3-29-93

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

MAR 2 9 1993

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. No. 003125-UER: NTN 33893 75 WP-WS. Evaluation of Acute Toxicity Data Submitted (Also NTN 33893 Mutagenicity Data -- Attached)

Tox. Chem. No. 497E
PC Code No. 129099
DP Barcode No. D183834
Submission No. S427958

From: Myron S. Ottley, Ph.D.
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Myron Ottley 3/15/93

To: Portia Jenkins/Dennis Edwards, Jr. (PM19)
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Through: Marion P. Copley, D.V.M., D.A.B.T.
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Marion Copley 3/16/93

Through: Karl Baetcke, Ph.D.
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I. CONCLUSION

The submitted toxicity studies on NTN 33893 75 WP-WS Formulation have been reviewed and support the requested registration for non-food/feed use. DERs are attached. Also attached is a summary memo on NTN 33893 Mutagenicity from Dr. Irvine Mauer, with the associated DERs.

II. ACTION REQUESTED

TB-1 received for evaluation the several studies required to fulfill data requirements for registration of NTN 33893 Technical and several formulations for non-food use. This memorandum is submitted as an addendum to the Toxicity Profile on NTN 33893 of 1/8/93.

III. DATA SUMMARY

CITATION	MRID #	RESULTS	TOX. CAT.	CORE-GRADE
Acute Oral/Rat Mobay 91-012-JJ Aug. 27, 1991	422563-12	NTN 33893 75 WP-WS was administered once orally to 5 male and 5 female Sprague-Dawley rats per group at 1063, 2180, 2750 (females only) and 3170 mg/kg and observed for 14 days. LD_{50}: Males: 2591 mg/kg, Slope = 2.3 Females: 1858 mg/kg, Slope 5.4 NOEL: <1063 mg/kg	III	Acceptable
Acute Dermal/Rat Mobay 91-022-JH Aug. 21, 1991	422563-14	NTN 33893 75 WP-WS was administered once dermally to 5 male and 5 female Sprague-Dawley Rats per group at 2000 mg/kg and observed for 14 days. LD_{50}: >2000 mg/kg (Local & Systemic) NOEL: <2000 mg/kg (Limit Test) LOEL: 2000 mg/kg Urine stains; alopecia.	III	Acceptable
Acute Inhalation/Rat Mobay 91-042-JZ Sep. 25, 1991	422563-16	NTN 33893 75 WP-WS was administered for 4 hr once by inhalation to six male and six female Sprague-Dawley rats per group at analytically confirmed doses of 0, 2110, 2.810 or 2.990 mg/L and observed for 14 days. LC_{50} Males: 2.650 mg/L Females: 2.750 mg/L	III	Acceptable
Eye Irrit./Rabbit Mobay 91-335-JK Jun. 25, 1991	422563-18	NTN 33893 75 WP-WS was introduced into the conjunctival sac of the left eye of six male New Zealand White rabbits at 0.1 ml of pulverized test material/animal. The right eye served as control in each animal. Animals were observed for 14 days. Minimal Eye Irritation, resolved by 7 days	III	Acceptable
Primary Dermal Irritation/ Rabbit Mobay 91-325-JG Aug. 15, 1991	422563-20	NTN 33893 75 WP-WS was administered for 4 hr once dermally to shaved backs of six male New Zealand White rabbits at 500 mg/animal, and observed for 7 days. PIS: 1.08 (mildly-irritating)	IV	Acceptable

CITATION	MRID #	RESULTS	TOX-CAT.	CORE-GRADE
Dermal Sensitization/ Guinea pig Mobay 91-324-JC Aug. 23, 1991	422563-22	NTN 33893 75 WP-WS was administered to shaved backs of 10 male DHPW guinea pigs at 0.4 ml of 7.5% (w/v) suspension per animal, following the induction/sensitization protocol. One week prior to the topical induction, intradermal induction was performed with 3 1 ml injections/animal. Not a Sensitizer	N/A	Acceptable

All data requirements on the Technical and this Formulation have been satisfied for this use.

IV. OTHER

Attached is the memorandum and DERs on the Mutagenicity of NTN 33893, prepared by Irving Mauer and referred to in the 1/8/93 memo.

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Section IV, Tox Branch I (H7509C) 3/2/93

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Oral—Rat** (81-1)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-12
TEST MATERIAL	NTN 33893 75 WP
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	91-012-JJ
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Oral Toxicity with BAY NTN 33893 75 WP-WS in Rats
AUTHOR	L.P. Sheets and S.D. Phillips
REPORT ISSUED	August 27, 1991

CONCLUSIONS:

NTN 33893 75 WP-WS was administered once orally to 5 male and 5 female Sprague-Dawley rats per group at 1063, 2180, 2750 (females only) and 3170 mg/kg and observed for 14 days.

LD_{50}:	Males: 2591 mg/kg, Slope = 2.3 Females: 1858 mg/kg, Slope=5.4
NOEL:	< 1063 mg/kg
Tox. Category:	III
Classification:	Acceptable

This study satisfies the guideline requirements (81-1) for Acute Oral Toxicity on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS
Description: viscous, light-tan powder. Batch No. 003-3005; Purity: 76.1%
Stability: Not specified. Stored under freezer conditions, with fresh preparations on the day of administration.

2. **Test Animal:** Species: Rat, Strain: Sprague-Dawley (Sas:CD(SD)BR)
Age: approx. 11 wks. Weight: Male—243-306 gm, Female—177-219 gm.
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, or 3000 mg/kg (nominal), and groups of five female rats received single doses of 1000, 2000, 2500 or 3000 mg/kg (nominal) by gavage in deionized water (10 ml/kg). Concentrations were analyzed for the active ingredient by HPLC and were found to be 1063, 2180, 2750 and 3170 mg/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 Aug. 21, 1991.

RESULTS AND DISCUSSION

Mortality As seen in Table 1, Male and female deaths occurred during the during the study in a dose-related manner, all occurring between days 0 and 10 post treatment.

TABLE 1. MORTALITY FOLLOWING TREATMENT

Dose Level, mg/kg*	Male (N=5)	Female (N=5)
1063	1	1
2180	2	1
2750	N/A	5
3170	3	5

* Actual Dose level, based on analytical determination

Clinical Signs Treatment-related signs of toxicity consisted of tremors, increased reactivity, decreased activity, eyes partially shut, labored or noisy breathing, diarrhea, red stains (oral, nasal, lacrimal and urinal), red stains on forepaws, urine perianal and brown-yellow ventrum stains, clear lacrimation and clear lacrimal stain. These signs were observed on the day of dosing, and were gone in survivors by day 14.

Body Weight Body weight gain decreased in surviving animals in a dose-related manner from days 0 through 7. Recovery was evident in survivors from days 7 through 14.

Gross Lesions Salivation, lacrimation reddened lungs and nasal stain were observed in animals found dead. With the exception of one male at 2180 mg/kg dose level which exhibited alopecia 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 acute the LD_{50} is 2591 mg/kg for males with a dose-mortality slope of 2.3. In females the LD_{50} is 1858 mg/kg, with a slope of 5.4. The NOEL was < 1063 mg/kg for males and females.

There were no major deficiencies in this study.

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DATA EVALUATION REPORT

STUDY TYPE:	**Acute Dermal Toxicity—Rat** (81-2)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-14
TEST MATERIAL	NTN 33893 75 WP
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	91-022-JH
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Dermal Toxicity with BAY NTN 33893 75 WP-WS in Rats
AUTHOR	L.P. Sheets and R.G. Gilmore
REPORT ISSUED	August 21, 1991

CONCLUSIONS:

NTN 33893 75 WP-WS was administered once dermally to 5 male and 5 female Sprague-Dawley Rats per group at 2000 mg/kg and observed for 14 days.

LD_{50}: >2000 mg/kg

NOEL (Local & Systemic): <2000 mg/kg (Limit Test)
LOEL (Local & Systemic): 2000 mg/kg Urine stains; alopecia.

Tox. Category: III

Classification: Acceptable

This study satisfies the guideline requirements (81-2) for Acute Dermal Toxicity on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS
   Description: light-tan powder. Batch No. 003-3005. Purity: 76.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rat, Strain: Sprague-Dawley (Sas:CD(SD)BR); Age: approx. 10 wks; Weight: Male—254 - 260 gm, Female—207 - 223 gm. Source: Sasco, Inc., St. Louis, Missouri.

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

METHODS

Backs of animals were shaved the day prior to exposure. Groups of five male and five female rats received a dose of 2000 mg/kg of test substance, applied moistened with tap water on 16 sq. cm. piece of gauze backed with plastic and secured with hypoallergenic tape. All items were removed 24 hr later, and the area was wiped to remove all visible residue.

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 (Carbon dioxide asphyxiation) on day 14 post treatment.

The quality assurance statement was signed by C.A. Halder on Aug. 16, 1991.

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 urine stains in one male (day 1) and one female (days 1 - 5). In the same female, alopecia developed on day 5 and persisted throughout the study. The only lesion observed was minimal alopecia on the posterior ventrum of one female.

It is concluded that the LD_{50} is >2000 mg/kg by the dermal route in rats. The NOEL was <2000 mg/kg for both sexes. No major deficiencies were identified in this study.

