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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. Nos.: 003125-UGU, 003125-UEI, 003125-UEG, 003125-UEE, 003125-URA, 3F4231, 3H05675, 4F04285, 003125-UEE. Imidacloprid. Evaluation of Toxicity Data Submitted and Identification of Outstanding Toxicology Data Requirements

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I. CONCLUSIONS

The existing database supports the following uses for the following submissions:

Chemical I.D.	Submission	Formulation	Application
003125-UGU	Registration	Gaucho 240 Flowable	Cotton
003125-UEI	Registration	Admire Solupak 75% WP	Grape
003125-UEG	Registration	Confidor 2.5% Granular	Fruiting vegetables e.g. tomato, Brassica (Cole) leafing vegetables e.g. broccoli, lettuce (head & leaf)
003125-UEE	Registration	Confidor 2 Flowable	Fruiting vegetables, Brassica (Cole) leafy vegetables, lettuce, grape
003125-URA	Registration	Merit 0.62% Granular	Turf
3F04231	Tol. Pet.		Fruiting vegetables, Brassica (Cole) leafy vegetables, lettuce, grape, fruit, milk, meat (fat & byproducts) of cattle, goats, hogs, horses & sheep
3H05675	Tol. Pet.		Fruiting vegetables, Brassica (Cole) leafy vegetables, lettuce, grape, fruit, milk, meat (fat & byproducts) of cattle, goats, hogs, horses & sheep
4F04285	Tol. Pet.		Mango
003125-UEE	Registration	Confidor 2 Flowable	Mango

II. ACTION REQUESTED

TB-1 received for evaluation the several studies required to fulfill data requirements for registration of NTN 33893 Technical and Formulations for food use. These data were submitted by Bayer AG and/or Miles, Inc.

III. RESULTS/DISCUSSION

The requirements (CFR 158.135) for Food Use for the Technical are listed in Table 1.

Table 1.

Test		Technical		Formulations§	
		Required	Satisfied	Required	Satisfied
81-1	Acute Oral Toxicity	Y	Y	Y	Y
81-2	Acute Dermal Toxicity	Y	Y	Y	Y
81-3	Acute Inhalation Toxicity	Y	Y	Y	Y
81-4	Primary Eye Irritation	Y	Y	Y	Y
81-5	Primary Dermal Irritation	Y	Y	Y	Y
81-6	Dermal Sensitization	Y	Y	Y	Y
81-7	Acute Delayed Neurotox. (Hen)	N	-	N	-
82-1	Oral Subchronic (Rodent)	Y	Y	N	-
82-1	Oral Subchronic (Non-Rodent)	Y	Y	N	-
82-2	21-Day Dermal	Y	Y	N	-
82-3	90-Day Dermal	N[1]	-	N	-
82-4	90-Day Inhalation	N[2]	Y[4]	N	-
82-5	90-Day Neurotoxicity (hen)	N[3]	-	N	-
82-6	90-Day Neurotoxicity (mammal)	N[3]	-	N	-
83-1	Chronic Toxicity (Rodent)	Y	Y	N	-
83-1	Chronic Toxicity (Non-rodent)	Y	Y	N	-
83-2	Oncogenicity (Rat)	Y	Y	N	-
83-2	Oncogenicity (Mouse)	Y	Y	N	-
83-3	Developmental Toxicity (one species)	Y	Y	N	-
83-3	Developmental Toxicity (two species—rodent & non-rodent)	Y	Y	N	-
83-4	Reproduction	Y	Y	N	-
83-5	Chronic/Oncogenicity	Y	Y	N	-
84-2	Mutagenicity—Gene Mutation	Y	Y	N	-
84-2	Mutagenicity—Structural Chromosomal Aberrations	Y	Y	N	-
84-4	Mutagenicity—Other Genotoxic Effects	Y	Y	N	-
85-1	General Metabolism	N	-	N	-
85-2	Dermal Penetration	N	-	N	-
86-1	Domestic Animal Safety	N	-	N	-
Special Studies for Ocular Effects					
	Acute Oral (Rat)	N	-	N	-
	Subchronic Oral (Rat)	N	-	N	-
	Six-month Oral (Dog)	N	-	N	-

Y yes

N no

§ Confidor 2 Flowable (24.1%) and Confidor 2.5% Granular Formulations

[1] Not required based on lack of dermal toxicity observed in the 21-day dermal study, and based on expected exposure.

