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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 5 1996

MEMORANDUM

Subject: I.D. Nos.: 011556-REN 011556-RER, 011556-RRA, 011556-RRI, 011556-RRO, 011556-RRT. Imidacloprid. Evaluation of Product Labeling Data Submitted and Identification of Outstanding Toxicology Data Requirements

Tox. Chem. No. 497E
PC Code No. 129099
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Submission Nos. S489234, S489235, S489237, S489241, S489250, S489251

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M. S. Ottley 3/5/96

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Marion Copley 3/1/96

I. CONCLUSIONS

The existing database supports the following proposed uses for Imidacloprid in the table below. Note the following modifications from the original requests: not for use on 1) kittens, or 2) dogs less than 4 months of age.

The 6 acute studies conducted on the formulation (Imidacloprid (Bay T 7491) 10 %) in the above labels are all adequate. This formulation is toxicity category III for acute oral, dermal and inhalation, II for eye irritation, IV for dermal irritation and not a sensitizer.

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Product I.D.	Submission	Formulation	Application
011556-RRO (Bayer Corp.)	Registration	Advantage 10	For use on dogs 10 lb and under and at least four months old.
011556-RRT (Bayer Corp.)	Registration	Advantage 20	For use on dogs 11 - 20 lbs. body wt. and at least 4 months old.
011556-REN (Bayer Corp.)	Registration	Advantage 55	For use on dogs over 20 lbs. body wt. and at least 4 months old.
011556-RER (Bayer Corp.)	Registration	Advantage 110	For use on dogs over 55 lbs.
011556-RRA (Bayer Corp.)	Registration	Advantage 9	For use on adule cats 9 lbs. and under.
0011556-RR1 (Bayer Corp.)	Registration	Advantage 18	For use on cats over 9 lbs.

II. ACTION REQUESTED

TB-1 received for evaluation applications for registration of Advantage 10, Advantage 20, Advantage 55 and Advantage 110 for use on dogs; and Advantage 9 and Advantage 18 for use on cats. TB-1 was asked to evaluate these against the data submitted on the respective imidacloprid formulations to determine if it is adequate to fulfill relevant data requirements. Registration Division has informed TB1 that Imidacloprid formulation Spot On (Imidacloprid 10 %) is the same as Pour On (Imidacloprid 10 %) formulation used in the acutes. All the products identified in the above labels vary only by the size of the single use tubes and the species, age and weight of the animal to be treated.

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III. RESULTS/DISCUSSION

The requirements (CFR 158.135) for uses for Non-Food Uses on pets (for previously registered chemicals) for the Technical and formulation are listed in the following table.

Test	Technical		Formulations§	
	Required	Satisfied	Required	Satisfied
81-1 Acute Oral Toxicity	Y	Y	Y	Y
81-2 Acute Dermal Toxicity	Y	Y	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y	Y	Y
81-4 Primary Eye Irritation	Y	Y	Y	Y
81-5 Primary Dermal Irritation	Y	Y	Y	Y
81-6 Dermal Sensitization	Y	Y	Y	Y
86-1 Acute Dermal Toxicity (Cat)	N	-	Y	Y
86-1 General Safety Evaluation (Cat)	N	-	Y	Y
86-1 Acute Dermal Toxicity (Dog)	N	-	Y	Y
86-1 General Safety Evaluation (Dog)	N	-	Y	Y

Y=Yes N=no § Advantage-9, -10, -18, -20, -55, -110 Formulations

Data Gaps

The number of kittens tested with Imidacloprid (10 - 11 weeks (MRID 43679502)) was too small. The number of puppies (less than 4 months of age) was also too small (MRID 43679608). Since metabolic pathways are not fully developed in young animals, their toxicity profiles may be different after imidacloprid exposure from the adult animals tested. As a result, the labels for the imidacloprid formulations should restrict usage of the products to 1) adult cats, and 2) dogs above four months of age. It should be noted that puppies and kittens are considered as separate groups/sex from the adults. The optimum number/sex/age group is six, however 4 is currently being considered minimally adequate until new guidelines are approved. The current studies had only 0-3/sex for puppies (less than 4 months of age) and kittens. In this case, puppies greater than 4 months of age are being considered with the adult groups (this combining is being considered on a case by case basis). Therefore, there are no adequate safety data on 1) kittens, and 2) dogs below the age of 4 months.

The usages/labels covered in this memo should be modified as follows:

Label	Usage (current label)	Restrictions to be added
Advantage 9	For cats and kittens 9 lb and under	Label modification and usage restriction: Not for use on kittens.
Advantage 18	For cats over 9 lb.	None

Label	Usage (current label)	Restrictions to be added
Advantage 10	For small dogs and puppies 10 lbs and under	Label modification and usage restriction: Not for use on puppies under four months.
Advantage 20	For Dogs 11 - 20 lbs	Label modification and usage restriction: Not for use on puppies under four months.
Advantage 55	For dogs over 20 lb	Label modification and usage restriction: Not for use on puppies under four months weeks.
Advantage 110	For dogs over 55 lb	None

No other outstanding data gaps have been identified for these proposed registrations.

Margins of Safety

Dogs and cats were tested at levels up to 50 mg/kg without significant adverse effects. Below is a tabulation of the dose levels expected from exposure to the formulation, and the margins of safety expected at that dose compared with the dose level tested.

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Label	Dose Volume, ml	A.I. conc. %	Total Dose, mg	Min. animal wt, lb (kg) on label	Dose level, mg/kg from label use	Margin of Exposure
Advantage 9	0.4	9.1	36.4	≤ 9 (4.1)	≥ 8.9	≤ 5.6
Advantage 18	0.8	9.1	72.8	≥ 9 (4.1)	≤ 14.8	≥ 2.8
Advantage 10	0.4	9.1	36.4	≤ 10 (4.5)	≤ 8.0	≤ 6.2
Advantage 20	1.0	9.1	91.0	11 - 20 (5.0 - 9.1)	≤ 18.2	≥ 2.7
Advantage 55	2.5	9.1	227.5	≥ 20 (9.1)	≤ 25.0	≥ 2.0
Advantage 110	5.0	9.1	445.0	≥ 55 (25)	≤ 17.8	≥ 2.8

The NOEL was 50 mg/kg/day for both dogs and cats.
the Margin of Exposure is the NOEL / proposed dose level

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IV. SUMMARY OF THE TOXICITY DATA BASE FOR IMIDACLOPRID 10% FORMULATION

