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

010079

MAR 10 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA ID No. 003125-EUP: NTN 33893 (a.i.). Request for Experimental Use Permit 003125-EUP-ENU for NTN 33893 (Imidacloprid—proposed), an end-use formulation containing 21% NTN 33893 active ingredient.

Tox. Chem. No. 497E
Submission No. S428979

DP Barcode No. D184479
PC Code No. 129099

From: Myron S. Ottley, Ph.D.
Section IV, Toxicology Branch I
Health Effects Division (H7509C)
MSOttley 3/1/93

To: Portia Jenkins/Dennis Edwards, Jr. (PM19)
Registration Division (H7505C)

Through: Marion P. Copley, D.V.M., D.A.B.T.
Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)
Marion Copley 3/9/93

CONCLUSION

Toxicology Branch I has no objections to the Experimental Use Permits 003125-EUP-ENU for NTN 33893 21% formulation at this time.

The acute oral, dermal and inhalation toxicities demonstrated by NTN 33893 are low; however, it is a moderate eye irritant. Adequate precautions are described on the label for this formulation, and no additional toxicity data are required prior to registration of this EUP.

ACTION REQUESTED

Review the data extant and determine any additional toxicity data requirements and/or the adequacy of the proposed label prior to registration of the EUP for the use of this NTN 33893 formulation in terrestrial non-food applications. Proposed period of use is from January 1, 1993 through January 1, 1996.

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BACKGROUND

NTN 33893 240 F.S. had already passed the New Chemicals Screen (See 12/18/92 memo re: 0003125-UEE), and already has been approved for registration for non-food use (See 1/8/93 memo re: 0003125-URI). The current name for this chemical is PREMISE Termicide, but it is also referred to in various submitter documents as PREMISE 2 TC, NTN 33893 2, and NTN 33893 240 FS.

DISCUSSION

EUP Program

The purpose of the EUP is to test NTN 33893 for effectiveness as a termiticide under normal use conditions under the name PREMISE Termiticide.

The EUP is requested for a period of three years, starting January 1, 1993. A total or 90 homes/yr for 3 yr will be treated with PREMISE Termicide.

A single application will be made to confirmed termite-infested dwellings using established procedures. Based on an application solution volume of 200 gallons/dwelling, at a concentration range of 0.01% to 0.1%, it would require up to 0.859 gallons of NTN 33893 240 F.S. per dwelling. At 90 dwellings per year, approx. 78 gallons/year of NTN 33893 would be required.

Application is restricted to 90 sites within 22 states, namely, North and South Carolinas, Georgia, Alabama, Florida, Oklahoma, Arkansas, Louisiana, Mississippi, Tennessee, Texas, Ohio, Missouri, Illinois, Indiana, Connecticut, Virginia, Maryland, Pennsylvania, New Jersey, Arizona and California.

Supporting Toxicity Data

As stated in CFR 158.340, the following studies comprise the minimal data requirements for an EUP without temporary tolerances for the end product and technical:

81-1	Acute Oral—Rat	81-2	Acute Dermal
81-3	Acute Inhalation—Rat	81-4	Prim. Eye Irrit.—Rabbit
81-5	Prim. Dermal Irritation	81-6	Dermal Sensitization

The following studies have been submitted in support of this EUP. Data evaluated include the technical and the 23.1% formulation. All data were found to be acceptable.