[2] Not required since significant exposure via inhalation not expected.

[3] Not required since no evidence of neurotoxicity observed in acute or chronic exposure.

[4] Although not required in this case, TB-1 received from the Submitter, and reviewed a subchronic inhalation study (MRID 422730-01) and classified it as Core Minimum, acceptable for regulatory purposes.

Data Gaps No outstanding data gaps have been identified for these formulations.

A. ACUTE TOXICITY

The Acute toxicity data on the Technical is summarized below in Table 2A. Tables 2B and 2C summarize the acute toxicity data on the 24.1% and 2.5% Formulations, respectively.

TABLE 2A. SUMMARY OF ACUTE TOXICITY OF NTN 33893 TECHNICAL

TEST	RESULTS	CATEGORY
81-1 Acute Oral Toxicity—Rats Study No.: T 2033060 Date: December 15, 1989 MRID No.:420553-31	LD50: Males: 424 mg/kg Females: >450 to <475 mg/kg Study is Acceptable Toxic Signs: Apathy, labored or transient labored breathing, transient accelerated breathing, decreased motility, transient staggering gait, blepharophimosis, transient trembling and transient spasms.	II
81-2 Acute Dermal Toxicity—Rabbit Study No.: T 5033063 Date: November 15, 1989 MRID No.: 420553-32	LD50: >5000 mg/kg (Limit Test) Study is Acceptable Toxic Signs: decreased body weight gain in females	IV
81-3 Acute Inhalation Toxicity—Rat Study Nos.: T 2025951 T 3025952, T 4025953 Date: June 6, 1988 MRID No.: 420553-33	LC50: ♂ & ♀: One 4-hr dose: >5.323 mg/L Five 6-hr doses: >0.505 mg/L Study is Acceptable Toxic Signs: Single exposure → Difficult breathing, reduced motility, piloerection, slight tremors, decreased body weight gains Repeated exposure → transient decrease in female body wt. gain, dark spleen & isolated foci, increase microsomal enzyme induction.	III
81-4 Primary Eye Irritation—Rabbit Study No.: T 8025515 Date: February 15, 1988 MRID No.: 420553-34	Primary Irritation Index: 0.0 Study is Acceptable Toxic Signs: Minimal redness and/or swelling of conjunctivae, clearing within 24 hours.	IV
81-5 Primary Dermal Irritation—Rabbit Study No.: T 8025515 Date: February 25, 1988 MRID No.: 420553-35	PIS: 0.0 (non-irritating) Study is Acceptable Toxic Signs: Slight erythema.	IV
81-6 Dermal Sensitization—Guinea Pig Study No.: T 9025651 Date: March 15, 1988 MRID No.: 420553-36	Not a Sensitizer Study is Acceptable Toxic Signs: None except in positive controls	--

TABLE 2B. SUMMARY OF ACUTE TOXICITY OF NTN 33893 24.1% FLOWABLE FORMULATION

TEST	RESULTS	CATEGORY
81-1 Acute Oral/Rat Study No. 89-012-DV Date: Feb. 26, 1990 MRID No.: 422563-13	LD50 Male >4870 mg/kg Female 4143 mg/kg (calculated Study is Acceptable Toxic Signs: Tremors, Decreased activity, lacrimation with stain, convulsions, oral discharge and stain, urine stain, alopecia, decreased body weight gain.	III
81-2 Acute Dermal/Rat Study No. 89-025-EB Date:Feb. 22, 1990 MRID No.: 422563-15	LD50 >2000 mg/kg NOEL (local and systemic): <2000 mg/kg (Limit Test) LOEL (local and systemic: 2000 mg/kg Study is Acceptable Toxic Signs: Transient erythema and muscle fasciculation, decreased body weight gain in males.	III
81-3 Acute Inhalation/Rat Study No. 89-042-EG Date: Feb. 27, 1990 MRID No.: 422563-17	LC50 >5330 mg/m3 NOEL <5060 mg/m3 LOEL 5060 mg/m3 Study is Acceptable Toxic Signs: Death, hypoactivity, dyspnea, lethargy, tremors, decreased body weight gain in males.	IV
81-4 Eye Irrit./Rabbit Study No.:89-335-DZ Date: Jan. 15, 1990 MRID No.: 422563-19	TIS: TIME 1hr 24hr 48hr 72hr 7d 14d IRRIT. SCORE 1.0 0.3 0.2 0.0 0 0 Study is Acceptable Toxic Signs: Conjunctival redness and discharge, chemosis.	III
81-5 Primary Dermal Irritation/Rabbit Study No. 89-325-DU Date: Jan. 15, 1990 MRID No.: 422563-21	PIS: 0.0 Non-irritating. Study is Acceptable Toxic Signs: None	IV
81-6 Dermal Sensitization/Guinea pig Study No. 89-324-DO Date: Feb. 22, 1990 MRID NO. 422563-23	Conclusion: Not a Sensitizer Study is Acceptable Toxic Signs: None except in positive controls.	N/A