Study Identification	Material	MRID No.	Results	Classification
81-1 Acute Oral Toxicity in rats Bayer Corp. Study #95-012-DO, April 25, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679601	<p>Groups of fasted, eight to 10 week old Sprague-Dawley rats (6/sex) were given a single oral dose of Bay t 7391 Pour On (Imidacloprid 10%), at doses of 495, 1020, 1430, 1910 or 2620 mg/kg and observed for 14 days.</p> <p>Oral LD₅₀ Males = 1943 mg/kg (95% C.I. not calculable) Females = 1732 mg/kg (95% C.I. 1416 - 2147 mg/kg) Combined = 1838 mg/kg (95% C.I. not calculable)</p> <p>Imidacloprid Bay T-7391 10% Pour-On is TOXICITY CATEGORY III based on the LD₅₀ in females.</p> <p>Treatment related clinical signs such as hypoactivity, clonic convulsions, labored breathing, and oral staining, were observed at all dose levels. No treatment-related body weight changes were observed at any dose level.</p> <p>Treatment-related necropsy signs were observed in those that died during the study, and included nasal staining, red fluid in bladder, bilaterally reddened lungs, and reddened mucosae.</p>	Acceptable
81-2 Acute Dermal Toxicity in rats Bayer Corp. Study #95-022-DQ, April 25, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679602	<p>Groups of young adult Sprague-Dawley rats, six/sex, were dermally exposed to Imidacloprid (Bay t 7391) Pour-On 10% Formulation for 24 hours to a minimum of 10% of body surface area) at doses of 0 or 2000 mg/kg (Limit Dose). Animals then were observed for 14 days.</p> <p>Dermal LD₅₀ Males = >2000 mg/kg (Limit Test) Females = >2000 mg/kg Combined = >2000 mg/kg</p> <p>Pour-On 10% is TOXICITY CATEGORY III. There were no treatment related clinical signs, necropsy findings or changes in body weight.</p>	Acceptable

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Study Identification	Material	MRID No.	Results	Classification
81-3 Acute Inhalation Toxicity in rats Bayer Corp. Study #94-042-CT, April 25, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679603	<p>Groups of young adult Sprague-Dawley rats (six/sex) were exposed by inhalation route to Imidacloprid (Bay t 7391) Pour-On 10% formulation in respirable liquid aerosol form for four hours under nose-only conditions at a concentration of 2.415 mg/L. Animals then were observed for 14 days.</p> <p>LC₅₀ Males = >2.415 mg/L Females = >2.415 mg/L Combined = >2.415 mg/L</p> <p>No mortality was observed at this saturation dose level. Imidacloprid (Bay t 7391) Pour-On is TOXICITY CATEGORY IV.</p> <p>Oral staining was observed in treated females but not males. No changes in body weight gain were noted, and necropsy showed no gross lesions.</p>	Acceptable
81-4 Acute Eye Irritation in rabbits Bayer Corp. Study #94-335-CO, April 25, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679604	<p>0.1 ml of Imidacloprid (Bay t 7391) 10% Pour-On Formulation instilled into the conjunctival sac of the left eye of young adult male New Zealand White rabbits for four hours. Animals then were observed for 14 days. Irritation was scored by the FIFRA guideline method.</p> <p>The test substance produced corneal opacity, iritis, conjunctival redness and chemosis, and ocular discharge were observed in one or more animals. All signs had resolved within 14 days. In this study, Imidacloprid (Bay t 7391) 10% Pour-On Formulation is a moderate eye irritant and is considered as TOXICITY CATEGORY II for primary eye irritation.</p>	Acceptable

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Study Identification	Material	MRID No.	Results	Classification
81-5 Primary Dermal Irritation in Rabbits Bayer Corp. Study #94-325-CN, April 25, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679605	<p>six young adult male New Zealand White rabbits were dermally exposed to 0.5 ml of Imidacloprid (Bay T 7391) 10% Pour-On formulation for four hours to an unspecified surface area of the shaved back. Animals then were observed for seven days. Irritation was scored according to the US EPA Pesticides Assessment Guidelines, Subdivision F Series 81-5, January, 1988.</p> <p>Mild erythema was observed in one animal at 24 hrs, cleared up by 48 hours. In this study, Imidacloprid (Bay T 7391) 10% Pour-On formulation is a mild dermal irritant. Imidacloprid (Bay T 7391) 10% Pour-On formulation is TOXICITY CATEGORY IV for primary dermal irritation.</p>	Acceptable
81-6 Dermal Sensitization in guinea pigs Bayer Corp. Study #94-324-CW, April 27, 1995	Imidacloprid 10% formulation Batch #101191-031-S	43679606	<p>Using undiluted Imidacloprid (Bay T 7391) 10% Pour-On formulation, adult Hartley albino guinea pigs (10 inducible/sex, 5 controls/sex) were tested using the Buehler Topical Closed-Patch Technique.</p> <p>Clinical signs of toxicity were not observed following treatment. No observations of erythema were made from any animal at any time. In this study, Imidacloprid (Bay T 7391) 10% Pour-On formulation is not a dermal sensitizer.</p>	Acceptable

Study Identification	Material	MRID No.	Results	Classification
<p>86-1 Acute Domestic Animal Safety in Cats Miles Inc. Study #TR-94D-010, March 31, 1995</p>	<p>Imidacloprid 10% formulation Batch #101191-031-S</p>	<p>43679501</p>	<p>a total of 4 males and 5 females in 3 groups (1-2 sex/group) were dermally exposed to Imidacloprid, 10% Spot-On formulation. Dose levels were 50 mg/kg/day x 1 day, and 50 mg/kg/day x 3 days. Controls received placebo (Formulation less active ingredient) at 50 mg/kg/day x 3 days. Animals then were observed for 14 days.</p> <p>No major treatment related dermal, clinical signs, body weight effects or clinical chemistry changes were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that cats can tolerate 50 mg/kg without significant adverse reactions.</p> <p>This acute dermal study is classified as Acceptable when combined with another study (see below). The number of animals/group is too small and not in keeping with general study practice. However, when data are combined with the companion study in the cat (MRID 43679502), the information is considered useful. This satisfies the requirements for a domestic animal study in the cat.</p>	<p>Acceptable</p>

Study Identification	Material	MRID No.	Results	Classification
<p>86-1 Domestic Animal Safety in Cats Miles Inc. Study #TR-95F-006, April 24, 1995</p>	<p>Imidacloprid 10% formulation Batch #101191-031-S</p>	<p>43679502</p>	<p>In a repeated dose toxicity study (MRID 43679502), 18 cats of various and mixed breed (3 or 4 males, 2 or 3 females per group of which 1 or 2 males/group and 1 or 2 females/group were 11 - 12 weeks old) were dermally exposed to Imidacloprid, 10% Spot-On at seven-day intervals for a total of eight treatments. Dose levels were 10 or 50 mg/kg. Controls received placebo (formulation less active ingredient) at 50/mg/kg.</p> <p>No major treatment related dermal, clinical signs, body weight effects or clinical chemistry/hematology were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult cats can tolerate up to 50 mg/kg of the active ingredient without significant reactions.</p> <p>This repeated dose dermal study is classified as Acceptable only for adult cats and satisfies the requirement for a Domestic Animal Safety study for topical use in adult cats when combined with another study (MRID 43679501). There were not enough kitten to adequately test the safety of this chemical.</p>	<p>Acceptable</p>