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GUIDELINE		TEST(S) PERFORMED IN COMPLIANCE			
Ref. No.	Description	MRID No. (420553)	Test Substance	Tox. Cat.	Core Grade
81-1	Acute Oral—Rat	-31	Technical	II	Acceptable
		-13	240 F.S.	III	Acceptable
81-2	Acute Dermal	-32	Technical	IV	Acceptable
		-15	240 F.S.	III	Acceptable
81-3	Acute Inhalation—Rat	-33	Technical	IV	Acceptable
		-17	240 F.S.	IV	Acceptable
81-4	Primary Eye Irritation—Rabbit	-34	Technical	IV	Acceptable
		-19	240 F.S.	III	Acceptable
81-5	Primary Dermal Irritation	-35	Technical	IV	Acceptable
		-21	240 F.S.	IV	Acceptable
81-6	Dermal Sensitization	-36	Technical	NA*	Acceptable
		-23	240 F.S.	NA*	Acceptable

* Not a Sensitizer

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/1/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (H7509C) Marion Copley 3/8/93

DATA EVALUATION REPORT 010079

STUDY TYPE:	Acute Oral—Rat (81-1)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-13
TEST MATERIAL	NTN 33893 240 F.S.
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	89-012-DV
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Oral Toxicity with BAY NTN 33893 240 F.S. in Rats
AUTHOR	L.P. Sheets
REPORT ISSUED	February 26, 1990

CONCLUSION:

Tox. Category:	III
Classification:	Acceptable
LD_{50}:	Males: >4870 mg/kg Females: 4143 mg/kg Slope 2.06

This study satisfies the guideline requirements (81-1) for Acute Oral Toxicity on the 240 F.S. formulation, and is acceptable for regulatory purposes.

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MATERIALS

1. **Test Compound:** BAY NTN 33893 240 F.S.
   Description: viscous, light-tan liquid. Batch No. 9-03-0117
   Purity: 23.05%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rat, Strain: Sprague-Dawley (Sas:CD(SD)BR)
   Age: Male—approx. 8 wks; Female—approx. 10 wks. Weight: Male—204-295g, Female—178-232g. Source: Sasco Inc., Omaha, Nebraska.

3. **Environment:** Rats were housed individually in stainless steel cages suspended over bedding. Temperature: 18 to 26°F; Humidity: 40-70%; Photoperiod: 12 hours light/dark; Food: Purina Rodent Laboratory Chow *ad libitum*; Water: municipal *ad libitum*.

METHODS

Animals were fasted overnight prior to dosing. Groups of five male and five female rats received single doses of 1000, 2000, 3500, or 5000 mg/kg (nominal), and groups of five female rats received single doses of 2000, 3500 or 5000 mg/kg (nominal) by gavage in deionized water (5 ml/kg).

Observations for toxicity and mortality were made twice daily (once daily on weekends) for 14 days. Terminal body weights were taken on all animals that died during the study.

Animals were sacrificed by CO_2 asphyxiation on day 14 after treatment. Gross necropsy was performed on all animals that died during the study, and those sacrificed on day 14.

The quality assurance statement was signed by C.A. Halder on Feb. 23, 1990.

RESULTS AND DISCUSSION

Mortality As seen in Table 1, Male and female deaths occurred during the during the study. However, only female deaths appeared to be treatment related. Male deaths occurred on the day of treatment. Female deaths occurred between treatment day and day 2 post treatment.

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TABLE 1. MORTALITY FOLLOWING TREATMENT

Dose Level, mg/kg*	Male (N=5)	Female (N=5)
1030	0	N/A
2100	2	1
3595	0	2
4870	2	3

* Actual Dose level, based on analytical determination

Clinical Signs (Table 2) Treatment-related signs of toxicity consisted of lacrimation, decreased motor activity, tremors and convulsions. These signs were observed on the day of dosing, and were gone by day 2.

TABLE 2. CLINICAL SIGNS OBSERVED FOLLOWING TREATMENT

Clinical Signs	Dose Level, mg/kg*						
	Males				Females		
	1030	2100	3595	4870	2100	3595	4870
Tremors	-[a]	2/3[b]	2/5	1/5	2/5	3/4	2/5
Decreased Activity	-	2.3	1/5	-	1/4	1/4	1/3
Lacrimation, clear	-	-	-	-	1/4	1/4	1/3
Convulsions	-	-	-	-	-	-	1/3
Oral Discharge, white	-	-	-	1/3	-	-	-
Oral Stain	-	-	-	1/3	1/4	1/5	-
Lacrimation Stain	-	-	-	-	1/4	-	-
Urine Stain	-	-	-	-	1/4	-	-
Alopecia	-	-	-	-	1/4	-	-
Oral Stain, white	-	-	-	-	-	1/5	-

* Actual Dose level, based on analytical determination
a = Sign not observed; b = Highest incidence/greatest number alive at that observation period.

