute toxicity studies, the following is the acute toxicity profile of the material that was tested. It has not been established that these studies adequately define the acute toxicity profile of the formulation in the CSF dated 4-7-08:

Acute oral toxicity	III	Acceptable	MRID 47424502
Acute dermal toxicity	III	Acceptable	MRID 47424503
Acute inhalation toxicity	IV	Waived	[MRID 47424504]
Primary eye irritation	II	Acceptable	MRID 47424505
Primary dermal irritation	IV	Acceptable	MRID 47424506
Dermal sensitization	Non-Sensitizer	Acceptable	MRID 47424507

5. Based on the acute toxicity profile above, the following would be the precautionary and first aid labeling of the material that was tested, as obtained from the Label Review System. The signal word is WARNING based on the eye irritation potential, rather than the CAUTION proposed by the registrant:

PRODUCT ID #: **000773-00093**

PRODUCT NAME: **SPAH 1.0**

PRECAUTIONARY STATEMENTS

SIGNAL WORD: **WARNING**

Hazards to Humans and Domestic Animals:

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification. Child Resistant Packaging Required.

Causes substantial but temporary eye injury. Harmful if absorbed through skin. Harmful if swallowed. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse. Wear long-sleeved shirt and long pants, socks, shoes, and gloves.

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.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for 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.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical 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.

6. The CSF (dated 4-7-2008) for 773-OG should also be reviewed and accepted by the TRB Chemistry Team.

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL.

SYNONYMS: SPAH 1.0

CITATION: Mallory, V. (2008) Acute Oral Toxicity Study in the Rat - Up and Down Procedure with Indoxacarb Topical Solution (EAA): Amended Final Report. Project Number: 0406RS17/013, OT 07-0037. Unpublished study prepared by Calvert Preclinical Services, Inc. 69 p. February 18, 2008. MRID 47424502.

SPONSOR: Schering-Plough Animal Health Corporation, 556 Morris Avenue, Summit, NJ 07901.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47424502), eight fasted (overnight) adult female Sprague-Dawley rats (age: 11-15 weeks; body weight: 188-226 g; source: Harlan) were given a single dose of Indoxacarb Topical Solution (EAA), a light yellow liquid with a specific gravity of 1.12 g/mL containing 19.92% Indoxacarb at doses of 175 mg/kg (1 rat), 550 mg/kg (2 rats) and 2000 mg/kg (5 rats) using the up-and-down method. At 175 and 550 mg/kg the test article was diluted with 0.9% sodium chloride (saline) solution to dose volumes of 5 mL/kg; at 2000 mg/kg the test material was administered as received; since the specific gravity was 1.12 g/mL dosage was at 1.8 mL/kg. All dosage was by oral gavage. The rats were observed for 14 days following dosage.

There were no mortalities or signs of toxicity at 175 or 550 mg/kg. One out of five rats dosed at 2000 mg/kg was sacrificed in a moribund condition on Day 2 (Day 1 was the day of dosing) with symptoms that included decreased body tone, abnormal gait and stance, piloerection, decreased activity, gasping, vocalization and tearing eyes. One of the other rats dosed at 2000 mg/kg showed piloerection and decreased body tone on Days 8 through 10, otherwise appearing normal on Days 1-7 and 11-15. The remaining three rats dosed at 2000 mg/kg appeared normal throughout the observation period. All survivors gained weight from Day 1 to 8 with the exception of the rat which showed symptoms on Days 8-10 (this rat lost 8 g between Day 1 and 8). The other 3 survivors dosed at 2000 mg/kg showed reduced weight gains (from 7-9 g) between Day 1 and 8 relative to the animal dosed at 175 mg/kg (29 g) and the two dosed at 550 mg/kg (26 and 36 g). All surviving rats had weight gains from Day 8 to 15.

Gross necropsy findings from the rat that was sacrificed on Day 2 showed distended, air-filled stomach and intestines, along with bright red lungs and dark red lesions in the stomach lining. No visible lesions were observed in any of the animals which survived to termination.

Estimated female LD_{50} = 2000 mg/kg bw (Based on an assumed sigma of 0.5).

Approximate 95% confidence interval is 1590 to greater than 20000 mg/kg bw

Indoxacarb Topical Solution (EAA), Lot No./Batch No.: 7083B, a light yellow liquid with a specific gravity of 1.12 g/mL, is in EPA Toxicity Category III for oral toxicity.