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DATA EVALUATION REPORT

STUDY TYPE:	**Inhalation -- Rat** (81-3)
TOX. CHEM. NO.:	497E
PC NUMBER:	129099
MRID NO.:	422563-16
TEST MATERIAL:	**NTN 33893 75 WP-WS**
SYNONYMS:	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER:	91-042-JZ
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute 4 Hour Inhalation Toxicity Study with BAY NTN 33893 75 WP-WS in Rats
AUTHOR	D. L. Warren
REPORT ISSUED	September 25, 1991

CONCLUSIONS

NTN 33893 75 WP-WS was administered for 4 hr once by inhalation to six male and six female Sprague-Dawley rats per group at analytically confirmed doses of 0, 2110, 2810 or 2990 mg/m^3 and observed for 14 days.

LC_{50}	Males: 2650 mg/m^3 Females: 2750 mg/m^3
Toxicity Category:	III
Classification:	Acceptable.

This study satisfies the guideline requirements for an inhalation study in the rat (81-3) on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS; Description: light tan powder; Batch No. 003-3005; Purity: 76.1%; Stability: estimated at least two yr under freezer conditions.

2. **Test Animals:** Species & Strain: Rat, Sas: CD(SD)BR; Weight when tested: Males—186-244 gm, Females—177-230 gm; Source: Sasco, Inc., St. Louis, Missouri.

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 1:4 (w/w) 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 276, 235 or 480 g/hr for exposure concentrations of 2110, 2990 or 2810 mg/m_3. Compressed, filtered and dried air was supplied to the nebulizer at a rate of 17 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 0, 2110, 2810 or 2990 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

One male from the 2990 mg/m^3 group died during the study; in the lower dose groups, three males and three females died at 2110 mg/m^3, and five males and five

females died at 2.810 mg/L during the study. Clinical signs observed were ataxia, convulsions, hypoactivity, moribundity, nasal stain, urine stain and tremors. Each of these signs occurred in up to all six animals/sex/group, and were observed at all dose levels. All clinical signs had cleared by day 6 post treatment in surviving animals.

Body Weight Gain

Significant reductions ($p \leq 0.05$) in body weight gain were observed in males (-12.1%) and females (-7.6%) in the high-dose group, and in males (-8.9%) in the mid-dose group. These observations were made on day 3 post treatment. Body weight gain was not significantly different from controls at other times (days 0, 7 and 14 post treatment).

Gross Pathology

In the males and females that died during the study, evidence of salivation and ventral wet staining were observed. In dead females reddened turbinates and reddened lungs were also observed. None of the animals that survived to day 14 contained any observable gross lesions.

Particle Size (Table 1)

TABLE 1. AEROSOL PARTICLE SIZES AS MEASURED DURING THE 4 HR EXPOSURE

Mean Concentration	Mass Median Aerodynamic Diameter (μm) (Time Approximate)		Geometric Standard Deviation (Time Approximate)	
	1 hr Distrib.	3 hr Distrib.	1 hr Distrib.	3 hr Distrib.
2.110 mg/L	1.7	2.0	1.6	1.7
2.810 mg/L	2.2	1.9	1.7	1.7
2.990 mg/L	1.8	1.5	1.7	1.6

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

DISCUSSION

BAY NTN 33893 75 WP-WS was acutely toxic to male and female rats at the concentrations tested, causing death in 19 of 36 of the treated animals, and transient clinical signs. The LC_{50} is estimated to be 2650 mg/m^3 for males and 2750 mg/m^3 for females, with a Tox. Category of III.

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DATA EVALUATION REPORT

STUDY TYPE:	**Primary Ocular Irritation—Rabbit** (81-4)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-18
TEST MATERIAL	NTN 33893 75 WP-WS
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	91-335-JK
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Primary Eye Irritation Study with BAY NTN 33893 75 WP-WS in Rabbits
AUTHOR	L.P. Sheets and S.D. Phillips
REPORT ISSUED	June 25, 1991

CONCLUSION:

NTN 33893 75 WP-WS was introduced into the conjunctival sac of the left eye of six male New Zealand White rabbits at 0.1 ml of pulverized test material/animal. The right eye served as control in each animal. Animals were observed for 14 days.

Minimal Eye Irritation, resolved by 7 days

Tox. Category: III

Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary Ocular Irritation on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS
   Description: viscous, light-tan powder. Batch No. 003-3005
   Purity: 76.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rabbit (male), 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 (0.44 - 0.46 mg) 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, 7 days and 14 days post dosing, as long as irritation persisted.

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 seen in Table 1, there was conjunctival redness (grade 1), chemosis (grade 1) and ocular discharge (grades 2 or 3) observed in all six animals. All redness had resolved by 7 days, except for slight redness (grade 1) in one animal that was present at 7 days but resolved by day 14. This persistent redness in one animal was not consedered to be toxicologically significant. Discharge had resolved by 24 hours, and chemosis had resolved by 7 days.

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.

TABLE 1 RESULTS OF EYE IRRITATION TEST

Animal No./Sex	Time Post Dosing	Conjuntiva		
		Redness	Chemosis	Discharge
20	1 hr	1	1	3
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	1	0
	7 d	0	0	0
43	1 hr	1	2	2
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	1	0
	7 d	1	0	0
	14 d	0	0	0
44	1 hr	1	1	2
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	0	0	0
47	1 hr	1	1	3
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	0	0
	7 d	0	0	0
52	1 hr	1	1	3
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	0	0
	7 d	0	0	0
54	1 hr	1	1	2
	24 hr	1	1	0
	48 hr	1	1	0
	72 hr	1	0	0
	7 d	0	0	0
TOTAL AVERAGE SCORES	1 hr	1.0	1.2	2.5
	24 hr	1.0	1.0	0.0
	48 hr	1.0	1.0	0.0
	72 hr	0.8	0.3	0.0
	7 d	0.2	0.0	0.0
	14 d	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	1.6	0.7	0.7	0.4	0.1	0.0

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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.	422563-20
TEST MATERIAL	NTN 33893 75 WP-WS
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	91-325-JG
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Acute Dermal Toxicity with BAY NTN 33893 75 WP-WS in Rabbits
AUTHOR	L.P. Sheets and S.D. Phillips
REPORT ISSUED	August 15, 1991

CONCLUSION:

NTN 33893 75 WP-WS was administered for 4 hr once dermally to shaved backs of six male New Zealand White rabbits at 500 mg/animal, and observed for 7 days.

PIS: 1.08 (mildly-irritating)

Tox. Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-5) for Primary Dermal Irritation on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS
   Description: light-tan powder. Batch No. 003-3005
   Purity: 76.1%
   Stability: Estimated at least two years under freezer conditions.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: approx. 9 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 six male rabbits were shaved to expose 6 sq. cm per flank the day prior to treatment. 500 mg of the test substance (moistened with tap water) 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

Erythema (grade 2) was observed in five animals, and edema (grade 1) was observed in one animal one hr following exposure (see Table 1 and Appendix I, attached). All signs of irritation were resolved within 7 days. A Primary Irritation Index of 1.08 was calculated. No lesions or other toxic signs were observed. NTN 33893 75 WP-WS can be classified in Toxicity Category IV for dermal irritation.

Toxicology Review # 010128 3/29/93

Page_____ is not included in this copy.

Pages 17 through 18 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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____ Sales or other commercial/financial information.

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____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

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010128

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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:	**Dermal Sensitization—Guinea Pig** (81-6)
PC NO.	129099
TOX. CHEM NO.	497E
MRID NO.	422563-22
TEST MATERIAL	NTN 33893 75 WP-WS
SYNONYMS	1-[(Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine Imidachloprid (proposed)
STUDY NUMBER	91-324-JC
SPONSOR	Mobay Corporation
TESTING FACILITY	Mobay Corporation, Stilwell, KS 66085-9104
TITLE OF REPORT	Dermal Sensitization Study with BAY NTN 33893 75 WP-WS in Guinea Pigs
AUTHOR	L.P. Sheets and S.D. Phillips
REPORT ISSUED	August 23, 1991

CONCLUSION:

NTN 33893 75 WP-WS was administered to shaved backs of 10 male DHPW guinea pigs at 0.4 ml of 7.5% (w/v) suspension per animal, following the induction/sensitization protocol. One week prior to the topical induction, intradermal induction was performed with 3 1 ml injections/animal.

Not a Sensitizer

Core Classification: Acceptable

This study satisfies the guideline requirements (81-6) for Dermal Sensitization on the 75 WP-WS formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** BAY NTN 33893 75 WP-WS
   Description: light-tan powder. Batch No. 003-3005
   Purity: 76.1%
   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 a 7.5% suspension (w/v in deionized water) of 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 75 WP-WS -- 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 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 (scores of 1 or 2; incidence score = 0.4; severity score = 0.3). Challenge scores for DNCB were: Incidence score = 1.0; severity score = 1.2.

There was no mortality. Body weight gain for NTN 33893 75 WS-WP test animals was 173 g, compared with 196 g for non-induced control animals and 170 g for DNCB test animals. The authors attributed the reduced weight gain to the repeated handling and associated wrapping of the test animals, and concluded that the weight gain is not a toxicological effect. This view is supported by the occurrence of positive sensitization reaction that developed in the DNCB test group, in the presence of the body weight loss.

It is concluded that NTN 33893 75 WP-WS is not a dermal sensitizer in the guinea pig.

