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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.: 5F04480, 5H05718. Imidacloprid. Evaluation of Product Labeling Data Submitted and Identification of Outstanding Toxicology Data Requirements

Tox. Chem. No.	497E
PC Code No.	129099
DP Barcode Nos.	D213247, ~~D213249~~, D213250
Submission Nos.	S483726, ~~S483727~~, S483728

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I. CONCLUSIONS

The existing database supports the following uses for Imidocloprid:

Product I.D.	Submission	Formulation	Application
5F04480 (Miles, Inc.)	Tolerance Petition	Imidacloprid	Subject Tolerance
5H05718 (Miles, Inc.)	Tolerance Petition	Imidacloprid	Subject Tolerance

II. ACTION REQUESTED

TB-1 received for evaluation 1) an application for registration of Admire 2, an Imidacloprid formulation, for food/feed use; 2) an application for registration of Provado 1.6 Flowable, also an Imidacloprid formulation, for food/feed use; 3) a petition for tolerance for Admire 2 Flowable and Provado 1.6 Flowable formulations. All three applicatons are for the control of pests that infest green leafy vegetables and/or the pome fruit crop group (which includes, apple, pear, crabapple, loquat, mayhaw, oriental pear and quince). TB-1 was asked to evaluate these against the existing data base on imidacloprid to determine if it is adequate to fulfill relevant data requirements. The data available were previously submitted by Bayer AG, Miles, Inc., and Gustafson, Inc.

III. RESULTS/DISCUSSION

The requirements (CFR 158.135) for Food/Feed Use for the Technical are listed in the following table.

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	-
81-8-ss	Acute Neurotox. Screening Battery (Rat)	N[5]	-	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	-
82-5	90-Day Neurotoxicity (mammal)	N[3]	-	N	-
82-7	90 Day Neurotoxicity Screening Battery (Rat)	N[6]	-	N	-

Test		Technical		Formulations§	
		Required	Satisfied	Required	Satisfied
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				
85-1	General Metabolism	Y	Y	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
§	Confidore 2 and Provado 1.6 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. TB1 has received and reviewed a voluntary study from the Submitter. It is classified Core Minimum.

[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.

[5] This study is not required this the case, but has been submitted anyway, and reviewed and classified Core Accepatable.

[6] This study is not required in this case, but has been submitted anyway, and reviewed and classified Core Accepatable.

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

SUMMARY OF THE TOXICITY DATA BASE FOR IMIDACLOPRID TECHNICAL

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 75% and 40% 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 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.	IV
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

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
81-6 Dermal Sensitization—Guinea Pig Study No.: T 9025651 Date: March 15, 1988 MRID No.: 420553-36	Not a Sensitizer using Study is Acceptable Toxic Signs: None except in positive controls	--

TABLE 2B. SUMMARY OF ACUTE TOXICITY OF NTN 33893 75% FLOWABLE FORMULATION

CITATION	RESULTS	CATEGORY
Acute Oral/Rat Mobay 91-012-JJ Aug. 27, 1991 MRID 422563-12	LD_{50}: Males: 2591 mg/kg, Slope = 2.3 Females: 1858 mg/kg, Slope 5.4 NOEL: <1063 mg/kg Study is Acceptable Toxic Signs: Clinical: 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. Gross Lesions: salivation, lacrimation reddened lungs and nasal stain.	III
Acute Dermal/Rat Mobay 91-022-JH Aug. 21, 1991 MRID 422563-14	LD_{50}: >2000 mg/kg (Local & Systemic) NOEL: <2000 mg/kg (Limit Test) Study Is Acceptable Toxic Signs: Urine stains, alopecia	III
Acute Inhalation/Rat Mobay 91-042-JZ Sep. 25, 1991 MRID 422563-16	LC_{50} Males: 2.650 mg/L Females: 2.750 mg/L Study is Acceptable Toxic Signs: ataxia, convulsions, hypoactivity, moribundity, nasal stain, urine stain and tremors, decrease body weight, death	III
Eye Irrit./Rabbit Mobay 91-335-JK Jun. 25, 1991 MRID 422563-18	Conclusion: Minimal Eye Irritation, resolved by 7 days Study is Acceptable Toxic Signs: Conjunctival redness, chemosis and discharge	III
Primary Dermal Irritation/ Rabbit Mobay 91-325-JG Aug. 15, 1991 MRID 422563-20	Conclusion: PIS: 1.08 (mildly-irritating) Study is Acceptable Toxic Signs: Erythema (grade 2) was observed in five animals, and edema (grade 1) was observed in one animal one hr following exposure. All resolved within 7 days.	IV

CITATION	RESULTS	CATEGORY
Dermal Sensitization/ Guinea pig Mobay 91-324-JC Aug. 23, 1991 MRID 422563-22	Conclusion: Not a Sensitizer the Buehler Topical Patch technique Study is Acceptable Toxic Signs: None	N/A