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

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Data Confidentiality 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: Tuesday, March 03, 2009, 3:52:07 PM
Data file name: work.dat
Last modified: 3/3/2009 3:52:07 PM

Test/Substance: Indoxacarb Topical Solution
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	9292	175	O	O
2	9293	550	O	O
3	9294	2000	O	O
4	9295	2000	X	X
5	9296	550	O	O
6	9297	2000	O	O
7	9298	2000	O	O
8	9666	2000	O	O

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 3 at Limit Dose.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	1	0	1
550	2	0	2
2000	4	1	5
All Doses	7	1	8

Statistical Estimate based on long term outcomes:

Estimated LD50 = 2000 (The one dose with partial response).
95% PL Confidence interval is 1590 to Greater than 20,000.

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
9292	F	175	S
9293	F	550	S
9294	F	2000	S
9295	F	2000	D
9296	F	550	S
9297	F	2000	S
9298	F	2000	S
9666	F	2000	S

S = Survival, D = Death

A. **Mortality:** One out of five rats dosed at 2000 mg/kg was sacrificed in a moribund condition on Day 2 (Day 1 was the day of dosing) with symptoms that included decreased body tone, abnormal gait and stance, piloerection, decreased activity, gasping, vocalization and tearing eyes..

B. **Clinical observations:** The 175 mg/kg and both 550 mg/kg animals appeared normal for the duration of the study. In addition to the animal dosed at 2000 mg/kg that was sacrificed, one additional rat in the 2000 mg/kg group showed piloerection and decreased body tone on Days 8 through 10, otherwise appearing normal on Days 1-7 and 11-15. The remaining three rats dosed at 2000 mg/kg appeared normal throughout the observation period. All survivors gained weight from Day 1 to 8 with the exception of the rat which showed symptoms on Days 8-10 (this rat lost 8 g between Day 1 and 8). The other three survivors dosed at 2000 mg/kg showed reduced weight gains (from 7 to 9 g) between Day 1 and relative to the animal dosed at 175 mg/kg (29 g) and the two dosed at 550 mg/kg (26 and 36 g). All surviving rats had weight gains from Day 8 to 15.

C. **Gross necropsy:** Gross necropsy findings from the rat that was sacrificed on Day 2 showed distended, air-filled stomach and intestines, along with bright red lungs and dark red lesions in the stomach lining. No visible lesions were observed in any of the animals which survived to termination.

D. **Reviewer's conclusions:** This reviewer agrees with the study author that the acute oral LD_{50} of Indoxacarb Topical Solution (EAA) containing 19.92% Indoxacarb = 2000 mg/kg.

Reviewer: Byron T. Backus, Ph.D. **Date:** March 4, 2009
Risk Manager (EPA): 07

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL.

SYNONYMS: SPAH 1.0

CITATION: Mallory, V. (2007) Acute Dermal Toxicity Study in Rats with Indoxacarb Topical Solution (EAA): Final Report. Project Number: 0422RS17/013, OT/07/0038. Unpublished study prepared by Calvert Preclinical Services, Inc. 52 p. December 19, 2007. MRID 47424503.

SPONSOR: Schering-Plough Animal Health Corporation, 556 Morris Avenue, Summit, NJ 07901.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47424503), young adult Sprague-Dawley rats (5/sex; age: 8-10 weeks; body weight: males: 218-228 g and females: 194-206 g; source: Harlan) were dermally exposed for 24±0.5 hours on an area of approximately 10% of the total body surface area on the clipped dorsal trunk to 2000 mg/kg bw Indoxacarb Topical Solution (EAA), a light yellow liquid with a specific gravity of 1.12 g/mL containing 19.92% Indoxacarb, as received. The test material was covered with a gauze patch/dental dam, and the animal was wrapped with an elastic bandage which was secured with non-irritating tape. After 24 hours the bandages were unwrapped and the sites were wiped with water and gauze to remove any remaining test article. The animals were observed until Day 15 (application was on Day 1).

All animals survived. There were no signs of toxicity. One female lost weight (3 g) between Day 1 and 8; all others gained weight during this period. All rats gained weight from Day 8 to 15. There were no visible lesions in any animal at necropsy.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

Indoxacarb Topical Solution (EAA), Lot No./Batch No.: 7083B, a yellow liquid with a specific gravity of 1.12 g/mL containing 19.92% Indoxacarb, is in EPA Toxicity Category III for dermal toxicity.

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

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

A. **Mortality:** All animals survived the study.

B. **Clinical observations:** All animals appeared normal for the duration of the study. One female lost weight (3 g) between Day 1 and 8; all others gained weight during this period. All rats gained weight from Day 8 to 15.