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

010128

JAN 27 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

SUBJECT: Imidacloprid---Data From Mutagenicity Studies, Submitted Under MRID Nos. 422563-41 to -53; and, 422563-65 to -74.

Chemical: 129099
RD Record: S-419490
HED Project: D180299/D179336

FROM: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I
Health Effects Division (H7509C)
01-12-93

TO: Myron Ottley, Ph.D.
Toxicology Branch-I
Health Effects Division (H7509C)

THRU: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I
Health Effects Division (H7509C)
1/27/93

Registrant: Mobay, Kansas City, MO (Division of Bayer AG).

Request: Review and evaluate the following mutagenicity studies (EPA Gdlns 84-2 and -4) with the parent compound (NTN 33893) and its metabolite (WAK 3839, aka NTN 37571); one-liners are attached to this summary memo [detailed reviews will follow]: Data requirements for these FIFRA TOX. Guidelines are satisfied by these submissions; no further studies need be submitted at this time.

Study Type (MRID No.)	Title (Report No.)	Reported Results	TB Evaluation
Gene mutation-Ames (422563-41)	"NTN 33893 Reverse Mutation Assay (Salmonella typhimurium and Escherichia coli)." Report No. 101276	Negative for inducing reverse mutation in bacteria exposed to doses up to 5000 ug/plate.	ACCEPTABLE
Gene mutation-mamm. cell (422563-42)	"NTN 33893 Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay in Vitro," Report No. 098584	Negative for inducing forward mutation in CHO (mammalian) cells treated up to 1222 ug/ml	ACCEPTABLE
Gene mutation-Ames (422563-43)	"NTN 33893 Salmonella/Microsome Test to Evaluate for Point Mutagenic Effects," Report No. 098570	Negative up to 12,500 ug/plate	ACCEPTABLE
Chromosome Ab. in vivo (422563-44)	"NTN 33893 In Vivo Cytogenetic Study of the Bone Marrow In Chinese Hamster to Evaluate for Induced Clastogenic Effects" Report No. 100021	Negative for chromosome breakage up to 2000 ug/ml	ACCEPTABLE
Chromosome Ab. in vitro (422563-45)	"NTN 33893 In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects," Report No. 099262	Positive at 500 ug/ml -S9 and 1300 ug ml +S9, both toxic doses	ACCEPTABLE

SCE in vivo (422563-46)	"NTN 33893 Sister Chromatid Exchange in Bone Marrow of Chinese Hamster in Vivo," Report No. 099257	Negative up to 2000 ug/ml	ACCEPTABLE
Chromosome Ab.- Mouse MT (422563-47)	"NTN 33893 Micronucleus Test on the Mouse to Evaluate for Clastogenic Effects," Report No. 102652	Negative, but only tested up to 80 mg/kg	UNACCEPTABLE (repeat not required at this time)
Chromosome Ab. in vivo (422563-48)	"Mouse Germ-Cell Cytogenetic Assay with NTN 33893," Report No. 102654	Negative, but only tested up to 80 mg/ml	UNACCEPTABLE (but not required at this time)
Other genotoxicity (422563-49)	"Clastogenic Evaluation of NTN 33893 in an In Vitro Cytogenetic Assay Measuring Sister Chromatid Exchange in Chinese Hamster Ovary (CHO) Cells," Report No. 102655	Positive at 500 ug/ml -S9 and 2000 ug/ml +S9, both toxic doses	ACCEPTABLE
Other genotoxicity (472563-50)	"Sister Chromatid Exchange Assay in Chinese Hamster Ovary Cells," Report No. 099676	Negative at toxic doses of 400 ug/ml/-S9, 1250 ug/ml/+S9	ACCEPTABLE
DNA repair (411563-51)	"NTN 33893 Rec-assay with Spores in the Bacterial System" Report No. 101275	Negative up to 5000 ug	ACCEPTABLE
DNA repair (422563-52)	"Mutagenicity Test on NTN 33893 In the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay," Report No. 098573	Negative up to 750 ug/ml, a toxic dose	ACCEPTABLE
Other genotoxicity (422563-53)	"NTN 33893 Test on S. Cerevisiae D7 to Evaluate for Induction of Mitotic Recombination," Report No. 102653	Negative for crossing-over in yeast up to 10,000 ug	ACCEPTABLE
Gene mutation- Ames (422563-63) 1/	"WAK 3839 Reverse Mutation Assay (Salmonella typhimurium and Escherichia coli)," Report No. 100668	Negative up to 5500 ug/plate	ACCEPTABLE
Gene mutation- mamm. cell (422563-64) 1/	"WAK 3839 Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HGPRT Assay In Vitro," Report No. 100662	Negative up to 2000 ug/ml	ACCEPTABLE
Gene mutation- mamm. cell (422563-65) 1/	"WAK 3839 Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay In Vitro," Report No. 100661	Negative up to 2000 ug/ml	ACCEPTABLE
Chromosome Ab.- Mouse MT (422563-66) 1/	"WAK 3839 or NTN 3/571 Micronucleus Test on the Mouse After Intraperitoneal Injection," Report No. 10064	Negative up to (toxic) 50 mg/kg (ip)	ACCEPTABLE
Chromosome Ab.- Mouse MT (422563-67) 1/	"NTN 37571 Micronucleus Test on the Mice after I.P. Treatment," Report No. 100679	Negative up to (toxic) 80 mg/kg (ip) a non-toxic dose.	UNACCEPTABLE (not required at this time)
Chromosome Ab.- Mouse MT (422563-68) 1/	"WAK 3839 Micronucleus Test on the Mouse After Oral Application," Report No. 100663	Negative up to 100 mg/kg (oral), a non-toxic dose	UNACCEPTABLE
Chromosome Ab.- Mouse MT (422563-69) 1/	"NTN 37571 Micronucleus Test on the Mice After Oral Treatment Pilot Study," Report No. 100680	Negative up to oral 160 mg/kg, toxic dose	ACCEPTABLE
Chromosome Ab.- in vitro (422563.70) 1/	"Chromosome Aberration Assay in Chinese Hamster V79 Cells In Vitro with WAK 38391," Report No. 100666	Negative up to 1000 ug/ml	ACCEPTABLE
Chromosome Ab.- in vitro (422563-71) 1/	"NTN 37571 In Vitro Cytogenetic Assay Measuring Chromosome Abberrations in CHO-K1 Cells," Report No. 100678	Negative up to 1000 ug/ml	ACCEPTABLE
DNA repair (422563-72) 1/	"Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats In Vitro with WAK 3839," Report No. 100665	Negative up to 1333 ug/ml	ACCEPTABLE

1/ DER on the metabolite to follow under separate cover.

ATTACHMENTS (DERs on NTN 33893, imidacloprid, parent)

Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

02-11-93

3/16/93

DATA EVALUATION RECORD

010128

MRID NUMBER No.: 422563-41
PC No.: 129099
RD Record No.: S419490
EPA ID No.: 003125-URU (NTN 33893 TECH)
Tox Chem. No. 497E
Project No.: 80299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---Ames Test

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay (Bayer), Kansas City, MO

TESTING FACILITY: Hino Institute, Tokyo (Japan)

TITLE OF REPORT: NTN 33893. Reverse Mutation Assay (Salmonella typhimurium and Escherichia coli)

AUTHOR(S): M. Watanabe

STUDY NUMBER: 90A032 (Report No. 101276)

DATE ISSUED: January 17, 1991

CONCLUSIONS: Negative for inducing reverse gene mutation in bacterial strains (Salmonella typhimurium TA 1535, 1537, 98, 100; Escherichia coli WP2 [uvrA) exposed with/without activation to test article up to limit concentration, 5,000 ug/plate.

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG).

Description:	White to light yellow powder
Batches (Lots):	180587
Purity (%):	93.7
Solvent/carrier/diluent:	Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Bacteria

Species:	Salmonella typhimurium and Escherichia coli
Strains:	TA98, TA 100, TA 1535, TA 1537 (his-), and WP2/uvrA (tryp-)
Source:	Institute of Environmental Toxicology, Tokyo (Japan)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the mutagenic potential of the test article when administered in vitro to bacterial cultures of Salmonella typhimurium and Esch erichia coli, and determining his+ and tryp+ revertents, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Test cultures of both bacterial species were exposed for 48 hours to graded concentrations of test article in triplicate (up to the limit, 5,000 ug/plate) in two independent experiments, both in the absence and presence of mammalian metabolic activation provided by the microsomal fr tion of the liver of rats pretreated with phenobarbital and 5,6-benzoflavone, (S9, purchased from KIKKoman Company), plus NADP(H)-generating co-factors (purchased from Oriental Yeast

Company). Other cultures were exposed to the solvent (DMSO), or to mutagens appropriate to each strain[1] to serve as positive controls.

After incubation, revertent (hist+, tryp+) colonies were enumerated, and mean values from each test dosage group compared to background.

E. RESULTS: No increases in revertents were found in any strain at any concentration up to 5,000 ug/plate in either of the two trials (Report Tables 1, 2---attached here). In contrast, all positive controls responded appropriately.

Hence, the investigations concluded that NTN 33893 was not mutagenic under conditions of these assays.

F. TB EVALUATION: ACCEPTABLE

ATTACHMENTS: (Data Tables)

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[1]Without S9: N-Ethyl-N'-nitro-N-nitrosoguanidine (ENNG) for TA 1535.
9-Aminoacridine (9-AA) for TA 1537.
2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF2) for TA 98, TA 100, WP2/uvrA

With S9: 2-Aminoanthracene (2AA) for all strains.