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Study Identification	Material	MRID No.	Results	Classification
<p>86-1 Domestic Animal Safety in Dogs Miles, Inc. Study #TR-94D-010, March 30, 1995</p>	<p>Imidacloprid 10% formulation Batch #101191-031-S</p>	<p>43679607</p>	<p>In a dermal toxicity study (MRID 4369607), nine adult dogs of mixed breed (3 males, 6 females, one male and two females/group) were dermally exposed to Imidacloprid, 10% Spot-On. Dose levels were 50 mg/kg/day x 1 day, and 50/mg/kg/day x 3 days. Controls received placebo (formulation less active ingredient) at 50/mg/kg/day x 3 days. Animals then were observed for 14 days.</p> <p>No major treatment related dermal, clinical signs, body weight effects or clinical chemistry changes were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult dogs can tolerate up 50 mg/kg without significant reactions.</p> <p>This acute dermal safety study is classified as Acceptable when combined with another study, and satisfies the requirements for a domestic animal study in the adult dog. The number of animals/sex/group is too small and not in keeping with general study practice. However, when data are combined with the companion study in the dog (MRID 43679608), the information is considered useful.</p>	<p>Acceptable</p>

Study Identification	Material	MRID No.	Results	Classification
<p>86-1 Domestic Animal Safety in Dogs Miles Inc. Study #TR-95D-005, April 17, 1995</p>	<p>Imidacloprid 10% formulation Batch #101191-031-S</p>	<p>43679608</p>	<p>In a repeated dose toxicity study (MRID 43679608), 18 adult dogs of various breeds (3 males and 3 females / group) were dermally exposed to Imidacloprid, 10% Spot-On formulation at seven-day intervals for a total of eight treatments. Dose levels were 10 or 50 mg/kg. Controls received placebo (formulation less active ingredient) at 50/mg/kg.</p> <p>No major treatment related dermal, clinical signs, body weight effects or clinical chemistry/hematology were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult dogs can tolerate up to 50 mg/kg of the active ingredient without significant reactions. Inadequate testing was done in dogs less than four months old.</p> <p>This repeated dose dermal study is classified as Acceptable for only for adult dogs (four months and older) and when combined with another study (MRID 43679607), and satisfies the requirements for a General Safety Evaluation for Topical Use (86-1) in the adult dog. There were not enough puppies to adequately test the safety of this chemical.</p>	<p>Acceptable</p>

IMIDACLOPRID

Domestic Animal Safety Study (86-1)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

MS Ottley, Date 3/4/96

Marion Copley, Date 3/1/96

DATA EVALUATION RECORD

STUDY TYPE: Domestic Animal Safety - Dog
OPPTS 870.7500 [86-1]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL (PURITY): Bay t 7391 Spot On (Imidacloprid 10%)

SYNONYMS: None

CITATION: J.A. Schmidl, R. G. Arther. 1995. Acute Toxicity Evaluation for Dermal Treatment of Dogs with Imidacloprid (Bay t 7391) Spot-On. Miles Inc. Study No. TR-94D-010, March 30, 1995. MRID 43679607

SPONSOR: Miles, Inc.

EXECUTIVE SUMMARY: In a dermal toxicity study (MRID 43679607), nine adult dogs of mixed breed (3 males, 6 females, one male and two females/group) were dermally exposed to Imidacloprid, 10% Spot-On. Dose levels were 50 mg/kg/day x 1 day, and 50/mg/kg/day x 3 days. Controls received placebo (formulation less active ingredient) at 50/mg/kg/day x 3 days. Animals then were observed for 14 days.

No major treatment related dermal, clinical signs, body weight effects or clinical chemistry changes were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult dogs can tolerate up to 50 mg/kg without significant reactions.

This acute safety dermal study is classified as Acceptable when combined with another study, and satisfies the requirements for a domestic animal study in the adult dog. The number of animals/sex/group is too small and not in keeping with general study practice. However, when data are combined with the companion study in the dog (MRID 43679608), the information is considered useful.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Flagging statements were provided. No claims of Data Confidentiality were made.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Spot-On Formulation
 Description: liquid. Color and viscosity not described
 Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
 Purity: 9.04 a.i.
 CAS #: 138261-41-3
 Verification of concentration/homogeneity: confirmed concentration of 9.04%
2. Vehicle: none
3. Test animals: Species: dog Sex: Three males, 6 females
 Strain: varied. 3 Hound, 3 Terrier, one each of Shar-Pei, Chow, Spitz.
 Age and weight at dosing: Age unspecified. Weight: 18-48 lb
 Source: Unspecified
 Acclimation period: Unspecified
 Diet: Science Diet: Maintenance for Dogs
 Water: *ad libitum*

B. STUDY DESIGN and METHODS:

1. In life dates - start: 12/7/94 end: 012/21/94
2. Animal assignment and treatment - Animals were given single or multiple daily doses of 50 mg/kg dermally (Table 1) to the unshaved shoulder area. Dogs were observed daily and weighed daily for 14 days after dosing.

TABLE 1. Doses, animals treated (body wt in lbs.)

Dose (mg/kg)	males	Females	Combined
50 mg/kg x 1 day	1 (48)	2 (22, 29)	3
50 mg/kg x 3 days	1 (46)	2 (30, 32)	3
50 mg/kg x 3 days (placebo**)	1 (23)	2 (23, 32)	3

** placebo: formulation without the active ingredient.

3. Blood Chemistry - Prior to the onset of treatment, blood samples were taken for serum chemistry and hematology. These parameters were compared with those measured in blood samples taken after treatment.

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4. Statistics - Statistical methods were not specified

II. RESULTS AND DISCUSSION:

- A. Clinical observations - no significant clinical observations were noted.
- B. Blood Effects - no significant effects on hematology or serum chemistry were observed.
- D. Body Weight - no adverse effects on body weight were noted.
- E. Necropsy - necropsy was not performed due to lack of toxicity
- F. Deficiencies - The number of animals/group is too small to provide biologically and statistically meaningful data, and is not in keeping with general study practice. The optimum number/sex/age group is six, however 4 is currently being considered minimally adequate until new guidelines are approved. However, the data are useful when combined with the results of the companion study (MRID 43679608). No other significant deficiencies were noted.
- F. Conclusions - This study helps demonstrate that adult dogs can tolerate 50 mg/kg of the a.i.

IMIDACLOPRID

General Animal Safety (86-1)

EPA Reviewer:

Myron S. Ottley, Ph. D.