TABLE 2C. SUMMARY OF ACUTE TOXICITY OF NTN 33893 2.5% GRANULAR FORMULATION

TEST	RESULTS	CATEGORY
81-1 Acute Oral/Rat Study No. 89-012-DY Date: Feb. 26, 1990 MRID No.: 422563-24	LD50 Male >4820 mg/kg (5000 mg/kg nominal, Limit Test) Study is Acceptable Toxic Signs: Increased body weight. No other signs	IV
81-2 Acute Dermal/Rat Study No. 89-025-DS Date: Jan. 15, 1990 MRID No.: 422563-25	LD50 >2000 mg/kg (Limit Test) Study is Acceptable Toxic Signs: None.	III
81-3 Acute Inhalation/Rat Study No. 89-042-DX Date: Feb. 26, 1990 MRID No.: 422563-26	LC50 >5092 mg/m3 (95% Confidence Intervals) Study is Acceptable Toxic Signs: None.	IV
81-4 Eye Irrit./Rabbit Study No.:89-335-DT Date: Jan. 15, 1990 MRID No.: 422563-27	TIS: TIME 1hr 24hr 48hr 72hr 7d 14d IRRIT. SCORE 2.3 1.2 1.0 0.5 0.2 0.0 Study is Acceptable Toxic Signs: conjunctival redness, chemosis and discharge	II
81-5 Primary Dermal Irritation/Rabbit Study No. 89-325-ED Date: Jan. 15, 1990 MRID No.: 422563-28	PIS: 0.0 Non-irritating. Study is Acceptable Toxic Signs: None	IV
81-6 Dermal Sensitization/Guinea pig Study No. 89-324-DN Date: Feb. 22, 1990 MRID NO. 422563-29	Conclusion: Not a Sensitizer Study is Acceptable Toxic Signs: None except in positive controls.	N/A

B. SUBCHRONIC TOXICITY

Two studies were reviewed: **a)** a 21-day dermal in rabbits (82-2; MRID 422563-29) and **b)** a 90-day inhalation in rats (82-4; MRID 422730-01). Each study is classified as Core-Minimum or Core-Guideline.

In the 21-day dermal study, New Zealand white rabbits (5 male and 5 female/group) were exposed to NTN Technical 6 hr/d, 5 d/wk for four weeks at 1,000 mg/kg/d, the limit dose. No dermal or systemic effects of

toxicological importance were observed. Based on these results the dermal and systemic NOEL is 1000 mg/kg/day, and the dermal and systemic LOEL is >1000 mg/kg/day.

In the 90-day inhalation study, groups of 10 male and 10 female Wistar rats were exposed (nose only) to analytical concentrations of 0.006, 0.031 or 0.191 mg/L, for 6hr/d, 5 d/wk for 4 weeks. No toxicological effects were observed. Based on these results, the NOEL is 0.191 mg/L and the LOEL is >0.191 mg/L.

C. CHRONIC/ONCOGENIC TOXICITY

Three chronic feeding and/or carcinogenicity studies are available: **a)** Chronic Study in Dogs (83-1b; MRID: 422730-02); **b)** Two-Year Feeding/Oncogenicity Study in Rats (83-1, 83-2; MRID: 422563-31 and 422563-32); and **c)** Two-Year Oncogenicity Study in Mice (83-2; MRID: 422563-35, 422563-36).