Body Weight (Table 3) Body weight gain decreased in surviving animals in a dose-related manner from days 0 through 7. There was also a corresponding dose-related increased in body weight gain in survivors from days 7 through 14.

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TABLE 3. BODY WEIGHT CHANGES

Dose Level	Body Weight			Body Weight Change	
	Day 0	Day 7	Day 14	Days 0-7	Days 7-14
Males					
1030	270	307	332	36	25
2100	244/243[a]	280	314	36	34
3595	259	281	324	21	43
4870	212/209	220	286	11	66
Females					
2100	198/199	228	240	29	12
3595	203/195	212	229	17	16
4870	185/186	185	230	-1	46

a = All animals/animals surviving to day 7

Gross Lesions (Table 4) With the exception of one female at 3595 mg/kg dose level which exhibited lacrimation at sacrifice, no animals surviving for 14 days showed gross lesions. In those that died during the study, one male was found to exhibit salivation. Among females, treatment-related occurrences of reddened lungs, salivation and nasal discharge were observed.

Based on these results, it is concluded that the LD_{50} is >4870 mg/kg for males. In females the LD_{50} is calculated to be 4143 mg/kg, with a slope in the dose-mortality curve of 2.96. The NOEL was 1030 mg/kg for males and <2100 mg/kg for females.

There were no major deficiencies in this study.

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MRID No. 422563-13
Study No 89-012-DU
Study Type: Acute Oral - Rat
Date Feb. 26, 1990

010079

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested. (for reregistration only)
2.* ✓ At least 5 young adult rats/sex/group
3. ✓ Dosing, single oral.
4.* ✓ Vehicle control if other than water.
5. ✓ Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6. ___ Individual observations for the entire day of dosing.
7. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
8. ✓ Individual daily observations.
9.* ✓ Individual body weights.
10.* ✓ Gross necropsy on all animals.

#1 23.1% Formulation reported
#6 Not reported. However, observations suggest continuing observations throughout the day.

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Criteria marked with a * are supplemental and may not be required for every study.

010072

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/1/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 3/8/93
Section IV, Tox Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Dermal Toxicity—Rabbit** (81-2)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-15
TEST MATERIAL	NTN 33893 240 F.S.
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	89-02-EB
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Dermal Toxicity with BAY NTN 33893 240 F.S. in Rabbits
AUTHOR	L.P. Sheets
REPORT ISSUED	February 22, 1990

CONCLUSION:

Tox. Category: III

Classification: Acceptable

LD_{50}: >2000 mg/kg

NOEL (Local & Systemic): <2000 mg/kg (Limit Test)
LOEL (Local & Systemic): 2000 mg/kg Transient erythema and muscle fasciculations; decreased body weight gain in males.

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This study satisfies the guideline requirements (81-2) for Acute Dermal Toxicity on the 240 F.S. formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 240 F.S.
   Description: viscous, light-tan liquid. Batch No. 9-03-0117
   Purity: 23.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: approx. 12 wks; Weight: Male—2.49 - 2.88 kg, Female—2.46 - 2.71 kg. Source: Small Stock Industries, Pea Ridge, Arkansas.

3. **Environment:** Animals were housed individually in stainless steel cages suspended over bedding. Temperature: 18 to 24°F; Humidity: 40 to 70%; Photoperiod: 12 hours light/dark; Food: 125 g Agway Prolab Rabbit Diet daily; Water: municipal *ad libitum*.

