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

009375

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAR 24 1992

MEMORANDUM:

Subject: EPA ID # 003125-EUP: NTN 33893 (a.i.). Request for Experimental Use Permit 003125-EUP-ENG and 003125 EUP-ENR for NTN 33893 (Imidachloprid--proposed) a crystalline end-use formulation containing 0.62% NTN 33893 active ingredient

Tox. Chem No. 497E
EPA PC No. 129059
Project Nos. 2-0288, 2-0494
Submission Nos. S406055, S406872

From: Myron S. Ottley, Ph. D.
Section 4, Toxicology Branch I
Health Effects Division (H7509C)
3/12/92

To: Dennis Edwards (PM19)
Registration Division (H7505C)

Through: Marion P. Copley, D.V.M., D.A.B.T.
Section Head, Section 4, Toxicology Branch I
Health Effects Division (H7509C)
3/12/92
KR 3/16/92

CONCLUSIONS

Toxicology Branch I has no objections to the Experimental Use Permits 003125 EUP-ENG and 003125-EUP-ENR for NTN 33893 0.62% Granular formulation at this time although the inhalation toxicity has not been adequately characterized. Data from the 2.5% formulation is acceptable for satisfying the data requirement for the 0.62% formulation (see Discussion). However, submission of appropriate data, specified in individual DERs, is required prior to full registration.

The acute oral and acute dermal 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

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registration of these EUPs. The 0.5%, 0.62% and 2.5% Granular formulations are unlikely to be a significant hazard under the normal use conditions described in the applications.

ACTION REQUESTED

Review the acute toxicity studies described below 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 NTN 33893 formulations in terrestrial non-food applications. Proposed period of use is from June 1, 1992 to May 30, 1993. The 0.62% formulation is the end-use product. Data were submitted on the Technical, the 0.5% formulation and the 2.5% formulation as a substitute for toxicity data on the 0.62% formulation.

DISCUSSION

EUP Program

The purpose of the EUP is to test NTN 33893 for effectiveness in the Japanese beetle quarantine program implemented by the US Dept. of Agriculture's Animal and Plant Health Inspection Service. The strategy is to make a single application, using commercial granular application equipment, in perimeter areas surrounding one civilian or military airport in a Japanese beetle infested zone.

One 50-acre site will be treated from five possible sites in Delaware, Kentucky, Maryland, New Jersey and Pennsylvania. The area will be a restricted entry zone, surrounded by 10' exclusion fencing. At the use rate of 0.5 lb. a.i./acre, the treatment of 50 total acres will require 25 lbs. of active ingredient or 4,000 lbs of 0.62% formulated product.

Supporting Acute 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:

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 were submitted in support of this EUP. All data were found to be acceptable except for the acute inhalation studies.

GUIDELINE		TEST(S) PERFORMED IN COMPLIANCE			
Ref. No.	Description	MRID No. (420553)	Test Substance: Technical or Formulation	Tox. Cat.	Core Grade
81-1	Acute Oral--Rat	-31	Technical	II	Acceptable
		-24	2.5% Formulation	IV	Acceptable
81-2	Acute Dermal	-32	Technical	IV	Acceptable
		-25	2.5% Formulation	III	Acceptable
81-3	Acute Inhalation--Rat	-33	Technical (Data Gap)	--	Not Acceptable
		-26	2.5% Formulation (Data Gap)	--	Not Acceptable
81-4	Primary Eye Irritation--Rabbit	-34	Technical	IV	Acceptable
		-30	0.5% Formulation	III	Acceptable
		-27	2.5% Formulation	II	Acceptable
81-5	Primary Dermal Irritation	-35	Technical	IV	Acceptable
		-28	2.5% Formulation	IV	Acceptable
81-6	Dermal Sensitization	-36	Technical	NA*	Acceptable
		-29	2.5% Formulation	NA*	Acceptable

* Not a sensitizer

The 0.62% formulation was not tested. Data from the following studies on the 2.5% formulation will be used to satisfy these data requirements and the following categories used:

81-1	Acute Oral--Rat	IV
81-2	Acute Dermal	III
81-3	Acute Inhalation--Rat	Data Gap
81-4	Primary Eye Irritation--Rat	II
81-5	Primary Dermal Irritation	IV
81-6	Dermal Sensitization	Not a Sensitizer

Data Gaps

Although there is a data gap for inhalation toxicity on the technical and 2.5% formulation, it is considered unlikely that the toxicity category would be less than III for these studies. This is based on 1) relatively low toxicity for other acute studies, and 2) relatively low (or no) toxicity in the currently unacceptable inhalation studies. The following problems exist with the inhalation studies:

1. TSI-APS Model 3300 aerodynamic particle sizer was used for determining particle size. This instrument is known to be inaccurate at the lower ranges, at or below 1 μm. The submitter provided no calibration methods and data, so the particle size information cannot be verified.

2. The exposure chamber used contained no distribution devices, and no data (or literature references) were provided on the uniformity of distribution of the test material in the exposure chamber. The particle size sampling locations were not detailed.

3. In addition to the above-mentioned deficiencies, in the NTN 33893 Technical study (MRID #420553-33) dust particle sizes (4.4 - 20 μm MMAD) were too large, particularly in the higher dose levels. The MMAD for 25% of particles should not exceed 1 μm. The submitter provided no justification for large particle sizes. It is uncertain whether the mild toxicity observed was a function of the innocuous nature of the test material, or limited bioavailability due to large particle size.

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C) Marion Copley 3/12/92

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Inhalation Toxicity--RAT (81-3)**
TOX. CHEM. NO:	497E
PC NO.:	129059
MRID NO.:	420553-26
TEST MATERIAL:	**NTN 33893 2.5% Granular**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER:	89-042-DX
SPONSOR:	Mobay Corporation
TESTING FACILITY:	Mobay Corporation, Kansas 66085-9104
TITLE OF REPORT:	Acute Four-Hour Inhalation Toxicity Study with BAY NTN 33893 2.5% Granular in Rats
AUTHOR:	D. L. Warren
REPORT ISSUED:	February 26, 1990

CONCLUSION:

Toxicity Category:	Cannot be determined
Classification:	Not Acceptable. Data submission is incomplete. Verification of particle size and distribution in exposure chamber not possible. See deficiencies Section.

tentative LC_{50}: >5092 mg/m^3 (95% confidence Intervals)

This study does not satisfy the guideline requirements (81-3) for Acute

Inhalation Toxicity on the 2.5% granular formulation and is not acceptable for regulatory purposes. The author may wish to submit adequate data on particle size and distribution so that the LC_{50} value can be verified.

