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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR # 0051292

DATE: October 31, 2002

MEMORANDUM

SUBJECT: **Imidacloprid** - Report of the Hazard Identification Assessment Review Committee.

FROM: David Nixon, Toxicologist
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Jennifer Tyler, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 129099

On October 8, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for **IMIDACLOPRID** with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to **IMIDACLOPRID** was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the February 2002 OPP 10X guidance document. The conclusions drawn at this meeting are presented in this report.

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Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Jonathan Chen, Steve Knizner, Elizabeth Doyle, John Liccione, Susan Makris, Elizabeth Mendez, David Nixon, Jess Rowland, Brenda Tarplee

Member(s) in absentia: Pamela Hurley

Data evaluation prepared by: David Nixon, RAB 1

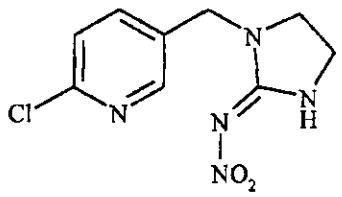
Also in attendance were: William Sette

Data Evaluation / Report Presentation

David Nixon
Toxicologist

INTRODUCTION

On October 8, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for imidacloprid with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to imidacloprid was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the February 2002 OPP 10X guidance document. This is a re-evaluation of the toxicology database since the initial evaluation by the HIARC on September 11, 1997.



Imidacloprid

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for imidacloprid is complete.

2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to imidacloprid. The following studies are available:

- Two developmental toxicity studies - Rat and Rabbit
- Two-generation reproduction toxicity study - Rat
- Acute neurotoxicity study - Rat
- Subchronic neurotoxicity study - Rat
- Developmental neurotoxicity study - Rat

Acute Neurotoxicity

In an acute neurotoxicity study (MRIDs 43170310, 43285801), groups of Sprague-Dawley rats (18/sex/dose) were given a single oral administration of imidacloprid (97.6% a.i.) in 0.5% methylcellulose with 0.4% Tween 80 in deionized water at 0, 42, 151 or 307 mg/kg. Parameters evaluated included: clinical pathology (6/sex/dose); Functional Observation Battery (FOB) measurements (12/sex/dose); and neuropathology (6/sex/dose). FOB measurements were made approximately 90 minutes post-dosing, and on days 7 and 14. Motor activity measurements were made at approximately 2.5 hours post-dosing.

At 307 mg/kg, 4/18 males and 10/18 females died and both sexes of rats at this dose exhibited decreased number of rears, grip strength (forelimb and hindlimb) and response to stimuli (auditory, touch, or tail pinch) as well as increased gait abnormalities and righting reflex impairments and body temperatures. These symptoms regressed by day 5. At 151 mg/kg, cage side FOB assessments revealed tremors in one male and one female and red nasal staining in one male. On the day of dosing, a dose-related decrease in total session motor activity was observed in males at 151 mg/kg (25% decrease) and 307 mg/kg (73% decrease) and in females at all dose levels with the decreases (25, 48 and 81%, respectively at 42, 151 and 307 mg/kg) reaching statistical significance ($p<0.05$) at 151 and 307 mg/kg dose levels. Decreases in motor activity was seen at all time intervals. Total session locomotor activity was also decreased to about the same percentage difference but statistical significance were not reported. On days 7 and 14, decreases (not statistically significant) were still observed in motor and locomotor activity in surviving high-dose males. **The LOAEL was 42 mg/kg based upon the decrease in motor and locomotor activities observed in females; a NOAEL was not established.**

This study is classified as **acceptable/guideline** and satisfies the requirements for an acute neurotoxicity screening battery in rats (§81-8; 870.6200a).

Subchronic Neurotoxicity

Four groups of 12/sex Fischer strain rats were dosed as control, 150, 1000 or 3000 ppm imidacloprid (technical 98% purity, corresponding to 9.3, 63.3 or 196 in males and 10.5, 69.3 or 213 in females mg/kg/day imidacloprid) for 13 weeks in a subchronic neurotoxicity screen study. Six additional rats/ sex/dose were also assessed for clinical chemistry and hematology (MRID No.: 43286401).

The LOAEL for neurotoxicity is > 3000 ppm (196/213 mg/kg/day, M/F).