METHODS

Backs of animals were shaved the day prior to exposure. Groups of five male and five female rabbits received a dose of 2000 mg/kg of test substance, applied undiluted to approx. 240 sq. cm shaved area of back, and covered with gauze secured with hypoallergenic tape. The gauze was covered with plastic, and rabbits were restrained with a plastic collar. All items were removed 24 hr later, and the area was wiped to remove all visible material.

Observations for toxicity and mortality were made twice daily (once daily on weekends) for 14 days. Body weights were taken on days 7 and 14 post treatment.

Animals were subjected to gross pathological examination after sacrifice (T-61 euthanasia solution) on day 14 post treatment.

The quality assurance statement was signed by C.A. Halder on Feb. 19, 1990.

RESULTS AND DISCUSSION

No deaths occurred at the limit dose of 2000 mg/kg during this study, therefore LD_{50} estimates were not determined. Treatment-related clinical signs consisted of erythema of two females, and muscle fasciculations in one male and one female. All signs were resolved by day 2 post treatment. Male rabbits had a negative body weight gain of 0.02 kg during days 7 - 14 post treatment, compared

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with a positive weight gain in females of 0.05 kg during this period.

It is concluded that the LD_{50} is >2000 mg/kg by the dermal route. No major deficiences were identified in this study.

MRID No: 422563-15

Study No: 89025-EB

Study Type: Acute Dermal Tox. - Rabbit

Date : Feb 22, 1990

010072

81-2 Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

(1) ___ Technical form of the active ingredient tested. (for reregistration only)
2.* ✓ At least 5 animals/sex/group
3.* ✓ Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4. ✓ Dosing, single dermal.
5. ✓ Dosing duration at least 24 hours.
6.* ✓ Vehicle control, only if toxicity of vehicle is unknown.
7. ✓ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).
8. ✓ Application site clipped or shaved at least 24 hours before dosing
9. ✓ Application site at least 10% of body surface area.
(10) ✓ Application site covered with a porous nonirritating cover to retain test material and to prevent ingestion.
(11) ___ Individual observations for the entire day of dosing.
12. ___ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ✓ Individual daily observations.
14.* ✓ Individual body weights.
15.* ✓ Gross necropsy on all animals.

#1 23.1 No formulation

#10 Covered with gauze, + then possibly non-porous plastic

#11 Not specifically reported. However, the reported finding suggest frequent checking on animals.

Criteria marked with a * are supplemental and may not be required for every study.

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/1/93
Section IV, Tox Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 3/8/93
Section IV, Tox Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Inhalation – Rat** (81-3)
TOX. CHEM. NO.:	497E
PC NUMBER:	129099
MRID NO.:	422563-17
TEST MATERIAL:	**NTN 33893 240 F.S.**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine **Imidachloprid (proposed)**
STUDY NUMBER:	89-042-EG
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute 4 Hour Inhalation Toxicity Study with BAY NTN 33893 F.S. in Rats
AUTHOR	D. L. Warren
REPORT ISSUED	February 27, 1990

CONCLUSIONS

Toxicity Category: IV

Classification: Acceptable.

LC_{50} >5330 mg/m³

This study satisfies the guideline requirements for an inhalation study in the rat (81-3)on the 240 F.S. formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 240 F.S.; Description: Viscous, light tan liquid; Batch No. 9-03-0117; Purity: 23.05% (100% a.i.); Stability: estimated at least two yr under freezer conditions. The test mixture (1:1 with water) was stable for at least 24 hr.

2. **Test Animals:** Species & Strain: Rat, Sas: CD(SD)BR; Weight when tested: Males (228-275 g), Females (189-230 g); Source: Sasco, Inc., Houston, Texas.

3. **Environment:** Animals were housed individually in stainless steel, wire-bottom, suspended cages. Temperature: 22 ± 2°. Relative Humidity: 50±10%. Photoperiod: 12 hour light-dark cycle. Food: Purina Rodent Laboratory Chow #5001-4, available *ad libitum*. Water: Municipal, available *ad libitum*.