C. **Gross necropsy:** There were no visible lesions in any of the animals at necropsy.

D. **Reviewer's conclusions:** This reviewer agrees with the study author that Indoxacarb Topical Solution (EAA) containing 19.92% Indoxacarb has an acute dermal LD_{50} of >2000 mg/kg.

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

TEST MATERIAL: Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5.

SYNONYMS: SPAH 1.0

CITATION: Mallory, V. (2007) Primary Eye Irritation Study in Rabbits with Indoxacarb Topical Solution (EAA): Final Report. Project Number: 0421LS17/013, OT/07/0039. Unpublished study prepared by Calvert Preclinical Services, Inc. 51 p. December 19, 2007. MRID 47424505.

SPONSOR: Schering-Plough Animal Health Corporation, 556 Morris Avenue, Summit, NJ 07901.

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47424505), 0.1 mL of Indoxacarb Topical Solution (EAA), a light yellow liquid with a specific gravity of 1.12 g/mL containing 19.92% Indoxacarb, as received, was instilled into the conjunctival sac of the right eye of three adult male New Zealand White rabbits (14 weeks old at dosing; 2.3-2.4 kg, source: Harlan). The animals were observed until all eye irritation had cleared (up to 15 days), and were scored for eye irritation at 1, 24, 48 and 72 hours and 5, 6, 7, 8 and 15 days after instillation of the test article.

Corneal opacity was observed in two rabbits from 48 hours through day 5, with clearing in both on day 6. Iritis was observed in two eyes from 1 hour through day 7, clearing in one eye by day 8 and in the other eye by day 15. Positive conjunctival irritation (score of 2 or more for redness and/or chemosis) was noted in one eye from 1 hour through 72 hours, and in another eye from one hour through day 5. One rabbit eye showed grade 1 redness and chemosis at 1 hour (not considered a positive effect), and showed no irritation at any other time.

In this study, Indoxacarb Topical Solution (containing 19.92% Indoxacarb), a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5, caused positive eye irritation effects (iritis) which persisted in 2/3 rabbit eyes through day 7, clearing in one eye by day 8 and in the other by day 15. Indoxacarb Topical Solution is classified as EPA Toxicity Category II for primary eye irritation.

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

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

	Number "positive"/Number treated							
	Hours				Days			
Observations	**1**	**24**	**48**	**72**	**5**	**7**	**8**	**15**
Corneal Opacity	0/3	0/3	2/3	2/3	2/3	0/3	0/3	0/3
Iritis	2/3	2/3	2/3	2/3	2/3	2/3	1/3	0/3
Conjunctivae:								
Redness*	1/3	2/3	1/3	1/3	0/3	0/3	0/3	0/3
Chemosis*	2/3	2/3	2/3	2/3	1/3	0/3	0/3	0/3
Discharge**	2/3	2/3	2/3	2/3	1/3	0/3	0/3	0/3

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

** Score of 2 or more, but discharge is not a positive effect according to the grading scale

A. **Observations:** Corneal opacity was observed in two rabbits from 48 hours through day 5, with clearing in both on day 6. Iritis was observed in two eyes from 1 hour through day 7, clearing in one eye by day 8 and in the other eye by day 15. Positive conjunctival irritation (score of 2 or more for redness and/or chemosis) was noted in one eye from 1 hour through 72 hours and in another eye from 1 hour through 72 hours. One rabbit eye showed grade 1 redness and chemosis (not considered a positive effect) at 1 hour

B. **Results:** Indoxacarb Topical Solution (containing 19.92% Indoxacarb), a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5, caused positive eye irritation effects (iritis) which persisted in 2/3 rabbit eyes through day 7, clearing in one of these eyes by day 8 and in the other by day 15.

C. **Reviewer's conclusions:** Since eye irritation was still present in two eyes on day 7, with clearing by day 8 and 15, Indoxacarb Topical Solution (containing 19.92% Indoxacarb) is in EPA Toxicity Category II for eye irritation.

Reviewer: Byron T. Backus, Ph.D. **Date:** March 5, 2009
Risk Manager (EPA): 07

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

TEST MATERIAL: Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5.

SYNONYMS: SPAH 1.0

CITATION: Mallory, V. (2007) Primary Dermal Irritation Study in Rabbits with Indoxacarb Topical Solution (EAA): Final Report. Project Number: OT/07/0040, 0420LS17/013. Unpublished study prepared by Calvert Preclinical Services, Inc. 48 p. December 19, 2007. MRID 47424506.