MS Ottley

Date 3/4/96

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

M Copley

Date 3/1/96

Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: General Safety Evaluation for Topical Use - Dog
OPPTS 870.7500 [S86-1]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL (PURITY): Bay t 7391 Spot On (Imidacloprid 10%)

SYNONYMS: None

CITATION: J.A. Schmidl, R.G. Arther. 1995. General Safety Evaluation for Topical Use of Imidacloprid (Bay t 7391) Spot-On on Dogs. Miles Inc. Study No. TR-95D-005, April 17, 1995. MRID 43679608

SPONSOR: Bayer Corporation

EXECUTIVE SUMMARY: In a repeated dose toxicity study (MRID 43679608), 18 adult dogs of various breeds (3 males and 3 females / group) were dermally exposed to Imidacloprid, 10% Spot-On formulation at seven-day intervals for a total of eight treatments. Dose levels were 10 or 50 mg/kg. Controls received placebo (formulation less active ingredient) at 50/mg/kg.

No major treatment related dermal, clinical signs, body weight effects or clinical chemistry/hematology were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult dogs can tolerate up to 50 mg/kg of the active ingredient without significant reactions. Inadequate testing was done in dogs less than four months old.

This repeated dose dermal study is classified as Acceptable for only for adult dogs (four months and older) and when combined with another study (MRID 43679607), and satisfies the requirements for a General Safety Evaluation for Topical Use (86-1) in the adult dog. There were not enough puppies to adequately test the safety of this chemical.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Flagging statements were provided. No claims of Data Confidentiality were made.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Spot-On Formulation
 Description: liquid. Color and viscosity not described
 Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
 Purity: 9.04% a.i.
 CAS #: 138261-41-3
 Verification of concentration/homogeneity: confirmed at 9.04%
2. Vehicle: none
3. Test animals: Species: dog Sex: 9 M, 9 F, (3/sex/group)
 Strain: varied. 3 Pointer, 3 Shepherd, 3 Hound, 4 Beagle, 1 Collie, 2 Brittany Spaniel, 2 Terrier
 Age and weight at dosing: 8 weeks old through adults.
 Weight: 8 - 50 lb
 Source: Unspecified
 Acclimation period: Unspecified
 Diet: Science Diet: Maintenance for Dog
 Water: *ad libitum*

B. STUDY DESIGN and METHODS:

1. In life dates - start: 01/17/95; end: 03/14/95
2. Animal assignment and treatment - Animals were given eight weekly doses of 10 or 50 mg/kg dermally (Table 1) to the unshaved shoulder area, with special precaution to prevent runoff. Dogs were observed daily for clinical signs and weekly for evidence of dermal irritation. Body weights were taken three weeks into the study in order to adjust dosage volumes as necessary.

TABLE 1. Doses, No. animals treated, initial individual body weights

Dose (mg/kg)	males (bw, lb)	Females bw, lb)	Combined
10 mg/kg/week x 8 weeks	3 (9*, 33, 40)	3 (24, 33, 36)	6
50 mg/kg/week x 8 weeks	3 (8*, 36, 39)	3 (26, 28, 39)	6
50 mg/kg/week x 8 weeks (placebo**)	3 (32, 32, 50)	3 8*, 34, 36)	6

* Denotes puppies and/or small dogs

** Placebo = formulation without active ingredient

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3. Blood Chemistry - Prior to the onset of treatment, blood samples were taken for serum chemistry and hematology. These parameters were compared with those measured in blood samples taken after treatment.
4. Statistics - Statistical methods were not specified

II. RESULTS AND DISCUSSION:

- A. Clinical observations - no significant clinical observations were noted in any of the animals. No signs of dermal irritation were observed.
- B. Blood Effects - no significant effects on hematology or serum chemistry were observed.
- D. Body Weight - no adverse effects on body weight were noted.
- E. Necropsy - no significant findings were made at necropsy. No lesions were found upon histopathological examination.
- F. Deficiencies - Animal group sizes are small. The group sizes of the youngest dogs/puppies (8 weeks) is too small for meaningful evaluation. No other deficiencies were noted in this study.
- G. Conclusions - This study helps demonstrate that adult dogs (four months and older) can tolerate 50 mg/kg of the a.i. Although six dogs/sex/group is optimal (recommended group size in upcoming 86-1 guidelines), four dogs/sex/group is considered minimally adequate. Although this study has only three animals/sex/group, when these data are evaluated with the companion study (MRID 43679601) meaningful conclusions can be drawn.

IMIDACLOPRID

Domestic Animal Safety Study (86-1)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

MSO Ottley, Date 3/4/96

Marion Copley, Date 3/1/96

DATA EVALUATION RECORD

STUDY TYPE: Domestic Animal Safety - Cat
OPPTS 870.7500 [86-1]

DP BARCODE: D216769, D216775

SUBMISSION CODE: S489251, S489250

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL (PURITY): Bay t 7391 Spot On (Imidacloprid 10%)

SYNONYMS: None

CITATION: J.A. Schmidl, R. G. Arther. 1995. Acute Toxicity Evaluation for Dermal Treatment of Cats with Imidacloprid (Bay t 7391) Spot-On. Miles Inc. Study No. TR-94D-010, March 31, 1995. MRID 43679501

SPONSOR: Miles, Inc.

EXECUTIVE SUMMARY: In a dermal toxicity study (MRID 43679501), a total of 4 males and 5 females in 3 groups (1-2/sex/group) were dermally exposed to Imidacloprid, 10% Spot-On formulation. Dose levels were 50 mg/kg/day x 1 day, and 50/mg/kg/day x 3 days. Controls received placebo (Formulation less active ingredient) at 50/mg/kg/day x 3 days. Animals then were observed for 14 days.

No major treatment related dermal, clinical signs, body weight effects or clinical chemistry changes were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that cats can tolerate 50 mg/kg without significant adverse reactions.

This acute dermal study is classified as Acceptable when combined with another study (see below). The number of animals/group is too small and not in keeping with general study practice. However, when data are combined with the companion study in the cat (MRID 43679502), the information is considered useful. This satisfies the requirements for a domestic animal study in the cat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Flagging statements were provided. No claims of Data Confidentiality were made.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Spot-On Formulation
Description: liquid. Color and viscosity not described
Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
Purity: 9.04% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: at 9.04%
2. Vehicle: none
3. Test animals: Species: cat Sex: Four males, 5 females
Strain: varied. Six tabby, three Tiger
Age and weight at dosing: Age unspecified. Adult animals used. Weight: 6.0 - 12.1 lb
Source: Unspecified
Acclimation period: Unspecified
Diet: Science Diet: Feline *ad libitum*
Water: *ad libitum*

B. STUDY DESIGN and METHODS:

1. In life dates - start: 01/10/95 end: 01/24/95
2. Animal assignment and treatment - Animals were given a single dose of 50 mg/kg dermally (Table 1) to the unshaved shoulder area, with special precaution to prevent runoff. Cats were observed daily and weighed daily for 14 days after dosing.