METHODS

Aerosol Generation

The liquid aerosol was generated by a nebulization of a 50:50 mixture with water. The diluted test substance was delivered to the Rhea-Labortechnik (Hofheim, West Germany) nebulizer by an infusion pump at a constant rate of either 140 or 156 ml/hr. Compressed, filtered and dried air was supplied to the nebulizer at a rate of 15 l/min. the nebulized solution was introduced at the top of the exposure chamber. Test substance concentrations and particle size distribution were measured near the rats' breathing zone.

Exposure and Observations

Groups of six male and six female rats were exposed (nose only) in a single 4-hour exposure to analytical concentrations of 5060 or 5330 mg/m^3 of air. Animals were observed for signs of toxicity or mortality frequently on the day of exposure, and at least twice/day thereafter (once/day on weekends) for 14 more days. Individual body weights were recorded just prior to exposure, and on days 3, 7, and 14 post exposure. On day 14 post exposure, all surviving animals were sacrificed by CO_2 asphyxiation, and a complete gross necropsy was performed on each rat sacrificed at that time, and also on those that died during the course of the study.

RESULTS

Clinical Signs and Mortality

Two males from the 5330 mg/m^3 group, and one female from each dose-group

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died during the study. The two males and one female died on the day of exposure, while the other female died on day later. **Clinical signs** observed in were hypoactivity, dyspnea, lethargy and tremors. Each of these sign occurred in up to four of the six animals/sex/group, and were observed at both dose levels. All clinical signs had cleared by day 2 post treatment.

Body Weight Gain

No significant changes in body weight gain were observed in females in either dose group. In males at 5030 mg/m^3, body weight gain was 94% less than controls ($p \leq 0.05$) on day 3 post treatment. Body weight gain was similar to controls at all other times and in the 5330 dose level.

Gross Pathology

None of the animals contained any observable gross lesions

Particle Size. (Table 3)

TABLE 3. AEROSOL PARTICLE SIZES AS MEASURED DURING THE 4 HR EXPOSURE

Mean Concen-traton (nominal)	Mass Median Aerodynamic Diameter		Geometric Standard Deviation		% Particles < 1.1μ	
	1 hr Distrib.	3 hr Distrib.	1 hr Distrib.	3 hr Distrib.	1½ hr Distrib.	3¼ hr Distrib.
5060 mg/m^3 (68900)	2.67	2.88	1.64	1.65	10.2	10.6
5330 mg/m^3 (56900)	2.97	3.20	3.02	1.65	11.1	8.57

Due to the nature of the test compound, it was not possible to reduce the MMAD.

DISCUSSION

BAY NTN 33893 240 F.S. was acutely toxic to male and female rats at the concentrations tested, causing death in one-third of the animals, and transient clinical signs. The LD_{50} is greater than 5330 mg/m^3 with a Tox. Category of IV.

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MRID No: 422563-17 010072

Study No: ~~Acute Inhal. - Rat~~ 89-C42-EG

Study Type: Acute Inhal. - Rat

Date: Feb 27, 1990

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested. (for reregistration only)
2. ✓ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 um or less).
3.* ✓ At least 5 young adult rats/sex/group
4.* ✓ Dosing, at least 4 hours by inhalation.
5.* ✓ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6. ✓ Chamber temperature, 22° C (±2°), relative humidity 40-60%.
7. ✓ Monitor rate of air flow
8. ✓ Monitor actual concentrations of test material in breathing zone.
9. ✓ Monitor aerodynamic particle size for aerosols.
10. ✓ Doses tested, sufficient to determine a toxicity category or a limit dose (5 mg/L actual concentration of respirable substance).
11. ✓ Individual observations for the entire day of dosing.
12. ✓ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
13. ✓ Individual daily observations.
14.* ✓ Individual body weights.
15.* ✓ Gross necropsy on all animals.