TABLE 2C. SUMMARY OF ACUTE TOXICITY OF NTN 33893 40.7% FLOWABLE FORMULATION

TEST	RESULTS	CATEGORY
81-1 Acute Oral/Rat Study No. 9845-93 Date: March 25, 1993 MRID No.: 428577-02	LD50 Male 4687 mg/kg Female 4067 mg/kg Study is Acceptable Toxic Signs: Decreased body weight, clinical signs, and findings at necropsy	III
81-2 Acute Dermal/Rabbit Study No. 9846-93 Date: March 2, 1993 MRID No.: 428577-03	LD50 >5050 mg/kg (both sexes) Study is Acceptable Toxic Signs: Decreased body weight and body wt. gain in males	IV
81-3 Acute Inhalation/Rat Study No. 9847-93 Date: April 26, 1993 MRID No.: 422563-26	LC50 2.11 mg/L for males & females Study is Acceptable Toxic Signs: Decreased body weight gain, clinical signs & gross pathological findings.	III
81-4 Eye Irrit./Rabbit Study No. 9848-93 Date: Feb. 17, 1993 MRID No.: 428577-05	TIS: TIME 1hr 24hr 48hr 72hr IRRIT. SCORE 0.7 0.1 0.0 0.0 Study is Acceptable Toxic Signs: conjunctival redness	IV
81-5 Primary Dermal Irritation/Rabbit Study No. 9849-93 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. 9850-93 Date: March 22, 1993 MRID NO. 428577-07	Conclusion: Not a Sensitizer the Buehler Topical Patch technique Study is Acceptable Toxic Signs: None	N/A

B. SUBCHRONIC, CHRONIC, DEVELOPMENTAL, AND REPRODUCTIVE TOXICITY

Non-acute in vivo toxicity is summarized in the next table.

TABLE 3. SUMMARY OF NON-ACUTE TOXICITY NTN 33893

Guideline	Study Identification	Study Results
82-2	21-day Repeated Dose Dermal Species: Rabbit MRID: 422563-29 Core: Minimum DOC#: 009960	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.
83-4	28-Day Inhalation Study Species: Rat MRID: 422730-01 Core: Minimum DOC #: 010537	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 NTN 33893, for 6 hr/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.
83-1b	Chronic Species: Dog MRID: 422730-02 Core: Minimum DOC #s: 009960	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.
83-1a, 83-2a	Chronic/Onco Species: Rat MRIDs: 422563-31, 422563-32 Core: Minimum DOC #: 009960	NTN 33893 Technical was administered in the diet to 50 male and 50 female Bor WISW (SPF Cpb) rats per group at 0, 100, 300, 900 and 1800 ppm for 104 weeks. The 1800 ppm dose group tested in a separate study with its own concurrent controls. Results were as follows: The NOEL for Chronic Effects was 100 ppm (5.7 mg/kg/d in males, 7.6 mg/kg/d in females). The LOEL was 300 ppm based on increased thyroid lesions in males at 300 ppm (16.9 mg/kg/d) and above and in females at 900 ppm (73 mg/kg/d) and above; Decr. body wt. 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 males and/or females at 900 ppm (51.3 mg/kg/d in males, 73.0 mg/kg/d in females) or 1800 ppm. Oncogenicity: No apparent treatment-related effect at any dose.

Guideline	Study Identification	Study Results
83-2	2 Yr. Oncogenicity Species: Mouse MRID: 422563-35, 422563-36 Core: Minimum DOC #010537	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 (Two studies reviewed as one since dose levels were complementary). The NOEL was 1000 ppm (208 mg/kg/d in males, 274 mg/kg/d in females); the LOEL was 2000 ppm based on decreased body wt, decreased food consumption and decreased water intake. Oncogenicity: No apparent treatment-related effect at any dose.
83-3a	Developmental Toxicity Species: Rat MRID: 422563-38 Core: Minimum DOC #: 010537	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.
83-3b	Developmental Toxicity Species: Rabbit MRID: 422563-39 Core: Minimum DOC #s: 009960	NTN 33893 Technical was administered to 16 pregnant Chinchilla rabbits per group at 0, 8, 24, and 72 mg/kg/d during gestation days 6 through 19. The Maternal NOEL = 24 mg/kg/d; the LOEL = 72 mg/kg/d based on decreased food consumption; 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.
83-4	Reproductive Toxicity Species: Rat MRID: 422563-40 Core: Minimum DOC #010537	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.

C. MUTAGENICITY

Several mutagenicity studies are available. They are summarized on Table 4 below. Data requirements for these FIFRA TOX. Guidelines are satisfied by these submissions; no further studies need be submitted at this time.

RID: none

Table 4.