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Toxicology Review # 010128 3/29/93

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____ The product confidential statement of formula.

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

01-29-93

3/16/93

DATA EVALUATION RECORD

010128

MRID NUMBER No.: 422563-42
PC No.: 122099
RD Record No.: S419490
EPA ID No.: 003125URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---Gene mutation in mammalian cells (CHO/HGPRT)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, Kansas City

TESTING FACILITY: Bayer AG, Wuppertal (FRG)

TITLE OF REPORT: NTN 33893. Mutagenicity Study for the Detection of Induced Foreward Mutations in the CHO-HGPRT Assay in vitro.

AUTHOR(S): H. Lehn

STUDY NUMBER: T5029536 (Report No. 17578/098584)

DATE ISSUED: January 06, 1989

CONCLUSIONS: Negative for inducing foreward mutation at the hypoxanthine-guanine phosphoribosyl transferase locus (HGPRT) of Chinese hamster ovary cells (CHO) exposed in vitro with/without activation to cytotoxic doses (90-125 ug/ml/1-S9) or to limit dosage (1222 ug/ml/+S9)

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description:	Beige powder
Batches (Lots):	180587
Purity (%):	95.2
Solvent/carrier/diluent:	Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Mammalian cell line

Species:	Chinese hamster (ovary), CHO
Strain:	K_1-BH_4 ($HGPRT^{+/-}$)
Source:	Dr. A. W. Hsie, ORNL, Oak Ridge (TN)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the mutagenic potential of the test article when administered in vitro to cultures of CHO cells, and measuring foreward mutation at the hypoxanthine-quanine phosphoribosyl transferase locus (HGPRT), according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following cytotoxicity (dose-selection) testing, cultures of CHO cells were exposed for five hours to solvent (DMSO) or to graded concentrations of test article, in the absence and presence of a metabolic activation system consisting of the S9 fraction of liver S-D rats pre-treated with Aroclor 1254, (purchased from Litton Bionetics), plus NADP(H)-generating co-factors. factors. After a week's incubation to express mutant colonies, all cultures were exposed to 6-thioguanine (TG) for 6 days (to select for HGPRT mutants, since all normal cells are killed).

The mutagens ethylmethane-sulfonate (EMS) and dimethylbenz-anthracene (DMBA) served as positive controls, for the non-activated and S9 series, respectively.

The average number of colonies in four culture dishes was determined for each treatment for "Relative Survival" (RS) according to the following calculation:

RS (or Relative CE) (%) = [Average no. of colonies per treated culture/Average no. of colonies per vehicle control dish] x 100

"Relative Population Growth" (RPG), representing cumulative growth of the treated cell populations relative to the vehicle control (over the expression period and prior to mutant selection), was also calculated. Values of less than 100% indicate growth inhibition as a result of toxicity of the test substance.

RPG (%) = (Treated culture population increase /Vehicle control population increase) x 100

The ability of cells to form colonies at the time of mutant selection was measured as "Absolute Cloning Efficiency" (CE), and expressed by the average number of viable colonies per dish (200 cells/dish seeded).

Finally, mutant frequency (MF) was calculated for each treatment condition as the ratio of mutant colonies, corrected for the absolute CE. MF was expressed as TG-resistant mutants per 10^6 clonable cells.

This lab considers acceptable for mutant evaluation only assays which are repeated and also satisfy the following criteria:

(1) Average CE of negative controls must be 50% or greater.

(2) Background MF should not exceed 25 x 10^6.

(3) Absolute CE in test cultures must be 10% or greater.

(4) MFs must be determined at at least five treatment doses.

(5) MFs per dose per treatment must be derived from at least five dishes (preferably sets of 8-10 dishes).

(6) The positive control must induce a MF at least 3 X background.

This laboratory considers a substance <u>positive</u> if: i) a dose-dependent and reproducible increase in mutant frequency is observed for at least 3 doses and the response is at least twice that of the negative controls; or (ii) there is a reproducible increase greater than two times the minimum

criterion observed for a single dose near the highest testable concentration. An assay will be considered equivocal if there is no dose-relation but if one or more doses induce a mutant frequency which is considered significant and/or is at least twice that of the negative control.

An assay is considered negative if none of the doses tested (for a range of applied concentrations which extends to toxicity causing about 30% survival or less) induces a reproducible mutant frequency which is considered significant.

E. RESULTS: In cytotoxicity tests, test article concentrations under non-activation conditions of 25 ug/ml and above were severely toxic (RS < 5%) or lethal (Report Table 1), whereas doses up to 800 ug/ml in the presence of S9 were only moderately toxic (RS = 47.5% --- Report Table 2). Hence, for the main assay, the investigators initially selected 20 ug/ml as the HDT without activation (-S9), accompanied by five lower dosages down to 1.25 ug/ml; and five concentrations of the test article ranging from 100 to 1222 ug/ml in the presence of activation (+S9).

In the several repeats the dosages of NTN 33893 were boosted in non-activated cultures with no increased MF at concentrations up to 125 ug/ml (at which cytotoxicity proved to be not as severe as previously encountered in initial dose-selection testing), except for a singular statistically significant increase at an intermediate dose, 80 ug/ml, in only one of two trials (Report Tables 4, 5).

Under activation conditions, duplicate trials of the test article up to 122 ug/ml revealed dose-related cytotoxicity, and isolated increased MF at low to intermediate doses in one trial (Report Table 6), not repeated in the replicate experiment (Report Table 7).

By contrast, both positive controls, EMS and DMBA induced highly significant mutant increases at moderate toxicities in both trials.

Hence, the investigators concluded that NTN 33893 was not mutagenic for the HGPRT system in CHO cells treated under their procedures.

F. TB EVALUATION: ACCEPTABLE

ATTACHMENT: (Data Tables)

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Toxicology Review # 010128 3/29/93

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02-16-93

Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

3/16/93

DATA EVALUATION RECORD

010128

MRID NUMBER No.: 422563-43
PC No.: 129099
RD Record No.: S419490
EPA ID No.: 003125-URU (NTN 33893 Tech.)
Tox Chem. No.: 497E
Project No.: D180299/179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity --Ames Test

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, Kansas City, MO

TESTING FACILITY: Bayer, Wupertal (FRG)

TITLE OF REPORT: NTN 33893: Salmonella/Microsome Test to Evaluate for Point Mutagenic Effects

AUTHOR: B.A. Herbold

STUDY NUMBER: T 6030111 (Report 17577/098570)

DATE ISSUED: January 06, 1989

CONCLUSIONS: Negative for inducing reverse mutation in TA strains of S. typhimurium exposed, with/without activation, to doses of the test article up to cytotoxic levels (12,400 ug/plate)

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

010128

A. Test Material: NTN 33893

Description: White-light yellow powder
Batches (Lots): 180587
Purity (%): 95.0
Solvent/carrier/diluent: Dimethylsulfoxide (DMSO)

B. Test Organism: Bacterial cultures

Species: Salmonella typhimurium LT2
Strain: TA1535, TA1537, TA98, TA100 (his-)
Source: Dr. B.A. Ames (U Cal), Berkeley, CA

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the (reverse) gene mutagenic potential of the test article when administered in vitro to cultures of Salmonella typhimurium, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was also provided.

D. PROCEDURES/METHODS OF ANALYSIS: Cultures of all TA strains were exposed to solvent (DMSO) or to the test article (4 plates per strain per dose) both in the absence and presence of a mammalian metabolic activation system, consisting of the microsomal (S9) portion of livers from rats pre-treated with Aloclor 1254, plus NADP(H)-generating co-factors. After 48 hours incubation, revertent (his+) colonies were counted, and mean counts per strain per dose +/-S9 summarized. Concurrent with solvent controls, mutagens appropriate to each strain[1] were run in each assay as

---

[1] Without activation (-S9): Sodium azide (Na-azid), for TA1535.
Nitrofurantoin (NF), for TA100.
4-Nitro-1,2phenylene diamine (NPDA), for TA1537 and TA98.

With activation (+S9): 2-Aminoanthracene (AA) for all strains.

positive controls. Two complete (independent) assays were performed with the test article.

010128

This lab only accepts results from a study of this type for mutagenic evaluation if:

(1) Negative (solvent) control values are within expected ranges,, as defined either in current publications by expert workers in the field, or the lab's own background (historical) data (as submitted here by values from prior studies summarized as Section 9 of the Final Report).

(2) Positive controls show the expected significantly positive responses (Report Section 9).

(3) Bacterial background lawns must be normal, in character and density.

(4) Data generated in an initial assay must be confirmed in additional, independent, trials.

To be considered positive by this lab, a test substance must induce reproducible and dose-related increases in revertent bacterial counts in one (or more) TA strains: (i) for TA1535, TA100, and TA98, at least two-fold negative control values; whereas, (ii) for TA1537, at best three-fold.

E. RESULTS: Neither bacterotoxicity nor increases in revertent counts were found for any test strain in either trial at doses up to 6,200 ug/plate, either in the presence or absence of S9 (tabulated summary data of means attached to this DER, summarized from individual culture/strain Tables 1 thru 12 of the Final Report). Higher doses (12,400-12,500 ug/plate) were slightly toxic, but likewise induced no increased mutation. In contrast, all positive control mutagens produced highly significantly increased mutant counts.