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% Granular.
   Description: Blue Granules. Batch No. 9-03-3069
   Purity: 100% (2.6% a.i. in formulation)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rat; Strain: Sprague-Dawley (Sas:CD(SD)BR)
   Age: 7 to 9 wks
   Weight: 187 - 209 gm (male), 189 - 203 gm (female)
   Source: Sasco Inc., Omaha, Nebraska

3. **Environment:** Rats were housed individually in stainless steel wire-mesh cages suspended over bedding. Temperature: 22 ± 2°C; Humidity: 50 ± 10%; Photoperiod: 12 hours light/dark; Food: Purina Rodent Laboratory Chow *ad libitum*; Water: municipal *ad libitum*.

METHODS

Test Substance Generation

Dust particles of the test article were generated by using a Wright Dust Feed Mechanism. The test substance was micronized using a Micro-Mill sieve and packed into the dust feed cup at 377 psi or 2601 Kpa. This mechanism generated a mean gravimetric test concentration of 5092 ± 1111 mg/m^3 (nominal = 17,040 mg/m^3) at 1.60 rpm based on samples taken at 0.5, 1.5, 2.5 and 3.5 hours of exposure. The mass median aerodynamic diameter was 2.7 ± 1.7 (geometric standard deviation). The output of the dust feed generator was mixed with conditioned room air at the top of the chamber. The flow of dry, filtered air through the generator was 15 L/min while the flow through the chamber was 20 L/min. All flows were monitored continuously and recorded every 30 minutes.

Animal Exposure

Groups of six male and six female rats received a single continuous dose of 5092 mg/m^3 (gravimetric) by inhalation for four hours. The test substance was generated as dust. Test substance concentrations were monitored continuously. Control animals (six male and six female) received conditioned room air. All animals were exposed by the nose-only technique.

Shortly after exposure and/or just prior to the end of the day, all animals were observed for signs of toxicity and mortality. Thereafter, Observations for toxicity and

mortality were made twice daily (once daily on weekends) for 14 days. Individual body weights were taken on all animals just prior to exposure and on days 3, that died during the study.

Animals were sacrificed by CO_2 asphyxiation on day 14 after treatment. Complete gross necropsy was performed on all animals.

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

RESULTS AND DISCUSSION

No mortality occurred at 5092 mg/m^3 during this study, therefore LC_{50} estimates were not determined. No significant changes in body weights were observed when compared with controls. No clinical signs were observed throughout the study; no treatment-related gross lesions were observed at necropsy.

Deficiencies

1. TSI-APS Model 3300 aerodynamic particle sizer was used for determining particle size. This instument is known to be inaccurate at the lower ranges, at or below 1 μm. The submitter provided no calibration methods and data, so the particle size information cannot be verified.

2 The exposure chamber used contained no distribution devices, and no data (or liturature references) were provided on the uniformity of distribution of the test material in the exposure chamber. The particle size sampling locations were not detailed.

It is concluded from the data provided that the LC_{50} is >5092 mg/m^3 by the inhalation exposure route. However, because of the deficiences mentioned above, the actual concentrations reaching the test animals could not be established satisfactorily.

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/12/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion P. Copley
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Inhalation Toxicity--RAT (81-3)**
TOX. CHEM. NO:	497E
PC NO.:	129059
MRID NO.:	420553-26
TEST MATERIAL:	**NTN 33893 2.5% Granular**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER:	89-042-DX
SPONSOR:	Mobay Corporation
TESTING FACILITY:	Mobay Corporation, Kansas 66085-9104
TITLE OF REPORT:	Acute Four-Hour Inhalation Toxicity Study with BAY NTN 33893 2.5% Granular in Rats
AUTHOR:	D. L. Warren
REPORT ISSUED:	February 26, 1990

CONCLUSION:

Toxicity Category:	Cannot be determined
Classification:	Not Acceptable. Data submission is incomplete. Verification of particle size and distribution in exposure chamber not possible. See deficiencies Section.

LC_{50}: >5092 mg/m^3 (95% confidence Intervals) (TENTATIVE)

This study does not satisfy the guideline requirements (81-3) for Acute

Inhalation Toxicity on the 2.5% granular formulation and is not acceptable for regulatory purposes. The author may wish to submit adequate data on particle size and distribution so that the LC_{50} value can be verified.

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% Granular.
   Description: Blue Granules. Batch No. 9-03-3069
   Purity: 100% (2.6% a.i. in formulation)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rat; Strain: Sprague-Dawley (Sas:CD(SD)BR)
   Age: 7 to 9 wks
   Weight: 187 - 209 gm (male), 189 - 203 gm (female)
   Source: Sasco Inc., Omaha, Nebraska

3. **Environment:** Rats were housed individually in stainless steel wire-mesh cages suspended over bedding. Temperature: 22 ± 2°C; Humidity: 50 ± 10%; Photoperiod: 12 hours light/dark; Food: Purina Rodent Laboratory Chow *ad libitum*; Water: municipal *ad libitum*.

METHODS

Test Substance Generation

Dust particles of the test article were generated by using a Wright Dust Feed Mechanism. The test substance was micronized using a Micro-Mill sieve and packed into the dust feed cup at 377 psi or 2601 Kpa. This mechanism generated a mean gravimetric test concentration of 5092 ± 1111 mg/m^3 (nominal = 17,040 mg/m^3) at 1.60 rpm based on samples taken at 0.5, 1.5, 2.5 and 3.5 hours of exposure. The mass median aerodynamic diameter was 2.7 ± 1.7 (geometric standard deviation). The output of the dust feed generator was mixed with conditioned room air at the top of the chamber. The flow of dry, filtered air through the generator was 15 L/min while the flow through the chamber was 20 L/min. All flows were monitored continuously and recorded every 30 minutes.

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Shortly after exposure and/or just prior to the end of the day, all animals were observed for signs of toxicity and mortality. Thereafter, Observations for toxicity and mortality were made twice daily (once daily on weekends) for 14 days. Individual body weights were taken on all animals just prior to exposure and on days 3, that died during the study.

Animals were sacrificed by CO_2 asphyxiation on day 14 after treatment. Complete gross necropsy was performed on all animals.

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

RESULTS AND DISCUSSION

No mortality occurred at 5092 mg/m^3 during this study, therefore LC_{50} estimates were not determined. No significant changes in body weights were observed when compared with controls. No clinical signs were observed throughout the study; no treatment-related gross lesions were observed at necropsy.

Deficiencies

1. TSI-APS Model 3300 aerodynamic particle sizer was used for determining particle size. This instrument is known to be inaccurate at the lower ranges, at or below 1 μm. The submitter provided no calibration methods and data, so the particle size information cannot be verified.

2. The exposure chamber used contained no distribution devices, and no data (or literature references) were provided on the uniformity of distribution of the test material in the exposure chamber. The particle size sampling locations were not detailed.

3. Twenty-five percent or greater of the particles should have an MMAD of 1μ or less. If this is not feasible, the submitter should explain what efforts were made to achieve this level, thereby justifying that the size obtained was a best effort.

It is concluded from the data provided that the LC_{50} is >5092 mg/m^3 by the inhalation exposure route. However, because of the deficiencies mentioned above, the actual concentrations reaching the test animals could not be established satisfactorily.