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
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

Study Type (MRID No.)	Title (Report No.)	Reported Results	TB Evaluation
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

D. 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.

E. NEUROTOXICITY

An acute neurotoxicity screen test (81-8, MRID 43170301) and a subchronic neurotoxicity screen (82-7, MRID 43286401 were reviewed by TB-1 and found to be Core Acceptable and Core Minimum, respectively. The acute neurotoxicity study demonstrated a NOEL of 42 mg/kg and LEL of 151 mg/kg based on decreased activity and tremors. The subchronic study showed a NOEL of 213 mg/kg/d, the highest dose level tested, for specific neurotoxicity responses. The systemic NOEL and LEL were demonstrated to be 9.3 mg/kg/d and 63.3 mg/kg/d, respectively, based on decreased body weight gain. No additional series 81-8 or 82-7 studies are required at this time.

IV. OTHER TOXICOLOGICAL CONSIDERATIONS

This chemical has been determined to be a Group E Carcinogen.

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.

VI. LESS THAN LIFETIME COMMITTE REPORT

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Dermal Absorption Data (if available)

MRID: NONE

Percent Absorbed: Not available. However, Imidacloprid is not considered to present a hazard via the dermal route based on results of a 21-day dermal study (see occupational exposure discussions).

Acute Dietary Endpoint (One Day)

Studies Selected - Guideline No:

Developmental Toxicity in Rabbits (83-3b)

MRID: 422563-39

Summary (enter standard Executive Summary or equivalent):

Four groups of 16 rabbit dams were exposed to NTN 33893 Technical orally by gavage from days six through 18 post coitum at 0, 8, 24, and 72 mg/kg/d.

At 72 mg/kg/d, decreased body weight, increased resorption, increased abortion, and death were observed. These or other effects were not observed at 24 or 8 mg/kg/d. **The Maternal NOEL = 24 mg/kg/d; the LOEL = 72 mg/kg/d.**

In the conceptus, decreased body weight and increased skeletal abnormalities were observed at 72 mg/kg/d, but not at lower dose levels. **The Developmental NOEL = 24 mg/kg/d; the LOEL = 72 mg/kg/d.**

This study is classified as Core-Minimum data for developmental toxicity (83-3) and satisfies the guideline requirements for a reproductive toxicity study in rabbits.

Endpoint and Dose Level for use in risk assessment:

The endpoint for acute dietary risk assessment is the NOEL (24 mg/kg/day) from the rabbit developmental toxicity study. The LEL (72 mg/kg/day) was based upon decreased body weight, and increased resorptions, abortion and increased skeletal abnormalities.

Comments about study and/or endpoint:

None

This risk assessment is required.

Short-Term Occupational or Residential Exposure (1 to 7 days)

Studies Selected - Guideline No.: None

MRID: None

Summary (Enter Standard Executive Summary or Equivalent):

None

Endpoint and dose for use in risk assessment:

None

Comments about study and/or endpoints:

None

Risk assessment is not required. No effects were observed at the highest dose level tested (0.191 mg/L) in a Core-Minimum 28-day inhalation study (MRID #422730-01), and no systemic toxicity was observed at dose levels up to 1000 mg/kg/day in a 21-day dermal toxicity study (MRID #422563-29). **NTN 33893 is not an inhalation or dermal toxicant.** In addition, there is indication that there is very little absorption when systemic toxicity is compared between the oral and dermal routes.

Intermediate Term Occupational or Residential Exposure

Studies Selected - Guideline No.: None

MRID: None

Summary (Enter Standard Executive Summary or Equivalent):

None

Endpoint and dose for use in risk assessment:

None

Comments about study and/or endpoints:

None

Risk assessment is not required. No effects were observed at the highest dose level tested (0.191 mg/L) in a Core-Minimum 28-day inhalation study (MRID #422730-01), and no systemic toxicity was observed at dose levels up to 1000 mg/kg/day in a 21-day dermal toxicity study (MRID #422563-29). **NTN 33893 is not an inhalation or dermal toxicant.** In addition, there is indication that there is very little absorption when systemic toxicity is compared between the oral and dermal routes.

Cancer Classification and Basis

NTN 33893 has been classified by the HED Peer Review/Cancer Committee (cf. Nov 10, 1993 Report) as a Group E carcinogen based on the following evidence:

> No apparent treatment-related oncogenic effect at any dose in a chronic/onco feeding study in the rat (MRID #422563-31, 422563-32) or in a carcinogenicity study in the mouse (MRID #422563-35, 422563-36).

Classification: **Core Minimum**

Q_1 * = N/A

RfD and Basis: Set at 0.057 mg/kg/d by the RfD/Peer Review Committee (cf. Nov 10, 1993 Report), based upon a NOEL of 5.7 mg/kg/d in a chronic toxicity study in rats. The LEL was 16.9 mg/kg/d based on increased thyroid lesions in males.

NOEL for Critical Study: 5.7 mg/kg/d

Study Type - Guideline No: Chronic/onco feeding study in the rat (83-5)

MRID: 422563-31, 422563-32