SPONSOR: Schering-Plough Animal Health Corporation, 556 Morris Avenue, Summit, NJ 07901.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47424506), three male adult New Zealand White rabbits (age: 13-14 weeks; source: Harlan) were dermally exposed to 0.5 mL of undiluted Indoxacarb Topical Solution (EAA), a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5 containing 19.92% Indoxacarb for 4 hours on an 5 cm x 5 cm area of the clipped dorsal trunk. The test article was covered with a gauze patch which was held in contact with the skin with a sheet of rubber dam. The trunk of each rabbit was wrapped with an elastic bandage dressing, which was held in place with non-irritating tape. At the end of 4 hours residual test material was removed with water and gauze. The animals were observed and irritation was scored at 30-60 minutes and 24, 48, and 72 hours after patch removal.

No irritation was noted (all scores for erythema and/or edema were zero). The PDII = 0.0.

In this study, the formulation was non-irritating with the Primary Dermal Irritation Index (PDII) equal to zero. Indoxacarb Topical Solution (EAA), a light yellow liquid with a specific gravity of 1.12 g/mL and a pH ~5, with 19.92% Indoxacarb, is classified as EPA Toxicity Category IV for primary dermal irritation.

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

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Animal Number	Sex	Hours			
		½-1	24	48	72
2076	M	0/0[a]	0/0	0/0	0/0
2077	M	0/0	0/0	0/0	0/0
2078	M	0/0	0/0	0/0	0/0
Severity of Irritation – Mean Score		0.0/0.0	0.0/0.0	0.0/0.00	0.0/0.0

[a] Erythema/edema

A. **Observations:** No irritation was observed.

B. **Results:** The Primary Dermal Irritation Index (PDII) was 0.0 (all scores were zero).

C. **Reviewer's conclusions:** Indoxacarb Topical Solution (EAA) is in EPA Toxicity Category IV for dermal irritation.

Reviewer: Byron T. Backus, Ph.D. **Date:** March 5, 2009
Risk Manager (EPA): 07

STUDY TYPE: Dermal Sensitization – guinea pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5.

SYNONYMS: SPAH 1.0

CITATION: Mallory, V. (2007) Guinea Pig Sensitization - Maximization Test (Magnusson-Kligman Method) with Indoxacarb Topical Solution (EAA): Final Report. Project Number: OT/07/0041, 0423GS17/013. Unpublished study prepared by Calvert Preclinical Services, Inc. 105 p. December 20, 2007. MRID 47424507.

SPONSOR: Schering-Plough Animal Health Corporation, 556 Morris Avenue, Summit, NJ 07901.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47424507) with Indoxacarb Topical Solution containing 19.92% Indoxacarb, described as a light yellow liquid with a specific gravity of 1.12 g/mL, a group of 5 male and 5 female Hartley albino guinea pigs (Ages: ~3 weeks; males: 330-408 g; females: 304-381 g; source: Elm Hill Breeding Laboratories, Chelmsford, MA 01824) received (on Day 1) 3 pairs of 0.1 mL injections of the following: (1 & 2): Freund's Complete Adjuvant (FCA) 1:1 mixture with distilled water; (3 & 4): the test article (5% w/v) in vehicle; and (5 & 6): the test article (5% w/w) in vehicle emulsified with FCA. These concentrations were based on a preliminary irritation assay. After six days the test sites were reclipped and pretreated with 10% sodium lauryl sulfate. The following day (Day 8) 0.3 mL undiluted test article was spread over a 2 x 4 cm filter paper which was applied to the injection site area and occluded using Blenderm® tape, which was held in place for 48 hours, after which the induction sites were unwrapped and any residual material was removed with gauze and water.

A group of 5 (3 male and 2 female) animals was similarly treated with vehicle instead of test article in vehicle.

On Day 22 all 15 animals (10 induced, 5 controls) were challenged with 24-hour exposure to occluded patches (measuring 2 x 2 cm), one containing 0.2 mL of undiluted test article and one containing 0.2 mL vehicle (saline solution) on the left and right flanks, respectively. The sites were scored at 24 and 48 hours after the exposure ended.

Following challenge, all sites scored zero in all (previously induced and control) animals at 24 hours. A historical positive control study (conducted October-November 2007) with 1-chloro-2,4-dinitrobenzene (DNCB) elicited positive responses (scores of 2-4 at 24 and/or 48 hours) in 9/9 previously induced animals, but also gave positive responses (scores of 1-2) at 24 and/or 48 hours in controls.