TABLE 1. Doses, animals treated (from p.7 of study)

Dose (mg/kg)	males	Females	Combined
50 mg/kg x 1 day	1	2	3
50 mg/kg x 3 days	2	1	3
50 mg/kg x 3 days (placebo**)	1	2	3

** placebo: formulation without the active ingredient.

3. Blood Chemistry - Prior to the onset of treatment, blood samples were taken for serum chemistry and hematology.

These parameters were compared with those measured in blood samples taken after treatment.

4. Statistics - Statistical methods were not specified

II. RESULTS AND DISCUSSION:

- A. Clinical observations - no significant clinical observations were noted. Elizabethan collars were initially used, but were removed after 4 hours due to stress they induced.
- B. Blood Effects - no significant effects on hematology or serum chemistry were observed.
- D. Body Weight - no adverse effects on body weight were noted.
- E. Necropsy - necropsy was not performed due to lack of toxicity
- F. Deficiencies - The number of animals/group is too small to provide biologically and statistically meaningful data, and is not in keeping with general study practice. The optimum number/sex/age group is 6, however 4 is currently being considered minimally adequate until new guidelines are approved. However, the data are useful when combined with the results of the companion study (MRID 43679502). No other significant deficiencies were noted.
- G. Conclusions - This study helps demonstrate that cats can tolerate 50 mg/kg of the a.i.

IMIDACLOPRID

Domestic Animal Safety Study (86-1)

EPA Reviewer:

Myron S. Ottley, Ph. D.

MS Ottley, Date 3/4/96

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Marion Copley, Date 3/1/96

Review Section IV, Toxicology Branch I (7509C)

DATA EVALUATION RECORD**STUDY TYPE:** Domestic Animal Safety Study - Cat
OPPTS 870.7500 [86-1]**DP BARCODE:** D216769, D216775**SUBMISSION CODE:** S489251, S489250**P.C. CODE:** 129099**TOX. CHEM. NO.:** 497E**TEST MATERIAL (PURITY):** Bay t 7391 Spot On (Imidacloprid 10%)**SYNONYMS:** None**CITATION:** J.A. Schmidl, R.G. Arther. 1995. General Safety Evaluation for Topical Use of Imidacloprid (Bay t 7391) Spot-On on Cats. Miles Inc. Study No. TR-95F-006, April 24, 1995. MRID 43679502**SPONSOR:** Bayer Corporation**EXECUTIVE SUMMARY:** In a repeated dose toxicity study (MRID 43679502), 18 cats of various and mixed breed (3 or 4 males, 2 or 3 females per group of which 1 or 2 males/group and 1 or 2 females/group were 11 - 12 weeks old) were dermally exposed to Imidacloprid, 10% Spot-On at seven-day intervals for a total of eight treatments. Dose levels were 10 or 50 mg/kg. Controls received placebo (formulation less active ingredient) at 50/mg/kg.

No major treatment related dermal, clinical signs, body weight effects or clinical chemistry/hematology were observed. Necropsy was not done due to lack of toxicosis. The study demonstrates that adult cats can tolerate up to 50 mg/kg of the active ingredient without significant reactions.

This repeated dose dermal study is classified as Acceptable only for adult cats and satisfies the requirement for a Domestic Animal Safety study for topical use in adult cats when combined with another study (MRID 43679501). There were not enough kittens to adequately test the safety of this chemical.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Flagging statements were provided. No claims of Data Confidentiality were made.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Spot-On Formulation
 Description: liquid. Color and viscosity not described
 Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
 Purity: 9.04% a.i.
 CAS #: 138261-41-3
 Verification of concentration/homogeneity: confirmed at 9.04%
2. Vehicle: none
3. Test animals: Species: cat Sex: 10 males, eight females
 Strain: varied. Nine Tabby, Nine Black/Brown/White (or some variation of)
 Age and weight at dosing: 10 - 11 weeks old for eight cats, age unspecified for the others, but young adult animals used. Weight: 1.9 - 13.1 lb (see table 1).
 Source: Unspecified
 Acclimation period: Unspecified
 Diet: Science Diet: Feline
 Water: *ad libitum*

B. STUDY DESIGN and METHODS:

1. In life dates - start: 01/24/95; end: 03/21/95
2. Animal assignment and treatment - Animals were given eight weekly doses of 10 or 50 mg/kg dermally (Table 1) to the unshaved shoulder area, with special precaution to prevent runoff. Cats were observed daily for clinical signs and weekly for evidence of dermal irritation. Body weights were taken three weeks into the study in order to adjust dosage volumes as necessary.

TABLE 1. Doses, animals treated, initial individual body weights (from p.7 of study)

Dose (mg/kg)	Males #/group (BWs, lb)	Females #/group (BWs, lb)	Combined
50 mg/kg/week x 8 weeks placebo **	3 (3.6*, 7.3, 13.1)	3 (2.0*, 2.9*, 5.8)	6
10 mg/kg/week x 8 weeks	4 1.9*, 2.5*, 8.1, 9.0)	2 (2.0*, 8.3)	6

Dose (mg/kg)	Males #/group (BWs, lb)	Females #/group (BWs, lb)	Combined
50 mg/kg/week x 8 weeks	3 (2.9*, 8.6, 8.8)	3 (2.2*, 5.1, 7.2)	6

* Denotes young cats, 10-11 weeks old

** Placebo = formulation without active ingredient.

3. Blood Chemistry - Prior to the onset of treatment, blood samples were taken for serum chemistry and hematology. These parameters were compared with those measured in blood samples taken after treatment.
4. Statistics - Statistical methods were not specified

II. RESULTS AND DISCUSSION:

- A. Clinical observations - no significant clinical observations were noted. One Control cat had transient (two days) diarrhea; one LDT cat had intermittent vomition over two days; one HDT cat had poor appetite for two days. These findings were considered normal in laboratory cats. Three Control cats had slight epidermal flaking at the application site after 4th and/or 5th treatments only.
- B. Blood Effects - no significant effects on hematology or serum chemistry were observed.
- D. Body Weight - no adverse effects on body weight were noted.
- E. Necropsy - no significant findings were made at necropsy. No lesions were found upon histopathological examination.
- F. Deficiencies - Animal group sizes are small. The group sizes of the small cats/kittens is too small for meaningful evaluation. No other deficiencies were noted in this study.
- G. Conclusion - This study is classified as ACCEPTABLE and demonstrates that adult cats can tolerate 50 mg/kg of the a.i. without significant reactions. Although six cats/sex/group is optimal (recommended group size in upcoming 86-1 guidelines), four cats/sex/group is considered minimally adequate. Although this study has only three animals/sex/group, when these data are evaluated with the companion study (MRID 43679501) meaningful conclusions can be drawn.

IMIDACLOPRID]

Acute Oral Study (81-1)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

M. Ottley, Date 2/21/96

M. Copley, Date 2/26/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - rat
OPPTS 870.1100 [S81-1]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay t 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. 1995. Acute Oral Toxicity Study with
Imidacloprid (Bay t 7391) Pour-On in Rats. Bayer Corp.
Study No. 95-012-DO, April 25, 1995. MRID 43679601

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID
43679601), groups of fasted, eight to 10 week old Sprague-Dawley
rats (6/sex) were given a single oral dose of Bay t 7391 Pour On
(Imidacloprid 10%), at doses of 495, 1020, 1430, 1910 or 2620
mg/kg and observed for 14 days.