#1 23.1 % formulation

#11 Observations made only twice

Criteria marked with a * are supplemental and may not be required for every study.

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Reviewed by: Myron S. Ottley, Ph.D. 3/1/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (H7509C) 3/8/93

DATA EVALUATION REPORT

STUDY TYPE:	**Primary Ocular Irritation—Rabbit** (81-4)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-19
TEST MATERIAL	NTN 33893 240 F.S.
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	89-335-DZ
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Dermal Toxicity with BAY NTN 33893 240 F.S. in Rabbits
AUTHOR	L.P. Sheets
REPORT ISSUED	January 15, 1990

CONCLUSION:

Minimal Eye Irritation, resolved by 72 hours

Tox. Category: III

Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary Ocular Irritation on the 240 F.S. formulation, and is acceptable for regulatory purposes.

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MATERIALS

1. **Test Compound.** BAY NTN 33893 240 F.S.
   Description: viscous, light-tan liquid. Batch No. 9-03-0117
   Purity: 23.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: 21 approx. wks; Weight: not specified; Source: Small Stock Industries, Pea Ridge, Arkansas.

3. **Environment:** Animals were housed individually in stainless steel cages suspended over bedding. Temperature: 18 to 24°F; Humidity: 40 to 70%; Photoperiod: 12 hours light/dark; Food: 125 g Agway Prolab Rabbit Diet daily; Water: municipal *ad libitum*.

METHODS

One-tenth of a ml of test substance was placed into the conjunctival sac of the left eye of each of six adult rabbits (three male, three female). The eye lids were held together for about one second. The right eye was not treated, and served as a control.

Rabbits were observed for signs of toxicity to the cornea, iris and conjunctivae according to the Draize method. Lacrimation was also assessed. Observations were made 1 hr, 24 hr, 48 hr, 72 hr, 7 days and 14 days post dosing.

The quality assurance statement was signed by C.A. Halder on Feb. 19, 1990.

RESULTS AND DISCUSSION

The cornea and iris were not adversely affected in any of the animals. As sin in Table 1, there was redness and discharge in the conjunctivae of all six animals; chemosis was observed in four animals. All redness had resolved by 72 hours; discharge had resolved by 48 hours, and chemosis had resolved by 24 hours.

Non-ocular lesions or other signs of toxicity were not observed. The test substance is considered a minimal eye irritant with a toxicity category of III.

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TABLE 1 RESULTS OF EYE IRRITATION TEST

Animal No./Sex	Time Post Dosing	Conjuntiva		
		Redness	Chemosis	Discharge
87/M	1 hr	1	0	1
	24 hr	1	0	1
	48 hr	1	0	0
	72 hr	0	0	0
88/M	1 hr	1	1	1
	24 hr	1	0	0
	48 hr	0	0	0
	72 hr	0	0	0
96/M	1 hr	1	1	1
	24 hr	0	0	0
	48 hr	0	0	0
	72 hr	0	0	0
121/M	1 hr	1	0	1
	24 hr	0	0	0
	48 hr	0	0	0
	72 hr	0	0	0
122/M	1 hr	1	1	1
	24 hr	0	0	0
	48 hr	0	0	0
	72 hr	0	0	0
124/M	1 hr	1	1	1
	24 hr	0	0	0
	48 hr	0	0	0
	72 hr	0	0	0
TOTAL AVERAGE SCORES	1 hr	1.0	0.7	1.0
	24 hr	0.3	0.0	0.2
	48 hr	0.2	0.0	0.0
	72 hr	0.0	0.0	0.0

SUMMARY OF RESULTS

TIME (hour, day)	1 hr	24 hr	48 hr	72 hr	7 days	14 days
IRRITATION SCORE	0.9	0.2	0.1	0	0	0

MRID No 422563-19
Study No 89-335-DZ
Study Type Prim. Eye Irit. - Rabbit
Date Jan. 15, 1990

010079

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested. (for reregistration only)
2. ✓ Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.* ✓ 6 adult rabbits
4. ✓ Dosing, instillation into the conjunctival sac of one eye per animal.
5.* ✓ Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6. N/A Solid or granular test material ground to a fine dust.
7. ___ Eyes not washed for at least 24 hours.
8. ✓ Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9. ___ Individual observations for the entire day of dosing.
10. ✓ Individual daily observations.