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Reviewed by: Myron S. Ottley, Ph.D. MSO 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion P. Copley 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Ocular Irritation--RABBIT (81-4)

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-34

TEST MATERIAL: NTN 33893 Technical

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine

STUDY NUMBER: T 8025515

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, West Germany

TITLE OF REPORT: Study for Irritant/Corrosive Potential on the Eye (Rabbit) According to OECD Guideline No. 405

AUTHOR: Dr. J. Pauluhn

REPORT ISSUED: February 25, 1988

CONCLUSION:

None irritating, Resolved by 24 hours.

Toxicity Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary ocular Irritation on the technical and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** NTN 33893 Technical.
   Description: Light yellow crystals. Batch No. 17001/87
   Purity: 94.2%
   Stability: Guaranteed by analysis through 9/25/87 (study conducted 5/87).

2. **Test Animals:** Species: Rabbit (Male), Strain: HC:NZW; Age: not specified; Weight: 2.8 - 3.4 kg; Source: Interfauna UK Ltd.

3. **Environment:** Rabbits were housed individually in wire cages suspended over bedding. Temperature: 20 ± 2°C; Humidity: approx. 50%; Photoperiod: 12 hours light/dark; Food: "ssnif K4 Diet *ad libitum*; Water: tap *ad libitum*.

METHODS

100 ul of test solution containing approx 60 mg of test substance was instilled into the conjunctival sac of one eyelid of each of three adult rabbits (two males, one female). The eye lids were held together for about one second. The other eye was not treated and served as a control. The treated eye was rinsed with physioligical salin after 24 hours.

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, and 7 days post dosing.

RESULTS AND DISCUSSION

One of the three animals scored '2' for redness of conjunctivae and '1' for conjunctival swelling scale at 1 hr. A second animal scored '1' for redness of conjunctivae at 1 hr. No other indications of primary ocular irritation were observed in any other time, or in any of the other animals.

A Primary Irritation Index of 0.0 was calculated. NTN 33893 can be classified in Toxicity Category IV for primary ocular irritation.

Signed Quality Assurance and Good Laboratory Practice statements were present.

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/19/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity--RAT (81-1) TOX. CHEM. NO: 497E

PC NO.: 129059 MRID NO.: 420553-31

TEST MATERIAL: NTN 33893 Technical

SYNONYMS: 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine (CA)
Imidachloprid (proposed)

STUDY NUMBER: T 2033060

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, West Germany

TITLE OF REPORT: Study for Acute Dermal Toxicity to Rats

AUTHOR: Dr. W. Bomann

REPORT ISSUED: December 15, 1989

CONCLUSION:

Toxicity Category: II

Classification: Acceptable

LD_{50}: Male: 424 mg/kg
Female: >450 to <475 mg/kg
(400 mg/kg) (450 mg/kg)

In males and females there was apathy, labored or transient labored breathing, transient accelerated breathing, decreased motility, transient staggering gait, blepharophimosis, transient trembling and transient spasms. All signs were reversible in 2 - 6 days.

This study satisfies the guideline requirements (81-1) for Acute Oral Toxicity on the technical and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** NTN 33893 Technical
   Description: Light Yellow crystalline powder
   Batch No.: 180587
   Purity: 94.2%
   Stability and homogeneity:Confirmed by analysis, approved until May 1, 1990 (4.5 months beyond conclusion of study)

2. **Test Animals:** Species: Rat, Strain: WISW (SPF-Cpb) Wistar;
   Age: 7 - 8 wks (male), 10 - 12 wks (female)
   Weight: 167 - 187 gm (male), 168 - 194 gm (female);
   Source: Winkelmann, Borchen, Kreis Paderborn

3. **Environment:** Rats were housed in groups of five in Type III Makrolon® cages. Low-dust wood-shaving was used as litter. Temperature: 22 ± 2°C; Humidity: approx 50%; Photoperiod: 12 hours light/dark; Food: Altromin® 1324 diet for rats and mice *ad libitum*.; Water: tap (in bottles) *ad libitum*.

METHODS

The test substance was prepared in a mortar with 2% v/v Cremophor EL in demineralized water, and homogenized for 45 minutes by magnetic stirrer prior to each treatment. Aliquots for treatment (10 ml/kg) were withdrawn during stirring.

Animals were fasted 17 hours before dosing, and two hours post dosing. Doses of 50, 100, 250, 315, 400, 450, 500, and 1800 mg/kg were administered to groups of five males each; doses of 100, 250, 315, 400, 450, 475, 500, and 1800 mg/kg were administered to groups of five females each.

Rats were observed for mortality and signs of toxicity several times on the day of treatment, and at least once daily for 14 days post treatment. Upon sacrifice by diethyl ether inhalation, terminal body weights were recorded.

RESULTS AND DISCUSSION

Mortality

As seen in Table 1, animal deaths occurred at dose levels of 400 mg/kg and above. The male LD_{50} was calculated to be approximately 424 mg/kg; the female LD_{50} was estimated to be between 450 mg/kg and 475 mg/kg. Confidence limits were not given for males or females.

TABLE 1. ANIMAL MORTALITY FOLLOWING TREATMENT

Dose Level, mg/kg	Number (Day) of Deaths			
	Male	Total	Female	Total
50	0	0	N/A*	N/A
100	0	0	0	0
250	0	0	0	0
315	0	0	0	0
400	1(1)	1	1(1)	1
450	4(1)	4	0	0
475	N/A*	N/A	5(1)	5
500	5(1)	5	5(1)	5
1800	5(1)	5	5(1)	5

* Animals not tested at this dose level.

Clinical Signs

Apathy, labored or transient labored breathing, transient accelerated breathing, decreased motility, transient staggering gait, blepharophimosis, transient trembling and transient spasms were observed at 100 mg/kg and above in males, and 250 mg/kg and above in females. These effects were observed within a few minutes of treatment, and were reversible in survivors within two to six days.

Body Weight

No effect was observed on body weight development in any group during the study.

Gross Pathology

No treatment related finding were made in animals surviving to scheduled necropsy. In animals that died during the study, the following observations were made: dark liver; pale spleen (and slightly dark in one animal); lungs - dark, patchy and distended; glandular stomach with mucosa slightly reddened. Conclusions can be summarized as follows:

Endpoint	Male, mg/kg	Female, mg/kg
Clinical or Pathological Signs	100	250
LD_{50} §	424	>450, <475

§ calculated in males, estimated in females.

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Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/12/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: **Acute Inhalation Toxicity RAT** (81-3)
Subacute Inhalation Toxicity Rat

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-33

TEST MATERIAL: **NTN 33893** Technical

SYNONYMS: 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine (CA)
Imidachloprid (proposed)

REPORT NUMBER: 16777
STUDY NUMBERS: T 2025951, T 3025952, T4025953

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, West Germany

TITLE OF REPORT: Study for Acute Inhalation Toxicity in the Rat in Accordance with OECD Guideline No. 403.