Oral LD₅₀ Males = 1943 mg/kg (95% C.I. not calculable)

Females = 1732 mg/kg (95% C.I. 1416 - 2147 mg/kg)

Combined = 1838 mg/kg (95% C.I. not calculable)

Imidacloprid Bay T-7391 10% Pour-On is TOXICITY CATEGORY III
based on the LD₅₀ in females.

Treatment related clinical signs such as hypoactivity, clonic
convulsions, labored breathing, and oral staining, were observed
at all dose levels. No treatment-related body weight changes were
observed at any dose level. Treatment-related necropsy signs were
observed in those that died during the study, and included nasal
staining, red fluid in bladder, bilaterally reddened lungs, and
reddened mucosae.

This acute oral study is classified acceptable. This study does
satisfy the guideline requirement for an acute oral study (81-1)
in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
 Description: Clear yellow liquid.
 Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
 Purity: 10.1% a.i.
 CAS #: 138261-41-3
 Verification of concentration/homogeneity: confirmed at
 9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle: PEG 400/deionized water (1:1, v/v)
3. Test animals: Species: Rat
 Strain: Sprague-Dawley
 Age and/or weight at dosing: Eight to 10 weeks; Males: 179
 - 260g; Females: 171 - 209g
 Source: sasco Inc., Omaha, Nebraska
 Acclimation period: at least 6 days
 Diet: Purina Rodent Laboratory Chow (formulation #5001-4)
ad libitum
 Water: Municipal tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 01/24/95 end: 02/14/95
2. Animal assignment and treatment - Animals were assigned to the test groups noted in table 1. Following an overnight fast, rats were given a single dose of 495, 1020, 1430, 1910, or 2620 mg/kg by gavage then observed twice daily (once/day on weekends) and weighed every seven days for 14 days. Survivors were sacrificed and a necropsy performed.

TABLE 1. Doses, animals treated

Dose (mg/kg)	Males	Females	Combined
0	6	6	12
495	6	6	12
1020	6	6	12
1430	5	6	12
1910	6	6	12
2620	6	6	11

3. Statistics - The oral LD₅₀ was calculated using an unspecified method.

II. RESULTS AND DISCUSSION:

- A. Mortality is given in table 2. All animals that died were dead by day 3. Seven of the ten died on the day of treatment (day 0).

Dose (mg/kg)	Mortality--No. Dead/No. Exposed		
	Males	Females	Combined
0	0/6	0/6	0/12
495	0/6	0/6	0/12
1020	0/6	0/6	0/12
1430	0/5	1/6	1/11
1910	2/6	4/6	3/12
2620	6/6	6/6	12/12

The oral LD₅₀ Males = 1943 mg/kg (95% C.I. not calculable)
 Females = 1732 mg/kg (95% C.I. 1416 - 2147 mg/kg)
 Combined = 1838 mg/kg (95% C.I. not calculable)

- B. Clinical observations - In general, signs were first observed in both sexes shortly after dosing, and were resolved by day three. Treatment related signs clonic convulsions, hypoactivity, increased reactivity, labored breathing, locomotor incoordination, moribundity, oral and nasal staining, urine staining and tremors.
- C. Body Weight - No significant differences or trends toward differences were noted in the rate of body weight gain between groups of controls and surviving animals.
- D. Necropsy - In males and females that died during the study, the following treatment-related findings were made: evidence of salivation, nasal staining, red fluid located in the bladder, bilaterally reddened lungs; and reddened stomach mucosae.
- E. Deficiencies - No deficiencies in study design or conduct were noted.

IMIDACLOPRID

Acute Dermal Study (81-2)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

M. Ottley, Date 2/21/96

M. Copley, Date 2/26/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - rat
OPPTS 870.1200 [S81-2]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay t 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. 1995. Acute Dermal Toxicity Study with Imidacloprid (Bay t 7391) Pour-On in Rats. Bayer Corp. Study No. 95-022-DQ, April 25, 1995. MRID 43679602

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 43679602), groups of young adult Sprague-Dawley rats, six/sex, were dermally exposed to Imidacloprid (Bay t 7391) Pour-On 10% Formulation for 24 hours to a minimum of 10% of body surface area) at doses of 0 or 2000 mg/kg (Limit Dose). Animals then were observed for 14 days.

Dermal LD₅₀ Males = >2000 mg/kg (Limit Test)

Females = >2000 mg/kg

Combined = >2000 mg/kg

Pour-On 10% is TOXICITY CATEGORY III. There were no treatment related clinical signs, necropsy findings or changes in body weight.

This acute dermal study is classified as Acceptable. It satisfies the guideline requirement for an acute dermal study (81-2) in the rat.

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

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
Description: Clear yellow liquid.
Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
Purity: 10.1% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: confirmed at
 9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle: None
3. Test animals: Species: Rat
Strain: Sprague-Dawley
Age and/or weight at dosing: Eight to 10 weeks; Males: 232
 - 271g; Females: 206 - 244g
Source: Sasco Inc., Omaha, Nebraska
Acclimation period: at least 6 days
Diet: Purina Rodent Laboratory Chow (formulation #5001-4)
ad libitum
Water: Municipal tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 01/25/95 end: 02/09/95
2. Animal assignment and treatment - Animals were assigned to the test groups noted in table 1. Animals were given a single dose of Imidacloprid 10% Pour-On dermally, applied to a shaved portion of the back via plastic backed gauze pad held in place with hypoallergenic tape and an elastic bandage. After 24 hours the test substance was removed by wiping the area with damp paper towels. Animals were observed twice daily (once/day on weekends) and weighed every seven days for 14 days after dosing. Survivors were sacrificed and a necropsy was performed.

TABLE 1. Doses, mortality/animals treated

Dose (mg/kg)	males	Females	Combined
0	6	6	12
2000	6	6	12

3. Statistics - The dermal LD₅₀ was not calculated due to low toxicity.

II. RESULTS AND DISCUSSION:

A. Mortality All animals survived the study.

The dermal LD₅₀ for males is >2000 mg/kg
females is >2000 mg/kg
combined is >2000 mg/kg

B. Clinical observations - No treatment-related effects were noted in males or females.

C. Body Weight - No treatment-related changes in body weight gain were observed.

D. Necropsy - No treatment-related gross pathological observations were noted. No dermal irritation was reported.

E. Deficiencies - No deficiencies were noted.

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

Date

2/21/96

Date

2/26/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - rat
OPPTS 870.1300 [S81-3]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay t 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. and Berry, L.A. 1995. Acute Four-Hour Inhalation Toxicity Study with Imidacloprid (Bay t 7391) 10% Pour-On in Rats. Bayer Corp. Study No. 94-042-CT, April 25, 1995. MRID 43679603

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 43679603), groups of young adult Sprague-Dawley rats (six/sex) were exposed by inhalation route to Imidacloprid (Bay t 7391) Pour-On 10% formulation in respirable liquid aerosol form for four hours under nose-only conditions at a concentration of 2.415 mg/L. Animals then were observed for 14 days.