The authors concluded that under conditions of these assays, NTN 33893 was not mutagenic in Ames testing.

F. TB EVALUATION: Acceptable

ATTACHMENTS: (Data Tables)

DER/MAUER/Jacqueline/Disk 1

Toxicology Review # 010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

Irving Mauer 02-11-93
Karl P. Baetcke 3/16/93
010128

DATA EVALUATION RECORD

MRID NUMBER No.: 422563-44
PC No.: 129099
RD Record No.: S419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity--Chromosome aberrations in vivo (Chinese hamster BM)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay/Miles, Kansas City

TESTING FACILITY: Bayer AG, Wuppertal (FRG)

TITLE OF REPORT: NTN 33893: In vivo Cytogenetic Study of the Bone Marrow in Chinese Hamsters to Evaluate for Induced Clastogenic Effects.

AUTHOR(S): B. A. Herbold

STUDY NUMBER: T8032562 (Report No. 18557/100021)

DATE ISSUED: November 24, 1989

CONCLUSIONS: Negative for inducing structural chromosome aberrations in bone marrow cells of Chinese hamsters dosed acutely at 2000 mg/kg (limit dose)

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

010128

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description:	White yellowish powder
Batches (Lots):	180587
Purity (%):	94.6
Solvent/carrier/diluent:	0.5% Aqueous Cremophor (CMC) Emulsion

B. TEST ORGANISM: Rodent

Species:	Chinese hamster
Strain:	(Not stated)
Age:	8-12 weeks
Weights - males/females:	26-35 g
Source:	Bayer, Wuppertal (FRG)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the clastogenic (chromosome-breaking) potential of the test article when administered orally to Chinese hamsters, and examining bone marrow cells, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following dose-selection testing (at doses up to 10,000 mg/kg), groups of animals (5/sex) were administered test article by oral intubation at single doses of 2,000 mg/kg, and sacrificed 6, 24 and 48 hours later. In addition to carrier controls (Cremophor only), a fifth group of 10 received 30 mg/kg of the clastogenic mutagen, cyclophosphamide (CP , in DDW) as positive control. Two hours before sacrifice, all animals were injected with the mitotic-inhibiting alkaloid, Colcemid (3.3 mg/kg i.p.), to accumulate mitoses in metaphase.

At sacrifice, femoral bone marrow was prepared for microscopy on slides by standard cytological procedures, dried, fixed in methanol, stained with 5% Giemsa and covered. Metaphases (at least 100 per animal) on coded slides were scored under oil immersion optics for the conventional array of chromatid and chromosome aberrations. Chromosome data were analyzed for significance by one-sidedclic-square, with alpha set at 0.05.

E. RESULTS: In preliminary dose-selection testing (~~four~~ animals per group), all died at 5,000 and 10,000 mg/kg, 2 of 4 at 2,500 mg/kg, and none (of 8 dosed) at doses of 2,000 mg/kg and below (5 doses from 80 through 1,000 mg/kg). Doses of 640 mg/kg and above produced dose-dependent severe toxic signs (apathy, reduced activity and reflexes, shivering, etc.). Hence, 2,000 mg/kg was chosen as the (singular) dose to assay the test article for clastogenic potency.

In the main aberration assay, 4 animals died before scheduled sacrifice. Cytogenetic evaluation of bone marrow cells in the remainder, however, revealed that at no sacrifice time did 2,000 mg/kg NTN 33893 induced increased chromosome damage over control value. (Report Tables 1-10, summarized in Table II, attached here). By contrast, the positive control substance, CP, produced clearly increased clastogenicity.

Hence, the author concluded that NTN 33893 was not clastogenic in bone marrow cells of Chinese hamsters dosed at 2,000 mg/kg.

F. TB EVALUATION: ACCEPTABLE

ATTACHMENT: (Data Summary)

Toxicology Reviews # 010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

Irv Mauer 02-17-93
Karl P. Baetcke 3/16/93

DATA EVALUATION RECORD 010128

MRID NUMBER No.: 422563-45
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/179/336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---Chromosome aberrations in vitro (HLC)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Kansas City, MO

TESTING FACILITY: Bayer, Wuppertal (FRG)

TITLE OF REPORT: NTN 33893: In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic effects.

AUTHOR(S): B. A. Herbold

STUDY NUMBER: T6029654 (Report No. 18092/099262)

DATE ISSUED: June 16, 1989

CONCLUSIONS: Positive for inducing chromosome aberrations in human lymphocyte cultures exposed to doses of 500 ug/ml and above without activation, and 1300 ug/ml with activation.

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description:	Fine light-brown powder
Batches (Lots):	180587 (technical)/880226ELBO1 (analytical)
Purity (%):	95.2/99.8
Solvent/carrier/diluent:	Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Primary lymphocyte cultures

Species:	Homo sapiens (1 male; 1 female)
Age:	Adult
Source:	Venipuncture

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the clastogenic (chromosome-break) potential of the test article when administered in vitro to lymphocyte cultures established from human volunteers' blood specimens, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Blood drawn from human volunteers (1 male; 1 female) was established in tissue culture vials in vitro in the presence of the plant lectin, phytohemagglutinin (to stimulate mitosis in normally Go-lymphocytes). Forty-eight hours after culture initiation, the test article was added, both without and with supplements of a metabolic activation system, consisting of the microsomal fraction (S9) of livers from adult male S-D rats pre-treated with the PCB enzyme stimulator, Aroclor 1254, plus NADP (H)-generating co-factors. Twenty-one hours later, in non-S9-activated cultures, the mitotic-spindle inhibiting alkaloid, Colcemid, was added (to accumulate metaphases for analysis). On the other hand, activated cultures were washed free of S9 after two-hour treatment, then cultured in fresh medium for 19 hours, at which time Colcemid was added. In addition to DMSO (solvent) controls, other non-activated primary cultures were exposed to the directing-acting clastogens, mitomycin C (MMC) or Bayer "281355388," an antibiotic which inhibits DNA synthesis, whereas cyclophosphamide (CP) was employed under activation, to serve as positive controls.

At harvest, all cultures were subjected to standard cytological procedures for the preparation of microscope slides ensuring well-spread cells in metaphase, which were then stained with 5% Giemsa, cleared and coverslipped.

Mitotic indices in coded slides were determined by counting 1000 cells per culture/concentration under oil immersion (1000 X), followed by scoring 200 metaphases (100 per concentration from male cultures, 100 from comparable female cultures) for the conventional array of structural chromosome changes. In addition, the incidence of polyploidy was determined at each experimental point.

One-sided Chi-Square was used for statistical evaluation, with alpha set at 0.05. The test article was considered positive if there was a dose-dependent and statistically significant increase over solvent controls in the aberration rate; negative if there was no such increase in any of the concentrations tested; and equivocal if there was an increase which was statistically significant, but not concentration-related, or if a concentration-related increase occurred which was not statistically significant.

Two complete (independent) trials were run.

E. RESULTS: A preliminary dose-selection study to the limit dose revealed the following effect on mitotic index (MI):

Dose (ug/ml)	MI (%)	
	-S9	+S9
50	15.4	32.4
100	28.2	24.3
500	20.5	78.4
1000	35.9	46.0
5000	2.6	21.6

Therefore, the investigators chose 5000 ug/ml of the 95.2% technical formulation as the HDT for the initial assay (accompanied by two lower doses, 50 and 500 ug/ml), and 5200 ug/ml of the 99.8% analytical for the repeat (with two lower doses, 1300 and 2600 ug/ml).

In the initial non-activation assay, M1 decreased in a dose-related manner at 500 and 5000 ug/ml, providing indirect evidence of cytotoxicity (Report Table 1), accompanied by a statistically significant increase over solvent control value in metaphases with aberrations (principally simple breaks at the HDT, Report Tables 2 and 4, attached here)

The repeat assay (-S9) also showed decreased MI at all doses (Report Table 6), and comparable increases in aberrations (Table 9), again mostly simple breakages, but also including a few complex exchanges (Table 7).

In the presence of S9 activation, on the other hand, NTN 33893-treated cultures manifested only moderate cytotoxicity (Table 6), but also slightly increased (statistical significant) incidences of cytogenetically abnormal metaphases (Tables 8, 10).

Positive controls provided the expected highly significant increases in aberrant metaphases, including a high percentages of biologically significant complex rearrangements and/or exchanges.

The author concluded that under the conditions employed, NTN 33893 technical (95.2% a i) as well as the analytical formulation (99.8%) was definitively clastogenic in the absence of S9 activation, and weakly positive with S9 but only at toxic concentrations (as determined by decreased mitotic indices).

F. TB EVALUATION: ACCEPTABLE

ATTACHMENT: (Data Tables)

Toxicology Review # 010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

2-19-93
3/16/93

010128

DATA EVALUATION RECORD

MRID NUMBER No.: 422563-46
PC No.: 129099
RD Record No.: S419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity -- Other genotoxicity (SCE in vivo)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, Kansas City, MO

TESTING FACILITY: Bayer AG, Wuppertal (FRG)

TITLE OF REPORT: Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters in vivo.