AUTHOR: Dr. J. Pauluhn

REPORT ISSUED: June 6, 1988

CONCLUSION:

Toxicity Category: Cannot be Determined

Classification: Not Acceptable. Maximum dust particle size was exceeded. Data submission is incomplete. Verification of particle size and distribution in exposure chamber not possible due to absence of equipment calibration data. See deficiencies Section.

Tentative LC_{50}: Male: 1 4-hr dose: >5323 mg/m^3 5 6-hr doses: >505 mg/m^3
Female: 1 4-hr dose: >5323 mg/m^3 5 6-hr doses: >505 mg/m^3

This study does not satisfy the guideline requirements (81-3) for Acute Inhalation Toxicity on the technical and is not acceptable for regulatory purposes. The author may wish to submit adequate data on calibration of instruments and particle distribution in the exposure chamber so that the LC_{50} values can be verified.

MATERIALS

1. **Test Compound:** NTN 33893 Technical
   Description: Light Yellow crystalline powder
   Batch No.: 180 587
   Purity: 95.3%
   Stability and homogeneity: Confirmed by analysis, guaranteed until Nov. 12, 1987 (5 weeks beyond study date)

2. **Test Animals:** Species: Rat, Strain: WISW (SPF-Cpb) Wistar;
   Age: 8 - 12 wks; Weight: 160 - 210 gm;
   Source: Winkelmann, Borchen, Kreis Paderborn

3. **Environment:** Rats were housed in groups of five in Type III Makrolon® cages. Low-dust wood-shaving was used as litter. Temperature: 22 ± 2°C; Humidity: approx 50%; Photoperiod: 12 hours light/dark; Food: Altromin® 1324 diet for rats and mice *ad libitum.*; Water: tap (in bottles) *ad libitum.*

METHODS

Aerosol Generation

The test article was nebulized in Lutrol vehicle, with a mixing ratio of 1:1[1], into a cylindrical inhalation chamber with baffle. The PVC inhalation chamber was 30 cm in diameter by 28 cm high, with a volume of approx. 20 liters. Compressed air flow was 10 L/min at a pressure of approx. 600 kPa. During aerosol generation the ethanol component of the vehicle evaporated, promoting the formation of smaller particles. Concentration determinations were performed using HPLC. The following particle dimensions/specifications were reported for 69 mg/m³, the highest attainable concentration:

Nominal concentration	= 500 mg/m³
Number median aerodynamic diameter (NMAD)	= 0.945 μm
Mass median aerodynamic diameter (MMAD)	= 1.61 μm
Sigma	= 1.44
Mass Fraction < 5 μm	= 100%
Particles per cubic cm	= 2,827,744

[1]Lutrol--polyethylene glycol:E-400-ethanol mixture (1:1).

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Dust Generation

A glass cylinder was filled with the test article which was delivered to the dosing plate discontinuously by means of a stepping motor. From here the test article was dispersed by compressed air into the inhalation chamber. In the pause between impulses, the dust settled in the chamber relatively slowly, exposing the rats to a stable concentration (inlet air 35 L/min outlet air: approx. 7 L/min.; max. dispersion pressure: approx. 200 kPa; impulse duration: 0.2 to 0.2 sec.; impulse intervals: 3 to 5 sec. (single 4hr exposure) or 12.5 sec. (multiple 6hr exposures). Concentration determinations were performed using HPLC. The following particle dimensions/specifications were reported:

Nominal Concentration (mg/m^3)	20	100	500	1220	2576.7	5323.3
Computed Concentration (mg/m^3)	5.6	73.8	285.0	1117.5	2970.8	7066.7
MMAD[1] (μm)	5.56 $\pm$1.70	4.44 $\pm$1.98	7.99 $\pm$1.72	10.6 $\pm$1.82	14.2 $\pm$1.92	20.0 $\pm$2.15
NMAD[2] (μm)	2.35	1.08	3.29	3.62	3.91	3.39
SMAD[3] (μm)	4.17	2.77	5.94	7.45	9.27	11.0
Air Flow (L/min)	4.00	4.00	4.00	4.00	4.00	4.00
Respirability ($\% \leq 5 \mu m$)						
Mass Related[4]	43	57	20	11	6	4
Number Related[5]	92	99	78	71	65	70

[1] Mass Median Aerodynamic Diameter
[2] Number Median Aerodynamic Diameter
[3] Surface Median Aerodynamic Diameter
[4] Measured
[5] Calculated

Single Exposure

Groups of five male and five female rats per concentration received single continuous doses of 69 mg/m^3 aerosol, and 1220, 2577, and 5323 mg/m^3 dust for four hours. Test substance concentrations were monitored continuously. Control animals received conditioned room air (10 male and 10 female) or 20,000 μl vehicle per m^3 air (5 male and 5 female). All animals were exposed by the nose-only technique.

Appearance and behavior were individually assessed several times on the day of exposure. Assessments were made during treatment only if clear signs of toxicity were observed, such as spasms, abnormal movements or severe dyspnoea. Observations for toxicity and mortality were made daily, including weekends, for 14 days. Individual body weights were taken on all animals just prior to exposure and on days 3, 7 and 14 of the post treatment observation period.

Animals were sacrificed with Evipan-Natrium® (approx 350 mg/rat i.p.) on day 14 post treatment. Complete gross necropsy was performed on all animals.

Repeated Exposure

Groups of 10 male and 10 female rats per concentration received five daily 6 hr continuous doses of 20, 109, and 505 mg/m^3 dust by inhalation. Test substance concentrations were monitored continuously. Control animals received conditioned room air (10 male and 10 female). All animals were exposed by the nose-only technique.

Appearance and behavior were individually assessed several times on the day of exposure. Assessments were made during treatment only if clear signs of toxicity were observed, such as spasms, abnormal movements or severe dyspnoea. Observations for toxicity and mortality were made daily, including weekends, for 14 days. Individual body weights were taken on all animals just prior to exposure and on days 4 and 8 of the post treatment observation period.

Interim sacrifice took place on the first day after treatment on 10 animals/dose group (five of each sex). Animals were anesthetized by diethylene ether and sacrificed by heart puncture.

Animals were sacrificed with Evipan-Natrium® (approx. 350 mg/rat i.p.) on day 14 post treatment. Body and organ (liver and lung) weights were recorded. Complete gross necropsy was performed on all animals. Histopathological examinations were performed on liver, lung, larynx and trachea. The following clinical parameters were measured:

Blood:	Hematocrit
	Hemoglobin
	Leukocytes
	Erythrocytes
	Mean corpuscular erythrocyte volumes
	Mean erythrocyte hemoglobin concentration
	Mean erythrocyte hemoglobin content
	Blood coagulation (Hepatoquick)
	GOT/ASAT optimized (aspartate aminotransferase
	GPT/ALAT optimized (alanine aminotransferase)
	GLDH (glutamate dehydrogenase)
Liver:	Cytochrome P-450
	Triglyceride
	N-demethylase (aminopyrin-N-demethylase)
	O-demethylase (p-Nitroanisol-N-demethylase)

RESULTS AND DISCUSSION

Mortality

There were no deaths in any treatment group. Therefore the single acute LC_{50} (dust) was observed to be >5323 mg/m^3, and the repeated dose LC_{50} was observed tc be >505 mg/m^3 for both sexes.