In the chronic dog study, groups of 4 male and 4 female Beagle dogs were fed NTN Technical in the diet daily for 52 weeks, and examined for signs of toxicity. Dose levels were 0, 200, 500 and 1250 ppm (average intake was 0, 6.1, 15.0 and 41.0 mg/kg/d). The high dose was increased to 2500 ppm (72 mg/kg/d) from Week 17 onwards due to lack of toxicity at 1250 ppm. A transient decrease in food consumption, probably due to palatability, was observed during Weeks 1,2, 17, & 18 (males), and at Weeks 2 and 17 - 20 (females) at 1250/2500 ppm. Increased plasma cholesterol and liver cytochrome P-450 levels were seen at 2500 ppm. It was concluded that the NOEL is 1250 ppm, with a LOEL of 2500 ppm.

In two chronic/onco rat study (two studies reviewed as one since dose levels were complementary), groups of 50 male and 50 female Bor WISW(SPF Cpb) rats were administered NTN Technical in the diet for 24 months at 0, 100, 300 and 900 ppm, and at 0 and 1800 ppm and examined for signs of toxicity and carcinogenicity. The results are as follows:

Chronic Effects: NOEL: 100 ppm (5.7 mg/kg/d in ♂, 7.6 mg/kg/d in ♀)
LOEL: 300 ppm. Increased thyroid lesions in ♂ at 300 ppm and above and in ♀ at 900 ppm (73.0 mg/kg/d) and above; decreased body weight gain in females at 300 ppm (24.9 mg/kg/d) and above; weight changes in liver, kidney, lung, heart, spleen, adrenals, brain and gonads in ♂ and/or ♀ at 900 ppm (51.3 mg/kg/d in ♂, 73.0 mg/kg/d in ♀) or 1800 ppm.

Oncogenicity: No apparent treatment-related effect.

In the mouse onco study, (two studies reviewed as one since dose levels were complementary), groups of 60 male and 60 female B6C3F1 mice were fed daily doses of NTN 33893 Technical in the diet at 0, 100, 330, 1000 ppm and 0, 2000 ppm and examined for signs of toxicity and carcinogenicity. The results are as follows:

Chronic Effects: NOEL: 1000 ppm (208 mg/kg/d in ♂, 274 mg/kg/d in ♀)
LOEL: 2000 ppm, based on decreased body weight, decreased food consumption and decreased water intake, in both sexes.

Oncogenicity: No apparent treatment-related effect.

D. DEVELOPMENTAL TOXICITY

Two studies are available: **a)** Developmental toxicity in rats (83-3a; MRID 422563-38), and **b)** Developmental toxicity in rabbits (83-3b; MRID 422563-39).

In the rat study, NTN 33893 Technical was administered by gavage to HSD(SD) rats at 0, 10, 30, and 100 mg/kg/d during Gestational Days 6 - 16. The Maternal NOEL = <10 mg/kg/d; the LOEL = 10 mg/kg/d, based on decreased body weight gain. At 100 mg/kg/d, Decreased food consumption was observed. The Developmental NOEL = 30 mg/kg/d; the LOEL = 100 mg/kg/d, based on increased wavy ribs.

In the rabbit study, NTN 33893 Technical was administered by gavage to HSD(SD) rats at 0, 10, 30, and 100 mg/kg/d during Gestational Days 6 - 16. The Maternal NOEL = 24 mg/kg/d; the LOEL = 72 mg/kg/d, based on decreased body weight, increased resorption, increased abortion, and death. The Developmental NOEL = 24 mg/kg/d; the LOEL = 72 mg/kg/d, based on decreased body weight, increased skeletal abnormalities.

E. REPRODUCTIVE TOXICITY

One study is available, (83-4; MRID 422563-40) and is classified as Core Minimum.

In this study, Wistar/Han rats were fed NTN 33893 Technical in the diet during the mating, pregnancy, lactation and post-weaning periods at 0, 100, 250, or 700 ppm. (0, 100, 250 ppm and 700 ppm during premating.) The

Parental NOEL = 700 ppm (≈55 mg/kg/d); the LOEL >700 ppm. The Reproductive NOEL = 100 ppm (≈ 8 mg/kg/d); the LOEL = 250 ppm (≈ 19 mg/kg/d) based on decreased pup body weight in both generations.

F. MUTAGENICITY

Several mutagenicity studies are available. They are summarized on Table 3 below. Data requirements for these FIFRA TOX. Guidelines are satisfied by these submissions; no further studies need be submitted at this time.

Table 3.