Systemic effects include body weight gain decrease over the first four weeks for the 1000 (22% males, 18% females) and 3000 (50% males, 25% females) ppm dose groups and decreased terminal body weight for both sexes with an associated decrease in forelimb grip strength especially in males. The LOAEL for systemic effects is 1000 ppm (63.3/69.3 mg/kg/day, M/F) based on decreased body weight gain and the NOAEL is 150 ppm (9.3/10.5 mg/kg/day, M/F).

Classification: MINIMUM. The study did not demonstrate a LOAEL for neurotoxicity. The study satisfies the guideline requirement for a series 82-7 subchronic neurotoxicity screen study in rodents.

Developmental Neurotoxicity

In a developmental neurotoxicity study (MRID 45537501), Imidacloprid (98.2-98.4% a.i., batch # 803-0273) was administered to 30 parent female Wistar rats/group in the diet at concentrations of 0, 100, 250 or 750 ppm from gestation day 0 through postnatal day (PND) 21. The average daily intake of Imidacloprid was 0, 8.0-8.3, 19.4-19.7, and 54.7-58.4 mg/kg/day during gestation and 0, 12.8-19.5, 30.0-45.4, and 80.4-155.0 mg/kg/day during lactation, for the 0, 100, 250, and 750 ppm groups, respectively. A Functional Operational Battery (FOB) was performed on all dams on gestation days 6, 13, and 20 and on 10 dams/dose on lactation days 4, 11, and 21. On postnatal day 4, litters were culled to yield four males and four females (as closely as possible). Offspring, representing at least 20 litters/dose, were allocated for detailed clinical observations

(abbreviated FOB), assessment of motor activity, assessment of auditory startle response habituation, assessment of learning and memory, and ophthalmology. Neural tissues were also collected from selected offspring (10/sex/dose representing 20 litters) on PND 11 and at study termination (75 days of age). Pup physical development was assessed by bodyweight, day of surface righting, auditory startle, eye opening, pupillary constriction, vaginal patency in females and balanopreputial separation in males.

Treatment-related effects for maternal animals were limited to a 9% decrease (not significant) in food consumption for dams in the high dose group compared to controls during the third week of gestation and 14% decrease ($p<0.05$) for high-dose animals during week 1 of lactation. There was also a slight decrease in body weight gain (67% of controls) during lactation day 0-7. **The maternal LOAEL for Imidacloprid in rats is 55-58 mg/kg/day in the diet based on decreased food consumption and decreased body weight gain during lactation. The maternal NOAEL is 20 mg/kg/day in the diet.**

Treatment-related effects for offspring were limited to the high dose group. Body weights of high-dose males and females were significantly ($p<0.05$) decreased 9-13% prior to weaning, and from 3-11% after weaning, with recovery: in females to control levels by PND 50; and in males to a 4% difference that persisted to study termination. Body weight gains were also decreased 12-23% during lactation, with recovery by PND 17. Overall motor activity was decreased (not statistically significantly) on PND 17 in high-dose males (38%) and females (31%) and in PND 21 females (37%). High dose females at study termination had a statistically significant ($p<0.03$; t test) decrease in thickness of the caudate/putamen in comparison to controls (3.7504 vs 3.6774 mm (-2%).

The offspring LOAEL for Imidacloprid in rats is 55-58 mg/kg/day in the diet, based on decreased body weight and body weight gain, decreased motor activity, and decreased caudate/putamen width in females. The offspring NOAEL is 20 mg/kg/day.

This study is classified acceptable/ non-guideline and does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft). The study may be upgradable upon submission of (1) complete analytical data; (2) morphometric measurements for caudate/putamen for females at intermediate dose levels; and (3) additional positive control data, as described below.

No evidence of neurotoxicity was noted in any other oral toxicity studies submitted.

3. Developmental Toxicity Study Conclusions

Rat

In a developmental toxicity study (MRID 42256338) NTN 33893 Technical (Imidacloprid; 94.2% a.i., batch# PT. 17001/87) was administered to 25 mated female HSD(SD) rats/dose by gavage at dose levels of 0, 10, 30, or 100 mg/kg bw/day from gestation days (GD) 6 through 15, inclusive. On GD 21, dams were sacrificed and subjected to cesarean section, and all fetuses were weighed, sexed, and examined externally. Approximately one-half of the fetuses were examined for visceral alterations, and the remaining one-half of the fetuses were examined for skeletal alterations.