Single Exposure

Clinical Signs. No signs of toxicity were observed in Test Groups 1 through 4 (Table 1). In the two high groups (#5 and #6) signs such as difficult breathing, reduced motility were observed after exposure. Piloerection and slight tremors were also observed in Group 6. These toxicity signs had all cleared by the next day.

Body Weight. Body weights gains were adversely affected ($p \leq 0.05$) only in Group 6 females.

Gross Pathology. Necropsy revealed no specific macroscopic lesions to the lungs or other organs.

TABLE 1. ACUTE INHALATION TOXICITY (ONE 4-HR. EXPOSURE.)

Test Group	Test Concentration (mg/m^3)	Toxicological Result §		Duration of Sign	
		Male	Female	Male	Female
1	Air Control	0/ 0/10	0/ 0/10		
2	Vehicle Control	0/ 0/ 5	0/ 0/ 5		
3	69 (aerosol)	0/ 0/ 5	0/ 0/ 5		
4	1220 (dust)	0/ 0/ 5	0/ 0/ 5		
5	2577 (dust)	0/ 5/ 5	0/ 5/ 5	4hr - 6hr	4hr - 6hr
6	5323 (dust)	0/ 5/ 5	0/ 5/ 5	4hr - 6hr	4hr - 6hr

§ # mortalities / # animals with signs / # animals used

Repeated Exposure

Clinical Signs. No clinical signs of toxicity were observed in any of the four Test Groups.

Body Weight. A transient decrease in mean female body weight was observed in the mid-dose group (109 mg/m^3) on day 4 only. No other significant effects were at other times or in other dose groups.

Gross Pathology. At interim sacrifice, several high-dose females (500 mg/m^3) exhibited dark spleen and isolated hepatic foci. However, no other treatment related findings were made in any test groups, male or female.

Clinical Chemistry -- Blood. Statistically significant ($p \leq 0.01$) changes in coagulation time (+18%) and alanine aminotransferase (-16%) were observed in the high-dose males and females, respectively. These changes are not of toxicological significance.

Clinical Chemistry -- Hepatic Tissue. Statistically significant ($p \leq 0.01$) induction of microsomal enzymes was observed at the mid-dose level: n-demethylase (+29% in males, +142% in females) and o-demethylase (+35% in males). While these assays were not performed at the high dose level, it is expected that induction was also present there. Triglyceride concentration was also elevated ($p \leq 0.05$) at the high dose level(+6% in females).

Hematology. MCHC was elevated 3% in males at the high dose level, and 2% and 4% in mid- and high-dose females, respectively; leucocyte counts were up 5% in mid-dose females. These findings are not associated with toxicological significance.

Organ Weights. Absolute liver weights were decreased in the high-dose group (-10% in males, -7% in females). However, relative organ weights were decreased less (-4% and -6% respectively), which mutes concern for the toxicological importance of this observation. Changes in lung weights followed a similar profile.

Histopathology. Examination of the larynx, trachea, main bronchi, lungs and liver revealed no toxicologically significant findings.

Deficiencies

1. Dust particle sizes (4.4 - 20 μm MMAD) were too large, particularly in the higher dose levels. Twenty five percent of the MMAD ~~should not~~ of less than ~~exceed~~ 1 μm. The submitter provided no justification for large particle sizes. It is uncertain whether the mild toxicity observed was a function of the inoccuous nature of the test material, or limited bioavailability due to large particle size.

2. TSI-APS Model 3300 aerodynamic particle sizer was used for determining particle size. This instument is known to be inaccurate at the lower ranges, at or below 1 μm. The submitter provided no calibration methods and data, so the particle size information cannot be verified.

3. The exposure chamber used contained no distribution devices, and no data (or liturature references) were provided on the uniformity of distribution of the test material in the exposure chamber. The particle size sampling locations were not detailed.

CONCLUSIONS can be summarized as follows:

Endpoint	Male, mg/m^3	Female, mg/m^3
Clinical Signs		
1 x 4 hr	2577	2577
5 x 6 hr	505	505
Body Weight		
1 x 4 hr	5323	>5323
5 x 6 hr	>505	>5323
Gross Pathology		
1 x 4 hr	>5323	>5323
5 x 6 hr	>505	505
Clinical Chemistry--Liver		
5 x 6 hr	109	109
LC_{50}		
1 x 4 hr.	>5323	>5323
5 x 6 hr.	> 505	> 505

Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/12/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Dermal Toxicity--RABBIT** (81-2)
TOX. CHEM. NO:	497E
PC NO.:	129059
MRID NO.:	420553-25
TEST MATERIAL:	**NTN 33893 2.5% Granular**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER:	89-025-DS
SPONSOR:	Mobay Corporation
TESTING FACILITY:	Mobay Corporation, Kansas 66085-9104
TITLE OF REPORT:	Acute Dermal Toxicity Study with BAY NTN 33893 2.5% Granular in Rabbits
AUTHOR:	L.P. Sheets
REPORT ISSUED:	January 15, 1990

CONCLUSION:

Toxicity Category: III

Classification: Acceptable

LD_{50}: >2000 mg/kg (Limit Test)

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% Granular.
   Description: Blue Granules. Batch No. 9-03-3069
   Purity: 100% (2.6% in formulation)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rabbit, Strain: New Zealand White;
   Age: 13 weeks; Weight: 2.35-2.59 kg (male), 2.35-2.58 kg (female);
   Source: Small Stock Industries, Pea Ridge, Arkansas

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

METHODS

The backs of five male and five female rabbits were shaved to expose 240 cm^2 the day prior to treatment. Each animal received a dose of 2000 mg/kg. The area was covered with gauze and secured with hypoallergenic tape. A plastic collar was placed on each rabbit to prevent removal of test material. The test material was removed approximately 24 hr after treatment using a damp paper towel.

Rabbits were observed for mortality and signs of toxicity daily (twice daily on week days) for at least 14 days post treatment. Upon sacrifice by euthanasia, terminal body weights were recorded.

RESULTS AND DISCUSSION

No mortality occurred at the limit dose of 2000 mg/kg during this study, therefore LD_{50} estimates were not determined. No significant body weight loss was observed. No gross lesions were observed at necropsy.

It is concluded that the LD_{50} is >2000 mg/kg by the dermal route.