#1 23.1% formulation
#7 Not reported
#9 Not reported

Criteria marked with a * are supplemental and may not be required for every study.

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Reviewed by: Myron S. Ottley, Ph.D. 3/1/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/8/93
Section IV, Tox Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Irritation—Rabbit (81-5)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-21
TEST MATERIAL	NTN 33893 240 F.S.
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	89-335-DU
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Dermal Toxicity with BAY NTN 33893 240 F.S. in Rabbits
AUTHOR	L.P. Sheets
REPORT ISSUED	January 15, 1990

CONCLUSION:

PIS: 0.0 (non-irritating)

Tox. Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-5) for Primary Dermal Irritation on the 240 F.S. formulation, and is acceptable for regulatory purposes.

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MATERIALS

1. **Test Compound:** BAY NTN 33893 240 F.S.
   Description: viscous, light-tan liquid. Batch No. 9-03-0117
   Purity: 23.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: approx. 14 wks; Weight: Not specified; Source: Small Stock Industries, Pea Ridge, Arkansas.

3. **Environment:** Animals were housed individually in stainless steel cages suspended over bedding. Temperature: 18 to 24°F; Humidity: 40 to 70%; Photoperiod: 12 hours light/dark; Food: 125 g Agway Prolab Rabbit Diet daily; Water: municipal *ad libitum.*

METHODS

The backs and sides of three male and three female rabbits were shaved to expose 6 sq. cm per flank the day prior to treatment. 500 mg of the test substance was applied and secure with gauze and hypoallergenic tape; it was removed approximately 4 hr after treatment. The treated area was cleaned with moistened paper towels.

Animals were observed for signs of erythema and edema formation 1 hr, 24 hr, 48 hr, 72 hr and 7 days post dosing; findings were recorded in harmony with the Draize method.

The quality assurance statement was signed by C.A. Halder on Feb. 19, 1990.

RESULTS AND DISCUSSION

No indications of primary dermal irritation were observed in any of the animals, at any of the time periods. A Primary Irritation Index of 0.0 was calculated. NTN 33893 240 F.S. can be classified in Toxicity Category IV for dermal irritation.

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MRID No.: 412563-21

Study No.: 89-325-DU

Study Type: Prim. Dermal Irrit. - Rabbit

Date : Jan 15, 1990

010079

81-5 Primary Dermal Irritation Study
ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ___ Technical form of the active ingredient tested. (for reregistration only)
2. ✓ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. * ✓ 6 adult animals.
4. ✓ Dosing, single dermal.
5. ✓ Dosing duration 4 hours.
6. ✓ Application site shaved or clipped at least 24 hour prior to dosing.
7. ✓ Application site approximately 6 cm^2.
8. ✓ Application site covered with a gauze patch held in place with nonirritating tape
9. ✓ Material removed, washed with water, without trauma to application site
10. ✓ Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 days (whichever is shorter).
11. ___ Individual observations for the entire day of dosing.
12. ✓ Individual daily observations.

#1. 23.1% formulation
12 NA reported

Criteria marked with a * are supplemental and may not be required for every study.

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Reviewed by: Myron S. Ottley, Ph.D. 3/1/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/8/93
Section IV, Tox Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Sensitization—Guinea Pig (81-6)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-23
TEST MATERIAL	NTN 33893 240 F.S.
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	89-324-DO
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Dermal Sensitization Study with BAY NTN 33893 240 F.S. in Guinea Pigs
AUTHOR	L.P. Sheets
REPORT ISSUED	February 22, 1990

CONCLUSION:

Not a Sensitizer

Core Classification: Acceptable

This study satisfies the guideline requirements (81-6) for Dermal Sensitization on the 240 F.S. formulation, and is acceptable for regulatory purposes.