LC₅₀ Males = >2.415 mg/L

Females = >2.415 mg/L

Combined = >2.415 mg/L

No mortality was observed at this saturation dose level. Imidacloprid (Bay t 7391) Pour-On is TOXICITY CATEGORY IV. Oral staining was observed in treated females but not males. No changes in body weight gain were noted, and necropsy showed no gross lesions.

This acute inhalation study is classified as Acceptable. It satisfies the guideline requirement for an acute inhalation study (81-3) in the rat.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
Description: Clear yellow liquid.
Lot/Batch #: 101194-031-S
Purity: 9.88% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: confirmed at
9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle and/or positive control: None
3. Test animals: Species: Rat
Strain: Sprague-Dawley
Age and weight at dosing: Seven - eight weeks; Males:
203 - 228 g. Females: 189 - 211 g.
Source: Sasco, Inc.
Acclimation period: at least six days
Diet: Purina Rodent Laboratory Chow (formulation #5001-4)
ad libitum
Water: Municipal tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 12/05/94 end: 12/19/94
2. Exposure conditions - Animal exposures were conducted under dynamic operating conditions (continuous airflow through the chamber). During the exposure period, generator and exhaust air flows, temperature, and relative humidity in the chambers generally were recorded at approximately five-minute intervals. The desired ranges for chamber temperatures and humidity were 22 ± 2 C and $50 \pm 10\%$, respectively.
3. Animal assignment and treatment - Animals were assigned to the test groups noted in table 1. Rats were exposed to Imidacloprid 10% Pour-On by nose only exposure for 4 hours. They were observed twice daily (once on weekends) and weighed on days 3, 7 and 14 after dosing. Survivors were sacrificed and a necropsy performed.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Nominal Conc. (mg/L)	Analytical Conc. (mg/L)	MMAD μm	GSD μm	Males	Females	Combined
0	0			6	6	12
7.620	2.415	1.62	1.51	6	6	12

4. Generation of the test atmosphere and description of the chamber: The test substance was generated as liquid aerosol by nebulization. Supplied via peristaltic pump at a rate of approx. 0.14 ml/min, the aerosol was sprayed directly into the chamber, along with conditioned air at a flow rate of 20 l/min.

Test atmosphere concentration - Actual chamber concentrations were determined analytically. samples were taken at approx. hourly intervals near the breathing zone within the chamber. Sartorius TYPE PTFE filters (pore size of 0.45 μm) were used at a sampling rate of near 2 Lpm. The test substance was quantified from filtered material by liquid chromatography after extraction in acetonitrile. Chamber concentrations were calculated by correction of quantified Imidacloprid (Bay T-7391) 10% Pour On (mg/m^3) and were calculated by correction of quantified test substance formulation concentration and volume of air filtered. Results are in Table 1 above.

Particle size determination Samples were collected during generation within the chamber breathing zone by a TSE Aerodynamic Particle Sizer (Model 3310) and Diluter (Model 3302), interfaced to an IBM PS/2-50 computer. Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation were calculated from the values of cumulative percent mass. Results are in Table 1 above.

5. Statistics - The LC_{50} was not calculated due to lack of mortality.

II. RESULTS AND DISCUSSION:

A. Mortality is given in table 1. No deaths were observed.

The LC_{50} (C.I.) for males is >2.415 mg/L
 females is >2.415 mg/L
 combined is >2.415 mg/L

B. Clinical observations - Oral staining was observed in two of six treated females. Animals recovered fully by day 1 post exposure. No clinical signs of treatment-related toxicity were observed in males.

C. Body Weight - No treatment-related changes in body weight gain was observed in males or females.

D. Necropsy - No gross lesions were observed in any animal.

E. Deficiencies - None

IMIDACLOPRID

Primary Eye Irritation Study (81-4)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

M. Ottley

Date 2/26/96

M. Copley

Date 2/26/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Eye Irritation - Rabbit
OPPTS 870.2400 [§81-4]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay t 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. 1995. Primary Eye Irritation Study with Imidacloprid (Bay T 7391) Pour-On in Rabbits. Bayer Corp. Study No. 94-335-CO, April 25, 1995. MRID 43679604

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In a primary eye irritation study [MRID 43679604], 0.1 ml of Imidacloprid (Bay t 7391) 10% Pour-On Formulation instilled into the conjunctival sac of the left eye of young adult male New Zealand White rabbits for four hours. Animals then were observed for 14 days. Irritation was scored by the FIFRA guideline method.

The test substance produced corneal opacity, iritis, conjunctival redness and chemosis, and ocular discharge were observed in one or more animals. All signs had resolved within 14 days. In this study, Imidacloprid (Bay t 7391) 10% Pour-On Formulation is a moderate eye irritant and is considered as TOXICITY CATEGORY II for primary eye irritation.

This study is classified as Acceptable, and satisfies the guideline requirement for a primary eye irritation study (81-4) in the rabbit.

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

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
Description: Clear yellow liquid.
Lot/Batch #: 101194-031-S
Purity: 9.88% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: confirmed at 9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle: None
3. Test animals: Species: Rabbit
Strain: New Zealand White
Age and weight at dosing: 11 weeks, weight not specified
Source: Small Stock Industries, Pea Ridge, AR
Acclimation period: six days
Diet: Agway Prolab Rabbit Formula, approx. 125 g/animal/day
Water: Municipal tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 11/28/94 end: 12/12/94
2. Animal assignment and treatment - One-tenth of an ml of test substance was placed in the conjunctival sac of the left eye of each of six male rabbits, then the eye lid was held shut for one second. The right eye served as a control. Animals were examined one, 24, 48 and 72 hr following treatment and were graded according to criteria described in FIFRA guidelines [Subdivision F, Guideline 81-4, 1984]. Animals were also examined on days 7 and 14 post treatment to observe reversibility of ocular lesions.

II. RESULTS AND DISCUSSION:

- A. Table 1 shows the profile to eye irritation observed follow administration of the test substance. While effects on the cornea and iris were minimal, they persisted through the day seven observation point. Effects on the conjunctiva were more marked with moderate chemosis and discharge being observed in all animals. Mild redness was also observed in all animals. While these effects also persisted through the day seven observation point, all lesions had completely reversed by day 14.