AUTHOR(S): B.A. Herbold

STUDY NUMBER: T 8030302 (Report 18093/099257

DATE ISSUED: June 16, 1989

CONCLUSIONS: Negative for inducing sister chromatid exchanges (SCE) in bone marrow cells of Chinese hamsters treated orally at single doses up to 2000 mg/kg (cytotoxic level)

TB-I EVALUATION: Acceptable

II. DETAILED REVIEW

A. Test Material: NTN 33893

Description: White-yellowish powder
Batches (Lots): 180587
Purity (%): 95.0
Solvent/carrier/diluent: 0.5% Aqueous Cremophor (CMC)

B. Test Organism: Rodent

Species: Chinese hamsters
Strain: (Not stated)
Age: 8-12 wks
Weights - males/females: 28-32 g
Source: Bayer AG Tierfarm

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic potential of the test article when administered once by oral gavage to Chinese hamsters, and determining the induction of sister-chromatid exchanges in bone marrow cells, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Based on pilot dose selection testing, groups of animals (5 males: 5 females) were subcutaneously implanted with tablets of bromdeoxyuridine (50 mg, BrdU, cervically), then 2 hours later gavaged once with the test article at doses of 0 (carrier), 500, 1000 and 2000 mg/kg, and sacrificed 24 hours later. At sacrifice, femoral bone marrow cells were treated by conventional cytological procedures as microscope slide preparations, dried, stained (Hoechst 33258 chromophor stock, followed by Giemsa), and briefly exposed to u.v. light. A fifth group of 5 males and 5 females treated with cyclophosphamide (CP, 10 mg/kg) to serv as positive control. Two hours before sacrifice, each animal received an i.p. injection of the alkaloid Colcemid, to accumulate mitoses in metaphase.

Cytotoxicity was assessed by both mitotic index (MI) as well as by mitotic cycle traverse (ratios of first, second and/or third metaphases indicating any cell cycle delay). Then 50 metaphases per animal were scored for sister chromatid exchanges (SCE); only 2n cells were evaluated, i.e., only those with the normal diploid number of chromosomes.

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One-sided Chi Square was used for statistical evaluation of MI and cell cycle kinetics, standard deviation (1s range) for SCE means. In addition, high SCE test values were checked by Wilcoxon's non-parametric (rank sum) test. In both cases, alpha was set at 5%.

E. RESULTS:

In the pilot study, 2 of 4 animals given 2500 mg/kg, as well as all animals at 5000 and 10,000 mg/kg died; no mortalities occurred at 2000 mg/kg or any dose below that. Starting at 640 mg/kg, the following dose-related clinical effects were recorded: Apathy, reduced movement/reflexes, excessive grooming, bloody nose, palpitation and shivering. Hence, 2000 mg/kg was selected at the HDT, with two lower doses (500 and 1000 mg/kg), for the main study.

In the main assay, no animals died, nor were any clinical signs noted. Cytotoxicity was evident at 1000 and 2000 mg/kg. (Report Tables 1, 2), but no significant differences in SCE between test and solvent controls (Report Tables 3 to 7, summarized in Table 8, attached here). In contrast, the positive control, CP, induced a highly significant increase in SCE, coincident with moderate cytotoxicity.

Therefore, the investigator concluded that NTN 33893 was not genotoxic in the in vivo SCE assay as practiced by this lab.

F. TB EVALUATION: Acceptable

ATTACHMENT: (Summary Data Table)

Toxicology Review # 010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

2-22-93
3/16/93

010128

DATA EVALUATION RECORD

MRID NUMBER No.: 422563-48
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---Chromosome aberrations in vivo (mouse germ cells)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Miles (Mobay)

TESTING FACILITY: Cytest Cell Research, Robdorf (FRG)

TITLE OF REPORT: Mouse Germ-Cell Cytogenetic Assay with NTN 33893

AUTHOR(S): W. Volkner

STUDY NUMBER: T5032695/148004 (Report No. R-5063/102654)

DATE ISSUED: May 22, 1990

CONCLUSIONS: Reported negative for inducing chromosome aberrations in spermatogonial cells of male mice administered a single (non-toxic) dose of test article orally (80 mg/kg).

TB-I EVALUATION: UNACCEPTABLE

II. DETAILED REVIEW

010128

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description:	White/brownish powder
Batches (Lots):	180587
Purity (%):	94.1
Solvent/carrier/diluent:	0.5% Aq. Cremophor (CMC)

B. TEST ORGANISM: Rodent

Species:	Mouse
Strain:	NMRI
Age:	10 weeks
Weights - males (only):	30 g
Source:	BRL Tierfarm, Fullindorf (Basel)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the clastogenic (chromosome-breaking) potential of the test article when administered orally to male mice, and assessing its effect in germ cell spermatogonia, according to established (published) procedures and OECD Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following preliminary toxicity testing groups, of fasted males (6/dose/group) were administered a single oral dose of test article, and sacrificed 6, 24, or 48 hours later. Four hours before sacrifice, each animal received an i.p. injection of the mitotic inhibitor alkaloid, Colcemid (4 mg/kg). A fifth group of six males received the antibiotic Adriblastin (adriamycin, or doxorubicin sulfate, 10 mg/kg) as positive control; these animals were sacrificed 24 hours later.

At sacrifice (cervical dislocation), seminiferous tubules were dissociated enzymatically (collagenase), the resulting single cell suspension treated with hypotonic sodium citrate (to expand the germ cells), and prepared on standard glass slides for microscopy by standard cytological procedures. Fixed (Carnoy) cells were stained (Giemsa), cleared and coverslipped under mounting fluid (Eukitt).

One coded slide per animal (5 males/group) was examined under oil immersion optics, and 100 normal (i.e. diploid = 40 chromosomes) spermatogonial metaphases scored for the

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conventional array of chromosome aberrations. Cytotoxicity was assessed by mitotic index (% mitotic cells among 500 counted).

Cytogentic data were analyzed statistically by the non-parametric Mann-Whitney rank-sum test. Alpha was set at $\leq$ 0.05.

E. RESULTS: In preliminary tox testing 2/10 animals given 100 mg/kg test article died, and dose-related toxicity was evident at all other doses, beginning at 60 mg/kg. On this basis, 80 mg/kg was selected as the MTD (and only dose) for the main assay.

In none of the timed animals (6, 24, 48 hours sacrifice) did 80 mg/kg NTN 33898 cause significantly increased chromosome aberrations over Cremophor controls, but no induced test cytotoxicity was recorded, as determined from mitotic indices (Report Summary Table, attached here). In contrast, the expected positive response in the adriblastin (positive control) group was elicited, again without any substantial cytotoxicity.

Therefore, the investigator concluded that NTN 33893 was cytogentically negative in this mouse assay.

F. TB EVALUATION: Unacceptable, since only one demonstrably non-toxic dose was administered, with no other evidence submitted to confirm transport to target tissue.

ATTACHMENT: (Summary Data Table)

Toxicology Review # 010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

01-25-93
3/16/93

DATA EVALUATION RECORD 010128

MRID NUMBER No.: 422563-47
PC No.: 129099
RD Record No.: S419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity--Chromosome aberrations in vivo (Mouse MT)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay/Miles, Kansas City

TESTING FACILITY: Bayer AG, Wuppertal (FRG)

TITLE OF REPORT: NTN 33893: Micronucleus Test on the Mouse to Evaluate for Clastogenic Effects

AUTHOR(S): B. A. Herbold

STUDY NUMBER: T7027161 (Report No. 16837/102652)

DATE ISSUED: June 27, 1988

CONCLUSIONS: Reported as negative for inducing micronuclei in bone marrow cells of mice treated once orally at 80 mg/kg.

TB-I EVALUATION: UNACCEPTABLE, since only a single, non-cytotoxic dose was employed.

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description:	Beige powder
Batches (Lots):	180587
Purity (%):	95.3
Solvent/carrier/diluent:	0.5% Aqueous Cremophor (CMC)

B. TEST ORGANISM: Rodent

Species:	Mouse
Strain:	Bor:NMRI (SPF Han)
Age:	"Young (virgin) adult"
Weights - males:	(Not stated)
females:	(Not stated)
Source:	F. Winkelman, Borchen (FRG)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the clastogenic (chromosome damaging) potential of the test article in bone marrow cells when administered orally to mice, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice GLP was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Based on a preliminary pilot (dose selection) study, groups of mice (5 males: 5 females/group) were administered test article orally once at either 0 (carrier suspension only) or 80 mg/kg, and sacrificed 24, 48 or 72 hours later. A group of five males and five females were given cyclphosphamide (CP, 20 mg/kg) as the positive control, and sacrificed 24 hours later.

At sacrifice, femoral bone marrow as prepared as microscope slide smears, dried overnight and stained with H & E.

Coded slides were examined for micronuclei in polychromatic erythrocytes (PCE), and their incidence recorded in 1000 cells per animal. In addition, the ratio of PCE to normochromatic erythrocytes (NCE) was recorded, as an index of cytotoxicity (demonstrating the test compound reached the target tissue in effective concentrations).

Data were subjected to statistical analysis (Wilcoxon's non-parametric rank-sum test; one-sided Chi-Square), with alpha set at 5%. Only assays meeting strict acceptance criteria with respect to background negative and positive control values were evaluated.

E. RESULTS:

The single dose level of NTN 33893 was selected on the basis of the pilot study in which mortalities occurred at 100 mg/kg (2/10 animals) and 150 mg/kg (5/5), but none at 50 mg/kg. Clinical toxicity was observed at all doses (apathy, reduced movement shivering, rales). Hence, 80 mg/kg was chosen as the dose for the main study.