No irritation (all scores zero) was observed following the induction treatments. No dermal reactions (all scores zero) were noted in any animal (induced or naïve control) after challenge.

Based on the results of this study, Indoxacarb Topical Solution, containing 19.92% Indoxacarb, was not a dermal sensitizer. The mean challenge score was 0.0 for naive control and test animals at 24 and 48 hours.

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

COMPLIANCE: Signed and dated GLP, Quality Assurance and [No] Data Confidentiality statements were provided.

PROCEDURE:

A. **Induction**: The animals were induced and challenged according to the Maximization Test (Magnusson-Kligman Method). A group of 5 male and 5 female Hartley albino guinea pigs each received (on Day 1) three paired 0.1 mL injections: (1 & 2): Freund's Complete Adjuvant (FCA) 1:1 mixture in distilled water; (3 & 4): the test article (5% w/v) in vehicle; and (5 & 6): the test article (5% w/w) in vehicle emulsified with FCA. These concentrations were based on a preliminary irritation assay. After six days the test sites were reclipped and pretreated with 10% sodium lauryl sulfate. The following day (Day 8) 0.3 mL undiluted test article was spread over a 2 x 4 cm filter paper which was applied to the injection site area and occluded using Blenderm® tape, which was held in place for 48 hours, after which the tape and filter paper were removed and any residual test material was removed with gauze and water.

B. **Control:** The control animals (3 males and 2 females) were treated the same way as the induced animals during the induction phase, except they were dosed with vehicle instead of test article in vehicle.

C. **Challenge**: On Day 22 all 15 animals (10 induced, 5 controls) were challenged with 24-hour exposure to occluded patches (measuring 2 x 2 cm), one containing 0.2 mL of undiluted test article and one containing 0.;2 mL vehicle (saline solution) on the left and right flanks, respectively. These sites were scored at 24 and 48 hours after the exposure ended.

RESULTS and DISCUSSION:

A. **Reactions and durations**: No dermal irritation was noted on any test or naive control animal at 24 and/or 48 hours following challenge.

B. **Positive control**: The report included the results of a positive control (DNCB) study conducted October-November 2007; the study with Indoxacarb Topical Solution was conducted between October 22, 2007 (first day of dosing) and November 16, 2007.

C. **Reviewer's conclusion**: This reviewer agrees that there was no indication that the test material (Indoxacarb Topical Solution) is a dermal sensitizer.

D. **Reviewer's comment**: The positive control in this assay was DNCB. Although the 870.2600 guidelines specify only that a positive control be used, DNCB is a fairly strong sensitizer in the Maximization test (which may be why the untreated controls also gave a response). A more appropriate positive control material with this protocol would have been HCA (Hexylcinnamaldehyde).

1. **DP BARCODE:** DP353336
2. **PC CODE:** 067710 [Indoxacarb]
3. **CURRENT DATE:** March 6, 2009
4. **TEST MATERIAL:** Indoxacarb Topical Solution (EAA); Lot No./Batch No.: 7083B; containing 19.92% Indoxacarb; described as a light yellow liquid with a specific gravity of 1.12 g/mL and a pH of ~5.

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Calvert Preclinical Services Project No. 0406RS17/013, OT 07-0037 / February 18, 2008	47424502	Estimated female LD_{50} = 2000 mg/kg bw (assumed sigma of 0.5). Approximate 95% confidence interval is 1590 to >20000 mg/kg bw	III	A
Acute dermal toxicity/rat Calvert Preclinical Services Project No. 0422RS17/013, OT/07/0038 / December 19, 2007	47424503	LD_{50} Males > 2000 mg/kg bw LD_{50} Females > 2000 mg/kg bw LD_{50} Combined > 2000 mg/kg bw	III	A
Acute inhalation toxicity/rat	47424504 (waiver request)	Waiver is appropriate based on use pattern (spot-on product applied to cats)	IV	W
Primary eye irritation/rabbit Calvert Preclinical Services Project No. 0421LS17/013, OT/07/0039 / December 19, 2007	47424505	2/3 eyes positive for iritis on day 7; one eye was clear on day 8, other was clear on day 15.	II	A
Primary dermal irritation/rabbit Calvert Preclinical Services Project No. OT/07/0040; 0420LS17/013 / December 19, 2007	47424506	Non-irritating. PDII = 0.0	IV	A
Dermal sensitization/Guinea pig Calvert Preclinical Services Project No. OT/07/0041, 0423GS17/013 / December 20, 2007	47424507	Not a sensitizer.	-	A

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