Table 1. Eye Irritation and Lesions following Dosing of Left Eye with 0.1 ml of test substance [Values are means of six animals]

Time	Cornea	Iris	Conjunctiva		
			Redness	Chemosis	Discharge
1 Hour	1.00	0.17	0.00	3.00	2.00
24 Hrs	1.00	0.67	1.50	2.17	1.67
48 Hrs	1.00	0.67	1.33	1.50	1.50
72 Hrs	0.83	0.67	1.33	1.67	1.00
7 Days	0.17	0.17	0.67	0.67	0.00
14 Days	0.00	0.00	0.00	0.00	0.00

B. Deficiencies - None noted.

IMIDACLOPRID

Primary Dermal Irritation Study (81-5)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

M. Ottley
Date 2/11/96

M. Copley
Date 2/21/96

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS 870.2500 [§81-5]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay t 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. 1995. Primary Dermal Irritation Study with Imidacloprid (Bay T 7391) 10% Pour-On in Rabbits. Bayer Corp. Study No. 94-325-CN, April 25, 1995. MRID 43679605

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 43679605), six young adult male New Zealand White rabbits were dermally exposed to 0.5 ml of Imidacloprid (Bay T 7391) 10% Pour-On formulation for four hours to an unspecified surface area of the shaved back. Animals then were observed for seven days. Irritation was scored according to the US EPA Pesticides Assessment Guidelines, Subdivision F Series 81-5, January, 1988.

Mild erythema was observed in one animal at 24 hrs, cleared up by 48 hours. In this study, Imidacloprid (Bay T 7391) 10% Pour-On formulation is a mild dermal irritant. Imidacloprid (Bay T 7391) 10% Pour-On formulation is TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (81-5) in the rabbit.

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

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
Description: Clear yellow liquid.
Lot/Batch #: 101194-031-S (Placebo: 211194-026-S)
Purity: 9.88% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: confirmed at
9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle and/or positive control: None
3. Test animals: Species: Rabbit
Strain: New Zealand White
Age and weight at dosing: 11 weeks, weight not specified
Source: Small Stock Industries, Pea Ridge, AR
Acclimation period: six days
Diet: Agway Prolab Rabbit Formula, approx. 125
g/animal/day
Water: Municipal tap ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 11/28/94 end: 12/13/94
2. Animal assignment and treatment - Six male animals were given a single dose of test substance, applied dermally to the shorn back area via a plastic-backed gauze pad, secured by hypoallergenic tape and an elastic bandage. Exposure duration was four hours, after which the area was wiped to remove residue with paper towels moistened with tap water. Each site was evaluated 0.5-1, 24, 48 and 72 hrs after unwrapping using adjacent, untreated skin as a reference. The scoring method used is described in US EPA Guidelines (81-5).

II. RESULTS AND DISCUSSION:

- A. One animal of the six was observed to have erythema (grade one) 24 hr after dosing. This condition was resolved by the 48 hr observation point. No other signs of toxicity were observed. The calculated Primary Irritation Index is 0.04, Mildly Irritating.
- B. Deficiencies - The area of the dorsal surface treated with the test substance was not specified. However, since the guideline is not specific as to the minimum area to be treated, this deficiency does not disqualify the study.

IMIDACLOPRID

Dermal Sensitization Study (81-6)

EPA Reviewer:

Myron S. Ottley, Ph. D.

Review Section IV, Toxicology Branch I (7509C)

EPA Secondary Reviewer:

Marion P. Copley, D.V.M., D.A.B.T.

Review Section IV, Toxicology Branch I (7509C)

M. S. Ottley, Date 2/21/96

M. P. Copley, Date 2/26/96

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pigs
OPPTS 870.2600 [§81-6]

DP BARCODE: D216799, D216805, D216803, D216801

SUBMISSION CODE: S489241, S489234, S489235, S489237

P.C. CODE: 129099

TOX. CHEM. NO.: 497E

TEST MATERIAL: Bay T 7391 Pour On (Imidacloprid 10%)

SYNONYMS: None

CITATION: Warren, D.L. 1995. Dermal Sensitization Study with Imidacloprid (Bay T 7391) 10% Pour-On in Guinea Pigs. Bayer Corp. Study No. 94-324-CW, April 27, 1995. MRID 43679606

SPONSOR: Bayer Corp.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 43679606) with undiluted Imidacloprid (Bay T 7391) 10% Pour-On formulation, adult Hartley albino guinea pigs (10 inducees/sex, 5 controls/sex) were tested using the Buehler Topical Closed-Patch Technique.

Clinical signs of toxicity were not observed following treatment. No observations of erythema were made from any animal at any time. In this study, Imidacloprid (Bay T 7391) 10% Pour-On formulation is not a dermal sensitizer.

This study is classified as acceptable and satisfies the guideline requirement for a dermal sensitization study (81-6) in the guinea pig.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Imidacloprid 10% Pour-On Formulation
Description: Clear yellow liquid.
Lot/Batch #: 101194-031-S
Purity: 10.1% a.i.
CAS #: 138261-41-3
Verification of concentration/homogeneity: confirmed at
9.88% (11/23/94), 10.01% (02/20/95)
2. Vehicle and/or positive control: None
3. Test animals: Species: guinea pig
Strain: Hartley
Age and weight at start of treatment: Approx 5 weeks old,
weight not specified
Source: Sasco, Madison, WI
Acclimation period: six days
Diet: Agway Prolab Guinea Pig Formula ad libitum
Water: municipal tap water ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - start: 12/06/94 end: 01/06/95
2. Animal assignment and treatment - The test substance was evaluated using the Buehler Topical Closed-Patch Technique. The hair from the appropriate area of each animal was removed on the day preceding treatment using electric clippers. On the treatment day 0.4 ml of test substance was applied to the shorn dorsal area of the animal via an occlusive patch (2 cm x 2 cm) and secured in place. The induced and noninduced (control) groups consisted of 20 (10 male, 10 female) and 10 (5 male, five female) animals, resp. Animals in the induction group received three induction applications of six hours duration each, on study days 0, 7 and 14, followed by a challenge application of six hours duration on day 28. Animals in the control group received only a single six hour application at challenge on day 28. The dose site for all three induction applications was adjacent to the left shoulder and the challenge dose site was adjacent to the left hip. Following exposure the bandages and patches were removed and the dose site was wiped using damp paper towels to remove the test substance.

II. RESULTS AND DISCUSSION:

- A. Induction reactions and duration - No clinical signs of

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- toxicity were noted in any animal. No evidence of erythema was observed in any animal during induction.
- B. Challenge reactions and duration - No evidence of erythema was observed in any animal during challenge. These results indicate that the test substance is not a sensitizer.
- C. Positive control - A positive control study was conducted concurrently with the main study, following the same protocol, with the same number of animals. The positive control substance was 1-chloro-2,4-dinitrobenzene (DNCB). While no animals showed signs of edema at any time, erythema was observed in all treated animals late during the induction phase. The levels of severity were 1.2 in males and 1.4 in females.
- E. Deficiencies - No deficiencies were noted.