In the main assay, transient compound-related toxicity (but no mortality) was observed immediately after test article administration, subsiding six hours later. No increased micronucleated PCE over Cremophor controls were recorded at any sampling period, nor was there any, evidence of cytotoxicity (as determined from lack of alteration in PCE/NCE ratio). In contrast, CP-treated animals showed a significant increase in M-PCE, but again, no increased cytoxicity (Report Tables 1 to 5, summarized in Table 6, attached here).

Hence, the investigators concluded that NTN 33893 was not clastogenic (for micronucleus induction) in mice treated orally at a (presumed) clinically toxic dose.

F. TB EVALUATION: Not acceptable.

ATTACHMENT: (Summary Data Table)

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Toxicology Review #010128 3/29/93

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

1-12-93
3/4/93

DATA EVALUATION RECORD

010128

MRID NUMBER No.: 422563-49
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D1802999/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity --Other genotoxicity (SCE in CHO cells in vitro)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Miles (Mobay) KC

TESTING FACILITY: Hazleton Biotechnologies
Veenendaal (NETHERLANDS)

TITLE OF REPORT: Clastogenic Evaluation of NTN 33893 in an in vitro Cytogenetic Assay Measuring Sister Chromatid Exchange in Chinese Hamster Ovary (CHO) Cells.

AUTHOR: R.D.F.M. Taalman

STUDY NUMBER: R4407 (Report #102655)

DATE ISSUED: April 21, 1988

CONCLUSIONS: Positive for inducing sister-chromatid exchanges in Chinese hamster ovary (CHO) cells cultured in vitro at cytotoxic doses (500 ug/ml-S9; 2000 ug/ml/+S9).

TB-I EVALUATION: Acceptable

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description: Off-white powder
Batches (Lots): 180587
Purity (%): 95.2
Solvent/carrier/diluent:
Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Established mammalian cell strain

Species: Chinese hamster (ovary), CHO
Strain: WB-1
Source: Dr. S. Wolff (U Cal), SF/
Dr. A. Bloom (Columbia), NY

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic potential of the test article when administered in vitro to Chinese hamster ovary cells, and measuring the induction of sister-chromatid exchanges, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided, as was a statement of adherence to Good Laboratory Practice (GLP).

D. PROCEDURES/METHODS OF ANALYSIS: Following preliminary cytotoxicity (dose-selection) testing, duplicate cultures of CHO cells were exposed to solvent (DMSO) or graded concentrations of test material in the presence of a constant dose of bromdeoxyuridine (BrdU, 10 uM), both in the absence (24 hour exposure) and presence (only 2 hour exposure, followed by 22-23 hours in fresh BrdU medium) of a mammalian metabolic activation system, consisting of the microsomal (S9) fraction of livers from male rats pre-treated with the PCB, Aroclor 1254, plus NADP(H) generating co-factors. Other cultures were treated concurrently with the clastogens, mitomycin-C (MMC, 5 or 10 ug/ml), and cyclophosphamide (CP, 1.5 or 2.0 ug/ml), to serve as positive controls for non-activation and activation series, respectively. Two to three hours before harvest, all cultures were exposed to the mitotic inhibiter, Colcemid. Up to three completely separate (repeat) trials were run.

At harvest, cell cultures were attached to microscope slides, fixed in Carnoy's, then stained by a modification of the fluorescence-plus-Giemsa (FPG)

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technique (Perry and Wolff (1974); GOTO et al. (1978), following pre-treatment with the chromophor, Hoechst 33258. Under oil immersion optics, 25 normal (modal chromosome number, 2n=21+/-2) cells per culture in second division (M2) were scored.

This lab considers a test substance positive in this assay if there is at least a doubling of SCE over background at a minimum of three doses, and/or a statistically significant dose response, employing Student's t-test.

E. RESULTS:

In the first of two assays, precipitation was observed at the HDT, 5000 ug/ml with/without activation, and cytotoxicity (evidenced by 10-50% reduction in monolayer confluency, and/or cell cycle delay) at doses of 500 ug/ml and above with S9 (Report Table 1A, attached here). In addition, a statistically significant increase in SCE frequencies (56%) was recorded at 500 ug/ml, the highest dose analyzed, with smaller non-significant increases at lower doses, 166.7 and 50 ug/ml (Table 1B). In the repeat non-activation assay (tested at 25 to 2000 ug/ml), a (flat) dose-related increase in SCE were also recorded at 250,500 and 1000 ug/ml, but not at 100 ug/ml (Tables 2A/B).

In the presence of S9, precipitation was also observed at 5000 ug/ml, but no substantial cytotoxicity below that level (Table 3A). Although no significant changes in SCE were apparent in the first trial (at doses up to 5000 ug/ml) (Table 3B), repeat assays with S9 recorded both cytotoxicity and dose-related increased SCE at 2000 and 3000 ug/ml (Tables 4A/B). Both positive controls responded as expected with highly significant increased frequencies of SCE.

Hence, the investigators concluded that NTN 33898 was positive in inducing significantly increased SCE at demonstrably cytotoxic concentrations.

F. TB EVALUATION: Acceptable

ATTACHMENTS (Data Tables)

92

DER.MAU/jpf/422563.49/disk 1

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010128

EXPERIMENTAL DATA TABLES

9/4

Toxicology Review #010128 3/29/93

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____ The product confidential statement of formula.

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

03-22-93

3/16/93

DATA EVALUATION RECORD

010128

MRID NUMBER No.: 422563-50
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 3389 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity. Other genotoxicity (SCE in CHO cells in vitro)

CHEMICAL: Imidacloprid

SYNONYMNS: Bay NTN 33893

SPONSOR: Mobay, KS (Stilwell)

TESTING FACILITY: Microbiological Associates, Rockville, MD

TITLE OF REPORT: Sister Chromatid Exchange Assay in Chinese Hamster Ovary Cells

AUTHOR(S): D. L. Putnam and M. J. Morris

STUDY NUMBER: T8302.334 (Report No. 099676)

DATE ISSUED: September 12, 1989

CONCLUSIONS: Negative for the induction of sister-chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells exposed up to a cytotoxic dose (400 ug/ml/-S9) or to the limit of solubility (1250 ug/ml/+S9).

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893

Description: Tan powder
Batches (Lots): PF 17001/88
Purity (%): 95.2
Solvent/carrier/diluent: Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Established Cell Strain

Species: Chinese hamster (ovary), CHO
Strain: CCL-61
Source: American Type Culture Collection (CCL# 61), Rockville, MD

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic potential of the test article when administered in vitro to Chinese hamster ovary cell cultures, and sampling the induction of sister chromatid exchanges, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/ audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following cytotoxicity testing, duplicate cultures of CHO cells were exposed to graded concentrations of test article, for 29 hours in the absence of activation, but only for two hours in the presence of a mammalian metabolic activation system, consisting of the microsomal fraction (S9) of livers from male S-D rats pretreated with the PCB, Aroclor 1254, plus NADP(H)-generating co-factors. In addition to (DMSO) controls, other cultures were exposed concurrently to the genotoxins, triethylenemelamine (TEM, 0.025 ug/ml), and cyclophosphamide (CP, 2.5 ug/ml), as positive controls.

Two hours before harvest, all cultures were exposed to the mitotic poison, Colcemid, to accumulate dividing cells in metaphase, then fixed in Carnoy's Fluid and prepared on glass slides for microscopic examination of SCE by conventional cytological procedures (staining with Hoechst 33258, followed by exposure to u.v. light, then counterstained with 5% Giemsa). Coded slides were scanned for cells with normal genome (2n±2). 25 cells per culture (50 cells per treatment) which were scored for SCE, as well as for first, second and third division metaphase figures (M_1, M_2, M_3).

A test article is considered positive by this lab if a dose-related statistically significant increase in SCE is observed over at least two dose levels. Only those assays are considered valid for analysis in which the mean SCE/cell in the negative control is less than 16, and the mean SCE/cell in positive control(s) is statistically increased (at $p \leq 0.05$, by Student's t-test) over background.

E. RESULTS: In preliminary toxicity testing, precipitation occurred at 1250 ug/ml and above, and severe dose-related cytotoxicity (mitotic inhibition and cell cycle delay) was observed at 380 ug/ml without activation (-S9); but only minor cytotoxicity was found at the precipitation dose (Report Tables 1, 2). Hence the investigator selected dose levels of 25, 50, 100, 200 and 400 ug/ml for the non-activated portion of the assay, and 157, 313, 625, and 1250 ug/ml/+S9.

In the main assay, statistically significant increased SCE were found only in non-activated 200 ug/ml cultures (=13.28 SCE/cell), which is within the accepted background range for this lab., but at no other dose, including the cytotoxic 400 ug/ml (Report Table 3). No increased SCE (or toxicity) was recorded under activation up to precipitation concentrations (Report Table 4).

Therefore, the authors assess NTN 33893 was negative for the induction of SCE in CHO cells.