009375

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Oral Toxicity--RAT (81-1)** TOX. CHEM. NO: 497E
PC NO.:	129059 MRID NO.: 420553-24
TEST MATERIAL:	**NTN 33893 2.5% Granular**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER:	89-012-DY
SPONSOR:	Mobay Corporation
TESTING FACILITY:	Mobay Corporation, Kansas 66085-9104
TITLE OF REPORT:	Acute Oral Toxicity Study with BAY NTN 33893 2.5% Granular in Rats
AUTHOR:	L.P. Sheets
REPORT ISSUED:	February 26, 1990

CONCLUSION:

Toxicity Category: IV

Classification: Acceptable

LD_{50}: >4820 mg/kg (5000 mg/kg nominal, Limit Test)

This study satisfies the guideline requirements (81-1) for Acute Oral Toxicity on the 2.5% granular formulation and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% Granular.
   Description: Blue Granules. Batch No. 9-03-3069
   Purity: 100% (2.6% in formulation)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rat, Strain: Sprague-Dawley (Sas:DC(SD)BR)
   Age: 8 wks (male), 10 wks (female)
   Weight: 185 - 212 gm (male), 182 - 202 gm (female)
   Source: Sasco Inc., Omaha, Nebraska

3. **Environment:** Rats were housed individually in stainless steel cages suspended over bedding. Temperature: 18 to 26°C; Humidity: 40 to 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 a single dose of 4820 mg/kg (analytical) orally by gavage in deionized water (10 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

No mortality occurred at 4800 mg/kg during this study, therefore LD_{50} estimates were not determined. Body weights increased for all animals. No clinical signs were observed throughout the study; no gross lesions were observed at necropsy.

It is concluded that the LD_{50} is >4820 mg/kg by the oral exposure route.

009375

Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: **Primary Dermal Irritation--RABBIT (81-5)**

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-35

TEST MATERIAL: **NTN 33893 Technical**

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachloprid (proposed)

STUDY NUMBER: T 8025515

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, West Germany

TITLE OF REPORT: NTN 33893 Study for Irritant/Corrosive Potential on the Skin (Rabbit) According to OECD Guideline No. 404

AUTHOR: Dr. J. Pauluhn

REPORT ISSUED: February 25, 1988

CONCLUSION:

PIS: 0.0 (none irritating)

Toxicity Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-5) for Primary Dermal Irritation on the technical and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** NTN 33893 Technical.
Description: Light yellow crystals. Batch No. 17001/87
Purity: 94.2%
Stability: Guaranteed by analysis through 9/25/87 (study conducted 5/87).

2. **Test Animals:** Species: Rabbit (Male), Strain: HC:NZW; Age: not specified; Weight: 2.8 - 3.4 kg; Source: Interfauna UK Ltd.

3. **Environment:** Rabbits were housed individually in wire cages suspended over bedding. Temperature: 20 ± 2°C; Humidity: approx. 50%; Photoperiod: 12 hours light/dark; Food: "ssnif K4 Diet *ad libitum*; Water: tap *ad libitum*.

METHODS

The contralateral skin areas of the flanks of three rabbits were shaved to expose 6 cm² per flank the day prior to treatment. 500 mg of the test substance was mixed to a paste with water and applied to the unbroken skin on one flank using hypoallergenic dressing. The other flank was covered with moistened dressing only and served as the control; both flanks were secured with elastic adhesive tape. The test material was removed approximately 4 hr after treatment and the treated areas cleaned with water.

Rabbits were observed for signs of erythema/escharosis 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.

RESULTS AND DISCUSSION

One of the three animals scored '1' on the Erythema scale at 1 hr., that is, slight, barely perceptible redness was observed. No other indications of primary dermal irritation were observed in any other time, or in any of the other animals.

A Primary Irritation Index of 0.0 was calculated. NTN 33893 can be classified in Toxicity Category IV for dermal irritation.

Signed Quality Assurance and Good Laboratory Practice statements were present.

Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Skin Sensitization--GUINEA PIG (81-6) TOX. CHEM. NO: 497E

PC NO.: 129059 MRID NO.: 420553-36

TEST MATERIAL: NTN 33893 Technical

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachloprid (proposed)

STUDY NUMBER: T 9025651

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, West Germany

TITLE OF REPORT: NTN 33893 Study for Skin Sensitizing Effect on Guinea Pigs (Maximization Test)

AUTHOR: K. Ohta, Vet. Med.

REPORT ISSUED: March 15, 1988

CONCLUSION:

Not a sensitizer

Core Classification: Acceptable

This study satisfies the guideline requirements (81-6) for Dermal Sensitization on the technical and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** NTN 33893 Technical.
   Description: Beige powder; Batch No. 17001/87
   Purity: 94.2%.
   Stability: Guaranteed by analysis through 9/25/87 (study conducted 3/87).

2. **Test Animals:** Species: Guinea Pig (Male), Strain: DHPW;

Age: 5 - 8 weeks; Weight: 309 - 403 gm;
Source: Winkelmann, Borchen, Kreis Paderborn.

3. **Environment:** Guinea pigs were housed 5/cage in Makrolon® cages. Temperature: 22 ± 2°C; Humidity: approx. 50%; Photoperiod: 12 hours light/dark; Food: Altromin® 3022 Guinea Pig Diet *ad libitum*; Water: tap *ad libitum*.

METHODS

General

All animals were examined for clinical signs at least twice daily throughout the study (once/day on weekends and holidays). Body weights were recorded before the start of the study, and then once weekly, as well as on day 24. The treated skin sites were grossly assessed 24 and 48 hours after removing the dressings.

Positive control animals (10/group) were treated with formaldehyde 2% and formaldehyde 0.5%

Intradermal Induction

The backs and flanks of the animals were shorn the day before administration. Starting behind the neck, 3 intradermal 0.1 ml injections were administered 1-2 cm apart from anterior to posterior. The animals in the three groups were treated as follows:

Administration Site	Treatment	Number of Animals
1st injection site pair (cranial)	Freund's complete adjuvant ¶	10 Each had three injection areas, 2 injection sites per area.
2nd injection site pair (medial)	NTN 33893 technical §	
3rd injection site pair (caudal)	NTN 33893 technical§ and Freund's complete adjuvant¶	
Control groups (2)	Same as above, except no NTN 33893 technical used	20 (10 each)
Positive Controls	Formaldehyde 2.0%	10
	Formaldehyde 0.5%	10

¶ diluted 1:1 with sterile physiological saline solution
§ 1%, formulated with Cremophor EL (2% v/v) in sterile physiological saline solution.

Topical Induction

Topical induction was performed one week after intradermal induction. 24 hr before application, the treatment sites were shorn

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again, and pre-sensitized with 10% sodium lauryl sulphate formulated in paraffin oil. Hypoallergenic dressings were applied between and onto the injection sites, covered with aluminum foil and attached to the skin with self-adhesive dressing for two 24 hr periods. The hypoallergenic dressing were treated and soaked with 0.5 ml of NTN 333893 technical 25% in the formulation agent Cremophor EL 2% v/v in sterile saline solution. Control groups received the formulation agent only.