There were no deaths or treatment-related clinical signs. At the 10 mg/kg bw/day treatment level, body weight gain was transiently decreased during GD 6-11 (81% of controls; n.s), then increased during GD 11-16 and 16-21 (8 and 10%, respectively; n.s.). At the 30 mg/kg bw/day treatment level, body weight gains were decreased for the GD 6-11 and 6-16 intervals (76 and 89% of controls, respectively; n.s.). At the 100 mg/kg bw/day treatment level, body weight gains were decreased throughout dosing and for the post-dosing interval as well (57 and 87% of controls, respectively; n.s.). The mean corrected (for gravid uterine weight) GD 6-21 body weight gains of the mid- and high-dose groups were also decreased (71 and 53% of controls, respectively; $p<0.01$ for the high-dose group only). Food consumption (g/animal/day) by the high-dose group was decreased throughout treatment and increased during the post-dosing interval (27.2% less than controls, 20.5% greater than controls, respectively), while food consumption by the low- and mid-dose groups were decreased only during GD 6-11 (9.5 and 10.0% less than controls, respectively; $p<0.01$); however, the decreases noted for the low- and mid-dose groups were not considered treatment-related because similar decreases were not present when food consumption was evaluated on a g/kg bw/day basis. There were no treatment-related effects on intrauterine parameters. **The maternal toxicity LOAEL for imidacloprid in HSD(SD) rats is 30 mg/kg bw/day, based on decreased body weight gain and decreased corrected body weight gain. The maternal toxicity NOAEL is 10 mg/kg/day.**

There were no treatment-related effects on fetal deaths or resorptions, numbers of viable fetuses per litter, or fetal weights, sex ratios, or external or visceral structural alterations. Wavy ribs were observed in 2/158 (1/25), 1/155 (1/25), 0/153 (0/24), and 7/149 (4/25) fetuses (litters) of the control, low-, mid-, and high-dose groups, respectively, and were considered treatment-related. **The developmental toxicity LOAEL for imidacloprid in HSD(SD) rats is 100 mg/kg bw/day, based on a slight increase in the incidence of wavy ribs. The developmental toxicity NOAEL is 30 mg/kg bw/day.**

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study in the rat (OPPTS 870.3700a; OECD 414).

Rabbit

In a developmental toxicity study (MRID 42256339) NTN 33893 Technical (Imidacloprid; 95.3% a.i., batch # PT. 17001/87) was administered to 16 mated female Chinchilla (Chbb: CH Hybrids, SPF quality) rabbits/dose in distilled water with 0.5% Cremophor EL (BASF) by gavage at dose levels of 0, 8, 24, or 72 mg/kg bw/day from gestation days (GD) 6 through 18. On GD 28, does were sacrificed and necropsied. All fetuses were weighed, sexed, and examined for external, visceral, and skeletal alterations.

At 72 mg/kg bw/day, two pregnant females died, one each on GDs 18 and 19, and one of these females had white mucoid feces for three days prior to dying. Another high-dose female aborted on GD 26, and two additional high-dose females had total litter resorptions. Mean absolute body weights of the high-dose animals were decreased during GD 17-21 (10-11% less than controls; $p<0.01$). Decreased body weight gains were reportedly noted during treatment at 24 and 72 mg/kg bw/day (up to 9.2% less than controls for the high-dose group; n.s.). Mean food consumption of the high-dose animals was decreased during treatment (34-58% of controls;

p<0.01), then increased during the post-dosing interval (112-183% of controls). Mean food consumption of the mid-dose animals was transiently decreased during GD 6-11 only (84% of controls; p<0.05); however, the original reviewer did not consider this difference treatment-related because it was transient and because there were no other treatment-related effects noted at this dose level. **The maternal toxicity LOAEL for imidacloprid in Chinchilla (Chbb: CH Hybrids, SPF quality) rabbits is 72 mg/kg bw/day, based on maternal deaths and decreased maternal absolute body weights, body weight gains, and food consumption. The maternal toxicity NOAEL is 24 mg/kg bw/day.**