F. TB EVALUATION: ACCEPTABLE

ATTACHMENT: (Data Tables)

Disk 6:Mauer:422563.50

Toxicology Review #010128 3/25/93

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Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

03-03-93
3/14/95

010128

DATA EVALUATION RECORD

MRID NUMBER No.: 422563-52
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 33893)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity---DNA damage/repair in rat hepatocytes in vitro (UDS)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, Kansas City, MO

TESTING FACILITY: Hazleton Laboratories America (HLA), Kensington, MD

TITLE OF REPORT: NTN 33893 in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay

AUTHOR(S): M. A. Cifone

STUDY NUMBER: HLA-10237-0-447/T6027610 (Report No. 098573)

DATE ISSUED: December 21, 1988

CONCLUSIONS: Negative for inducing unscheduled DNA synthesis (UDS) in primary rat hepatocyte cultures treated up to cytotoxic doses (500-750 ug/ml)

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A. TEST MATERIAL: NTN 33893 (Bayer AG)

Description: Beige powder
Batches (Lots): 180587
Purity (%): 95.2
Solvent/carrier/diluent: Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Primary rodent hepatocyte cultures

Species: Rat
Strain: F-344
Age: "Adult"
Weights - males (only): 150-300 g
Source: Charles River

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic potential of the test article when administered in vitro to rat hepatocyte cultures, and measuring unscheduled DNA synthesis, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Following cytotoxicity (dose-selection) testing, monolayer (coverslip) hepatocyte cultures from two rats were separately exposed for 18-19 hours to a single concentration of tritiated thymidine (5 uCi/ml ^{3}H-TdR, of spec. act. = 20 Ci/m mole), together with either DMSO (solvent control) or graded concentrations of test article. After a 1 mM "cold" thymidine (non-radioactive) chase, viability (as relative cell survival, RCS) was determined for each treatment condition, while the cells in other coverslip aliquots were expanded in hypotonic saline (1% sodium citrate), fixed (3:1) and mounted (cell side out) on standard glass microscope slides. These were dipped in photographic emulsion (Kodak NTB-2), then stored under refrigeration in light-tight microscope slide boxes. After 7-10 days, stored cell preparation were treated to standard photographic developer (D19), fixed and stained with H & E. In each of two independent assays, other cultures were exposed to the mutagen 2-acetylaminofluorene (AAF) as positive control.

One hundred and fifty morphologically normal nuclei per treatment were examined under oil immersion optics and net

nuclear (silver) grain count (NNG) determined (NNG = nuclear grain count less average of 3 adjacent nuclear-sized cytoplasmic, background, counts).

The investigator reported the laboratory's routine criteria for both assay acceptance and evaluation, consistent with published accounts by experts in the field.

E. RESULTS: Test material was soluble in tissue culture medium up to 1000 ug/ml, but precipitated at higher concentrations. Five trials were initiated but three were not analyzed due to technical problems. Cytotoxicity was moderately severely (60-65% RCS) at 1000 ug/ml, less so (70%-80%) at the two next lower doses (750 and 500 ug/ml), and absent below these levels (to 5-10 ug/ml). In none of the trials, however, did the test material induce increased silver grain labelling (counts) significantly different from concurrent solvent controls and/or the laboratory's minimum background (Report Tables 1 thru 4, attached here).

Hence the author concluded that NTN 33893 was negative for inducing UDS in rat hepatocytes treated up to cytotoxic doses.

F. TB EVALUATION: ACCEPTABLE

ATTACHMENT (Data Tables)

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LABORATORIES AMERICA, INC.

XIII. TABLES

Toxicology Review # 010128 3/29/93

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Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

3-25-93
3/16/93

DATA EVALUATION RECORD 010128

MRID NUMBER No.: 422563-53
PC No.: 129099
RD Record No.: S-419490
EPA ID No.: 003125-URU (NTN 33893 tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Other genotoxicity - mitotic recombination in yeast

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, KC

TESTING FACILITY: Bayer AG, Wuppertal (FRG)

TITLE OF REPORT: NTN 33893: Test on S. cerevisiae D7 to Evaluate for Induction of Mitotic Recombination.

AUTHOR(S): B. A. Herbold

STUDY NUMBER: T5025954 (Report # 16832/102653)

DATE ISSUED: June 27, 1988

CONCLUSIONS: Negative for inducing evidence of mitotic recombination (crossing-over; gene conversion) in yeast cells (Saccharomyces cerevisiae D7) exposed with/without activation to pr ipitating levels of test article (5000 to 10,000 ug/ml)

TB-I EVALUATION: ACCEPTABLE

II. DETAILED REVIEW

A TEST MATERIAL: NTN 33893 (Bayer AG)

Description: Beige powder
Batches (Lots): 180587
Purity (%): 95.3
Solvent/carrier/diluent: Dimethylsulfoxide (DMSO)

B. TEST ORGANISM: Yeast

Species: Saccharomyces cerevisiae
Strain: D7 [ade-2(-); tryp-5(-); ilvI-92(-/-]
Source: F. K. Zimmerman, Darmstadt (FRG)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic potential of the test article when administered in vitro to strain D7 of Saccharomyces cerevisiae, and measuring the induction of mitotic recombination (MCO, MGC), according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: Suspensions of yeast cells were exposed to solvent (DMSO controls) or to graded concentrations of NTN 33893, then 16 hours later washed free of test substances, and assayed for toxicity and mitotic gene conversion (MGC, by induction of tryptophane independence), and mitotic crossing-over (MCO, induction of adenine dependence), in the absence or presence of mammalian metabolic activation[1]. The mutagens methyl methanesulfonate (MMS) and cyclophophamide served as positive controls for, respectively, the non-activation and activation series. Two complete independent assays were run.

E. RESULTS: At no concentration in either trial up to precipating levels (5000-10,000 ug/ml) were either cytotoxicity demonstrated, or tryptophane revertents or adenine mutant sectors induced (Report Tables 1 thru 8, attached here). In contrast, both positive controls, MMS and CP, significantly

[1]Microsomal fraction (S9) of livers from adult male sprague-Dawley rats pretreated with Aroclar (254, plus NADP(H)-generating co-factors (S9-mix)

increased mitotic recombination. Hence the investigator concluded that NTN 33893 was negative for genotoxic (mitotic recombination) potential.

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F. TB EVALUATION: ACCEPTABLE

ATTACHMENT: (Data Tables)

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Toxicology Review # 010128 3/29/93

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Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

02-24-93
3/16/93

DATA EVALUATION RECORD 010128

MRID NUMBER No.: 422563-51
PC No.: 129099
RD Record No.: S-419390
EPA ID No.: 003125-URU (NTN 33893 Tech)
Tox Chem. No.: 497E
Project No.: D180299/D179336

I. SUMMARY

STUDY TYPE: (84-2) Mutagenicity --Other genotoxicity (bacterial rec-assay)

CHEMICAL: Imidacloprid

SYNONYMNS: NTN 33893

SPONSOR: Mobay, Stillwell, KS

TESTING FACILITY: Hino Institute, Tokyo (Japan)

TITLE OF REPORT: NTN 33893: Rec-Assay with Spores in the Bacterial System

AUTHOR: M. Watanabe

STUDY NUMBER: 90A013

DATE ISSUED: June 18, 1990

CONCLUSIONS: Reportedly negative for DNA-damaging effects in B. subtilis M45 (rec-) bacteria compared to H17 (rec+) up to 5000 ug/disc, the limit of solubility, with or without activation

TB-I EVALUATION: ~~(NOT GRADABLE/NO TEST)~~ ACCEPTABLE

II. DETAILED REVIEW

A. Test Material: NTN 33893 (Bayer AG)

Description: White-yellow powder
Batches (Lots): 180587
Purity (%): 94.7
Solvent/carrier/diluent: Dimethylsulfoxide (DMSO)

B. Test Organism: Bacterial cultures

Species: Bacillus subtilis
Strains: H-17 (rec+, repair-proficient),
M-45 (rec-, repair-deficient)
Source: Institute for Environmental Toxicology, Tokyo (Japan)

C. STUDY DESIGN (PROTOCOL): This study was designed to assess the genotoxic (DNA-damaging) potential of the test article when administered in vitro to cultures of Bacillus subtilis (strains H-17 and M-45) and observing differential toxicity, according to established (published) procedures and FIFRA Test Guidelines.

A Statement of Quality Assurance measures (inspections/audits) was provided.

A Statement of adherence to Good Laboratory Practice (GLP) was provided.

D. PROCEDURES/METHODS OF ANALYSIS: H-17 and M-45 bacterial cultures were exposed to paper discs soaked with graded concentrations of the test article (to 5000 ug/disc, the limit of solubility), both in the absence and presence of mammalian metabolic activation provided by the microsomal fraction (S9) of livers from S-D rats pre-treated with the enzyme inducers, phenobarbital and 5,6 benzoflavone, plus NADP(H)-generating co-factors. In addition to negative controls (DMSO and kanamycin sulfate, KM), other cultures exposed to mitomycin-C (MMC) and 2 aminoanthracene (AA) served as positive controls.

E. RESULTS: As shown in Report Table 1 (attached here) no effects at all were observed with/without activation in test cultures, whereas both positive controls elicited significant degrees of growth inhibition (differential zones of toxicity) in rec-deficient (M-45) cultures.

Therefore the investigator concluded that NTN 33893 was negative for DNA-damaging effects.

F. TB EVALUATION: ("NO-TEST")
The assay cannot reasonably be assessed for the end point (differential toxicity to the rec- repair system), since no activity at all was apparently observed in NTN 33893-treated cultures (compared to both positive controls, and KM), possibly indicating lack of translocation of the test article from the carrier.

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