Sensitization Challenge

The challenge was carried out 3 wks after intradermal induction using the 1st control group. 24 hr before treatment the flanks and backs of the animals were shorn. The animals of the test article group and the 1st control group were treated on the left flank with a hypoallergenic dressing soaked in 0.5 ml of a 3% and 25% test article formulation, attached to the skin with occlusive dressing for 24 hr. Control dressing contain solvent only was applied to the right flanks.

RESULTS AND DISCUSSION

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

Guinea pigs evaluated 24 and 48 hr after challenge dose showed no sensitization response to NTN 33893. Animals treated only with a challenge dose of NTN 33893 also gave no response. Those treated only with the challenge dose of Cremophor EL did not respond. Seven positive control animals (corrected values) in each of the two groups showed a sensitization response to formaldehyde (scores of 1 or 2). The nature of the response was not specified or discussed.

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

Signed Quality Assurance and Good Laboratory Practice statements were present.

009375

Reviewed by: Myron S. Ottley, Ph.D.
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Dermal Toxicity--RAT (81-2)
TOX. CHEM. NO:	497E
PC NO.:	129059
MRID NO.:	420553-32
TEST MATERIAL:	NTN 33893 Technical
SYNONYMS:	1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine (CA) Imidachloprid (proposed)
STUDY NUMBER:	T 5033063
SPONSOR:	Mobay Corporation
TESTING FACILITY:	Bayer AG, West Germany
TITLE OF REPORT:	Study for Acute Dermal Toxicity to Rats
AUTHOR:	Dr. F. Krotlinger
REPORT ISSUED:	November 15, 1989

CONCLUSION:

Toxicity Category: IV

Classification: Acceptable

LD_{50}: >5000 mg/kg (Limit Test)

MATERIALS

1. Test Compound: NTN 33893 Technical

Description: Light Yellow crystalline powder
Batch No. mixed batch 180587
Purity: 94.2%
Stability: Approved until May 1, 1990 (5.5 months beyond conclusion of study)

2. **Test Animals:** Species: Rat, Strain: WISW (SPF-Cpb) Wistar; Age: 9 - 13 weeks; Weight: 207 - 234 gm (male), 204 - 214 gm (female); Source: Winkelmann, Borchen, Kreis Paderborn

3. **Environment:** Rats were housed individually in Type II Makrolon® cages. Low-dust wood-shaving litter was changed twice weekly. Temperature: 22 ± 2°C; Humidity: approx 50%; Photoperiod: 12 hours light/dark; Food: Altromin® 1324 diet for rats and mice *ad libitum.*; Water: tap (in bottles) *ad libitum.*

METHODS

The backs of five male and five female rats per dose group were shaved to expose 36 cm^2 (6 cm x 6 cm) the day prior to treatment. Each animal received a dose of 5000 mg/kg of the test article which was mixed with sterile 0.9% saline to produce a paste. The area was covered with aluminum foil and secured with an occlusive dressing. The test material was removed approximately 24 hr after treatment using soap and water.

Rats were observed for mortality and signs of toxicity several times daily for 14 days post treatment. Upon sacrifice by diethyl ether inhalation, terminal body weights were recorded.

RESULTS AND DISCUSSION

No mortality occurred at the limit dose of 5000 mg/kg during this study, therefore LD_{50} estimates were not determined. No significant body weight loss in males was observed. In females, a minimal decrease in body weight gain was observed, which the authors attributed secondary stress from the occlusion. No gross lesions were observed at necropsy.

It is concluded that the LD_{50} is >5000 mg/kg by the dermal route.

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009375

Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/9/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Skin Sensitization--GUINEA PIG (81-6) TOX. CHEM. NO: 497E

PC NO.: 129059 MRID NO.: 420553-29

TEST MATERIAL: NTN 33893 2.5% Granular

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachloprid (proposed)

STUDY NUMBER: 89-324-DN

SPONSOR: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Kansas 66085

TITLE OF REPORT: Dermal Sensitization Study with BAY NTN 33893 2.5% Granular 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 2.5% granular formulation and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% granular.
   Description: Blue granules; Batch No. 9-03-3069
   Purity: 100% (2.6% A.I. in formulation).
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Guinea Pig (Male), Strain: Hartley;
   Age: Approx. 5 weeks; Weight: 246 - 325 gm;
   Source: Sasco, Madison, WI.

3. **Environment:** Guinea pigs were housed individually in polycarbonate shoe box cages. Bedding was changed at least twice weekly. Temperature: 18 - 26°C; Humidity: 40 - 70%; Photoperiod: 12 hours light/dark; Food: Agway Prolab Guinea Pig Diet *ad libitum*; Water: tap *ad libitum*.

METHODS

A 4 cm by 4 cm area of each animal was clipped free of hair the day before administration. Aliquots of 0.4 ml undiluted test substance, moistened with deionized water, was applied to an occlusive pad on a hypoallergenic backing and taped to the shaved area. The test groups were as follows:

Treatment group	Number of Animals
2.5% Granular--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 2.5% Granular and DNCB non-induced control groups received only a single 24-hr topical application on day 27. The left shoulder 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 unwrapping for each induction and challenge treatment. After the challenge dose, the dose site and a naive area were depilated (with Nair Lotion Hair Remover) for scoring irritation.

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

RESULTS AND DISCUSSION

Guinea pigs evaluated 24 and 48 hr after challenge dose showed no sensitization (induction or challenge) response to NTN 33893 Granular 2.5%. Animals treated only with a challenge dose of NTN 33893 Granular 2.5% 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 = 0.8). Challenge scores for DNCB were similar (Incidence score = 1.0; severity score = 0.8).

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 is not a dermal sensitizer in the guinea pig.

Signed Quality Assurance and Good Laboratory Practice statements were present.

009375

Reviewed by: Myron S. Ottley, Ph.D. 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation--RABBIT (81-5)

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-28

TEST MATERIAL: BAY NTN 33893 2.5% Granular

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachlorprid (proposed)

STUDY NUMBER: 89-325-ED

SPONSOR: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Kansas 66085-9104

TITLE OF REPORT: Primary Dermal Irritation Study with BAY NTN 33893 2.5% Granular in Rabbits

AUTHOR: L. P. Sheets

REPORT ISSUED: January 15, 1990

CONCLUSION:

PIS: 0.0 (none irritating)

Toxicity Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-5) for Primary Dermal Irritation on this 2.5% granular formation and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 2.5% Granular
   Description: Blue granules; Batch No. 9-03-3069
   Purity: 100% (2.6% a.i. in formulation)
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rabbit, Strain: New Zealand White; Age: 26 weeks; Weight: Not given; Source: Small Stock Industries, Pea Ridge, Arkansas.

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

METHODS

The backs and sides six rabbits (three males, three females) were shaved the day prior to treatment. 500 mg of the test substance was mixed to a paste with water and applied to 6 cm^2 of skin, and covered with a gauze patch secured with hypoallergenic tape. A piece of plastic was then taped over treatment area. The test material was removed approximately 4 hr after treatment and the treated areas cleaned with damp paper towels.