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 (report 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

Study Type (MRID No.)	Title (Report No.)	Reported Results	TB Evaluation
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)	"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)	"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)	"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)	"WAK 3839 or NTN 37571 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)	"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)	"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)	"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)	"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)	"NTN 37571 In Vitro Cytogenetic Assay Measuring Chromosome Aberrations in CHO-K1 Cells," Report No. 100678	Negative up to 1000 ug/ml	ACCEPTABLE
DNA repair (422563-72)	"Unscheduled DNA Synthesis in Primary Hepatocytes of Male Rats In Vitro with WAK 3839," Report No. 100665	Negative up to 1333 ug/ml	ACCEPTABLE

G. METABOLISM

The metabolism of NTN 33893 in rats was reported in seven studies (85-1), and found to be Core Minimum. They are: a) Methylene- [^{14}C] Imidacloprid: Metabolism Part of the General Metabolism Study in the Rat (MRID 422563-54); b) [^{14}C]-NTN 33893. Biokinetic Part of the General Metabolism Study in the Rat (MRID 422563-56); c) [Imiazolidine-4,5-^{14}C] Imidacloprid: Investigation of the Biokinetic Behavior and Metabolism in the

Rat (MRID 422563-57); **d)** Imidacloprid - WAK 3839: Comparison of Biokinetic Behavior and Metabolism in the Rat Following Single oral Dosage and Investigation of the Metabolism after Chronic Feeding of Imidacloprid to Rats and Mice (MRID 422563-73); **e)** A Liquid Chromatographic Method for the Determination of NTN 33893 in Aqueous Dose Mixtures (MRID 422563-59); **f)** A Liquid Chromatographic Method for the Determination of NTN 33893 in Inhalation Chamber Atmospheres (MRID 422563-58); **g)** [^{14}C]-NTN 33893: Investigations on the Distribution of the Total Radioactivity in the Rat by Whole-body Autoradiography (MRID 422563-55).

These data show that Imidacloprid was rapidly absorbed and eliminated in the excreta (90% of the dose within 24 hours), demonstrating no biologically significant differences between sexes, dose levels, or route of administration. Elimination was mainly renal (70-80% of the dose) and fecal (17-25%). The major part of the fecal activity originated in the bile. Total body accumulation after 48 hr consisted of 0.5% of the radioactivity with the liver, kidney, lung, skin and plasma being the major sites of accumulation. Therefore, bioaccumulation of Imidacloprid is low in rats. Maximum plasma concentration was reached between 1.1 and 2.5 hr. Two major routes of biotransformation were proposed for Imidacloprid. The first route included an oxidative cleavage of the parent compound rendering 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxynicotinic acid and its mercapturic acid derivative. The second route included the hydroxylation followed by elimination of water of the parent compound rendering NTN 35884.

A comparison between [methylene-^{14}C]-Imidacloprid and [imidazolidine-4,5-^{14}C]-Imidacloprid showed that while the rate of excretion was similar, the renal portion was higher with the imidazolidine-labeled compound. In addition, accumulation in tissues was generally higher with the imidazolidine-labeled compound.

A comparison between Imidacloprid and one of its metabolites, WAK 3839, showed that the total elimination was the same for both compounds. The proposed metabolic pathways for these two compounds were different. WAK 3839 was formed following pretreatment (repeated dosing) of Imidacloprid.

H. NEUROTOXICITY

Since Imidacloprid is not an organophosphate, the following studies are not required: **a)** Acute Delayed Neurotoxicity in the Hen (81-7); **b)** Acute Neurotoxicity Screening Battery in the Rat (81-8-SS); **c)** 90 Day Neurotoxicity Screening Battery in the Rat (82-7). The Submitter has announced their intention to perform the 90-Day test (82-7) anyway, and has received TB-1

approval on the protocol.

IV. OTHER TOXICOLOGICAL CONSIDERATIONS

This chemical has been determined to be a Group E Carcinogen (cf. memo from 4/22/93 HED RfD Review Committee, attached).

The Metabolism Committee (see attached memo) has concluded that none is the metabolites of NTN 33893 is of toxicological concern at this time.

V. REFERENCE DOSE

On April 22, 1993, the HED Reference Dose (RfD) Peer Review Committee recommended that the RfD for NTN 33893 (Imidacloprid) be established at 0.057 mg/kg/d. This value was based on the systemic NOEL of 100 ppm (5.7 mg/kg/day) from the 24-month rat chronic/onco study (MRID 422563-31, 422563-32) and an uncertainty factor (UF) of 100. This RfD has not yet been confirmed by the Agency RfD Work-Group.