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MATERIALS

1. **Test Compound:** BAY NTN 33893 240 F.S.
   Description. viscous, light-tan liquid. Batch No. 9-03-0117
   Purity: 23.1% (100% a.i.)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Guinea Pig (male), Strain: Hartley albino; Age: not specified; Weight: 254 - 333 g; Source: Sasco, Madison, Wisconsin.

3. **Environment:** Animals were housed individually in suspended polycarbonate cages. Temperature: 18 to 26°F; Humidity: 40 to 70%; Photoperiod: 12 hours light/dark; Food: Agway Prolab Guinea Pig Diet *ad libitum*; Water: municipal *ad libitum*.

METHODS

Using the Buehler Topical Closed-Patch technique, a 0.4 ml volume of undiluted test substance was applied to a 2 cm by 2 cm Webril pad, and fixed to a shaved area of guinea pig backs with hypoallergenic tape. The test groups were as follows:

Treatment Group	Number of Animals
NTN 33893 F.S. 240 -- Induction and Challenge	15
Control -- Challenge Only	5
DNCB★ -- Induction and Challenge	5
Control -- Challenge Only	5

★ applied at 0.1% (w/v) conc. in 50% (v/v) ethanol/deionized water vehicle at a volume of 0.4 ml.

Animals in the test groups received three topical induction applications (6-hr duration) on days 0, 7 and 14 of the study followed by a topical challenge application (24 hr duration) on day 27. Animals in the NTN 33893 and DNCB non-induced control groups received only a single 24-hr application on day 27. The left should was used as the dose site for all three induction applications, and the left hip was used for the challenge dose site. At the end of the exposure period, the bandages and pad were removed and the dose site was wiped clean using a dampened paper towel.

Dermal irritation scores were determined approximately 24 and 48 hr after

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unwrapping for each induction a challenge treatment. After the challenge dose, the dose site and naive area were depilated (with Nair Lotion hair Remover) for scoring irritation.

Body weights were recorded for all animals on days 0 and 33.

The quality assurance statement was signed by C.A. Halder on Feb. 19, 1990.

RESULTS AND DISCUSSION

Guinea pigs evaluated 24 and 48 hr after challenge dose showed no sensitization (induction or challenge) response to NTN 33893. Animals treated only with a challenge dose of NTN 33893 also gave no response. All five DNCB animals had a positive response following the third induction dose (score of 1; incidence score = 1.0; severity score = 1.0). Challenge scores for DNCB were similar (Incidence score = 1.0; severity score = 1.2).

There was no mortality or significant weight loss, nor was there any evidence of adverse clinical signs in response to treatment.

It is concluded that NTN 33893 240 F.S. is not a dermal sensitizer in the guinea pig.

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MRID No 422563-23
Study No 89-324-DO
Study Type Dermal Sens. - Guinea Pig 010079
Date ☒ Feb 22, 1990

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?:

1. ✓ Technical form of the active ingredient tested. (for reregistration only)
2. ✓ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3. ___ One of the following methods is utilized:
   - ___ Freund's complete adjuvant test
   - ___ Guinea pig maximization test
   - ___ Split adjuvant technique
   - ✓ Buehler test
   - ___ Open epicutaneous test
   - ___ Mouse optimization test
   - ___ Footpad technique in guinea pig
   - ___ Other test accepted by OECD (specify)_____
4. ✓ Complete description of test
5. ✓ Reference for test.
6. ✓ Test followed essentially as described in reference document.
7. ✓ Positive control included.

#1 23.1% Formulation

Criteria marked with a * are supplemental and may not be required for every study.

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