Rabbits were observed for signs of erythema/escharosis and edema formation 30-60 min., 24 hr, 48 hr, and 72 hr, post dosing; findings were recorded in harmony with the Draize method.

RESULTS AND DISCUSSION

No indications of primary dermal irritation were observed at any time, in any of the animals.

A Primary Irritation Index of 0.0 was calculated based on the 24 48 and 72 hr scores. NTN 33893 can be classified in Toxicity Category IV for dermal irritation.

Signed Quality Assurance and Good Laboratory Practice statements were present.

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Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. MPCopley 3/5/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Ocular Irritation--RABBIT (81-4)

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-27

TEST MATERIAL: BAY NTN 33893 2.5% Granular

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachlorprid (proposed)

STUDY NUMBER: 89-335-DT

SPONSOR: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Kansas 66085-9104

TITLE OF REPORT: Primary Eye Irritation Study with BAY NTN 33893 2.5% Granular in Rabbits

AUTHOR: L. P. Sheets

REPORT ISSUED: January 15, 1990

CONCLUSION:

Moderate Irritation, resolved by 14 days

TIME (hour, day)	1 h	24 h	48 h	72 h	7d	14 d
IRRITATION SCORE	2.3	1.2	1.0	0.5	0.2	0.0

Toxicity Category: II

Core Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary Ocular Irritation on the 2.5% granular formulation and is acceptable for regulatory purposes.

MATERIALS

1. Test Compound: BAY NTN 33893 2.5% Granular.

Description: Blue Granules. Batch No. 9-03-3069
Purity: 100% (2.6% a.i. in formulation)
Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rabbit, Strain: New Zealand White;
Age: 14 weeks; Weight: Not given;
Source: Small Stock Industries, Pea Ridge, Arkansas

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

METHODS

0.1 ml of pulverized 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.

RESULTS AND DISCUSSION

The cornea and iris were not adversely affected in any of the animals. As seen in Table 1 (next page), there was redness, chemosis and discharge in the conjunctivae of all six animals. While the redness was most persistent, requiring up to 14 days for resolution, the discharge was the most severe (grade 2 and 3).

No non-ocular lesions or other signs of toxicity were observed. The test substance is considered a moderate eye irritant with a toxicity category of II.

Signed Quality Assurance and Good Laboratory Practice statements were present.

TABLE 1. Results of Eye Irritation Test

Animal No./Sex	Time Post Dosing	Conjuntiva		
		Redness	Chemosis	Discharge
82/M	1 hr	1	1	2
	24 hr	1	0	0
	48 hr	1	0	0
	72 hr	0	0	0
85/M	1 hr	1	1	3
	24 hr	1	2	3
	48 hr	1	1	0
	72 hr	1	0	0
	7 days	0	0	0
86/M	1 hr	1	1	2
	24 hr	1	2	1
	48 hr	1	1	0
	72 hr	1	0	0
	7 days	1	0	0
	14 days	0	0	0
113/F	1 hr	1	1	3
	24 hr	1	1	1
	48 hr	1	1	0
	72 hr	0	0	0
115/F	1 hr	1	1	2
	24 hr	1	0	0
	48 hr	1	0	0
	72 hr	0	0	0
116/F	1 hr	1	1	2
	24 hr	1	2	1
	48 hr	1	1	0
	72 hr	1	0	0
	7 days	0	0	0
TOTAL AVERAGE SCORES	1 hr	1.0	1.0	2.3
	24 hr	1.0	1.2	1.0
	48 hr	1.0	0.7	0.0
	72 hr	0.5	0.0	0.0
	7 days	0.2	0.0	0.0
	14 days	0.0	0.0	0.0

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 3/9/92
Section VI, Tox. Branch I (H7509C)
Secondary reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 3/9/92
Section IV, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Ocular Irritation--RABBIT (81-4)

TOX. CHEM. NO: 497E PC NO.: 129059 MRID NO.: 420553-30

TEST MATERIAL: BAY NTN 33893 0.5% Granular

SYNONYMS: 1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine
Imidachloprid (proposed)

STUDY NUMBER: 89-335-IG

SPONSOR: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Kansas 66085-9104

TITLE OF REPORT: Primary Eye Irritation Study with BAY NTN 33893 0.5% Granular in Rabbits

AUTHOR: L. P. Sheets and S.D. Phillips

REPORT ISSUED: December 11, 1990

CONCLUSION:

Moderate Irritation, resolved by 7 days

Toxicity Category: III

TIME (hour, day)	1 h	24 h	48 h	72 h	7d
IRRITATION SCORE	2.5	1.3	1.0	0.7	0.0

Core Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary Dermal Irritation of the 0.5% granular formulation and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 0.5% Granular.

Description: Gray Granules. Batch No. 0-03-0202
Purity: 100% (0.67% a.i. in formulation)
Stability: Estimated at least two years under freezer conditions.

2. **Test Animals:** Species: Rabbit, Strain: New Zealand White; Age: 14 weeks; Weight: Not given; Source: Small Stock Industries, Pea Ridge, Arkansas

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

METHODS

0.1 ml of test substance was placed into the conjunctival sac of the left eye of each of six adult male rabbits. 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, and 7 days days post dosing.

RESULTS AND DISCUSSION

The cornea and iris were not adversely affected in any of the animals. As seen in Table 1 (next page), there was redness, chemosis and discharge in the conjunctivae of all six animals. Redness and chemosis were more persistent than discharge, requiring up to 7 days for resolution, while chemosis and discharge were more severe (grade 3) than redness.

No non-ocular lesions or other signs of toxicity were observed. The test substance is considered a moderate eye irritant with a toxicity category of II.

Signed Quality Assurance and Good Laboratory Practice statements were present.

TABLE 1. Results of Eye Irritation Test

Animal No./Sex	Time Post Dosing	Conjuntiva		
		Redness	Chemosis	Discharge
282/M	1 hr	2	3	3
	24 hr	1	1	1
	48 hr	1	1	0
	72 hr	0	0	0
284/M	1 hr	1	2	3
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	0	0
	7 days	0	0	0
285/M	1 hr	1	2	3
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	0	0	0
286/F	1 hr	1	2	2
	24 hr	1	2	0
	48 hr	1	1	0
	72 hr	1	0	0
	7 days	0	0	0
287/F	1 hr	1	2	2
	24 hr	1	2	0
	48 hr	1	1	0
	72 hr	1	1	0
	7 days	0	0	0
289/F	1 hr	1	2	2
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	1	0
	7 days	0	0	0
AVERAGE SCORES	1 hr	1.2	2.2	2.5
	24 hr	1.0	1.3	0.2
	48 hr	1.0	1.0	0.0
	72 hr	0.7	0.3	0.0
	7 days	0.0	0.0	0.0