One high-dose female aborted on GD 26, and two additional high-dose females had total litter resorptions. Postimplantation loss of the high-dose females was increased compared to controls both with the data from the females with total litter resorptions included (32.5% vs. 4.2% for controls; p<0.01) and without it (10.8% greater than controls; p<0.05), and this increase was due to increased late resorptions (6.5% vs. 0.7% of implantations for controls, data from dams with total litter resorptions included; p<0.01). There was a corresponding decrease in this group's number of live fetuses per litter (31% less than controls; n.s. due to a high S.D.). At 72 mg/kg bw/day, mean litter weights and mean fetal weights were both decreased (9.7 and 9.9% less than controls, respectively; p<0.05 and p<0.01, respectively), and these differences were primarily due to decreased weights of female fetuses rather than males (12 and 8% less than controls, respectively; p<0.01, p<0.05, respectively). Several skeletal malformations not present in the 136 fetuses (16 litters) of the control group were noted in a total of 5/83 fetuses (3/11 litters) of the 72 mg/kg bw/day group, and included the following: fused sternebrae in 2 (2), asymmetric sternebrae in 3 (2), missing sternebrae in 2 (1), abnormally ossified sternebrae in 4 (2), and shortened tail in 1fetus (1 litter). These skeletal alterations were considered treatment-related by the original reviewer. **The developmental toxicity LOAEL for imidacloprid in Chinchilla (Chbb: CH Hybrids, SPF quality) rabbits is 72 mg/kg bw/day, based on abortion, total litter resorptions, increased postimplantation loss due to increased late resorptions, decreased fetal weights (more pronounced in female fetuses), and very low incidences of skeletal alterations, including fused, asymmetric, missing, and/or abnormally ossified sternebrae, and/or shortened tail. The developmental NOAEL is 24 mg/kg bw/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study in the rabbit (OPPTS 870.3700b; OECD 414).

4. <u>Reproduction Toxicity Study Conclusions</u>

In a 2-generation reproduction study (MRID 42256340) NTN 33893 Technical (Imidacloprid; 95.3% a.i., batch# Mischpartie 180587) was administered to 26 or 30 Wistar/HAN rats/sex/dose in the diet at concentrations of 0, 100, 250, or 700 ppm. Two litters were produced by each generation. Premating test compound intakes were 0, 8.1, 20.1, or 56.7 mg/kg bw/day, respectively, for F_0 males, 0, 8.8, 22.1, or 62.8 mg/kg bw/day, respectively, for F_0 females, 0, 6.4, 16.5, or 47.3 mg/kg bw/day, respectively, for F_1 males, and 0, 7.2, 18.9, or 52.3 mg/kg bw/day, respectively, for F_1 females. Parental animals were administered test or control diet for 84 or 105 days prior to the first mating, throughout mating, gestation, and lactation, and until necropsy. In addition, blood was collected from 10/26 F_1 animals/sex/dose for hematological and clinical

chemistry evaluations, and liver samples were taken from these same animals to measure triglycerides, cytochrome P-450, and O- and N-demethylase activity.

There were no treatment-related deaths or clinical signs. At the 700 ppm treatment level, F_0 males and females had decreased body weight gains during premating (10 and 12% less than controls, respectively), and F_1 females had decreased body weight gains during premating and their first and second gestations (10, 9, and 12% less than controls, respectively). High-dose females of both generations had increased weight gains during both lactations (19, 42, 38, and 66% greater than controls for the F_{1A}, F_{1B}, F_{2A}, and F_{2B} litters, respectively). Decreased food consumption was also noted at the highest dose level and reportedly followed a similar pattern to body weight gains; however, food consumption data were not included in the DER. There were no treatment-related effects on organ weights, or gross and microscopic pathology of either sex of either generation. There were no treatment-related effects on hematology or clinical chemistry parameters of the F_1 animals. At the 700 ppm treatment level, cytochrome p450 content was increased in males, and demethylase activity was increased in both sexes; however, these changes are considered an adaptive response to a xenobiotic agent rather than a toxicological response. **The parental systemic toxicity LOAEL for imidacloprid in Wistar/Han rats is 700 ppm (47.3-56.7 mg/kg bw/day in males, 52.3-62.8 mg/kg bw/day in females), based on decreased premating weight gain by F_0 males and females and F_1 females and decreased gestational weight gain by F_1 females. The parental systemic NOAEL is 250 ppm (16.5-20.1 mg/kg bw/day in males, 18.9-22.1 mg/kg bw/day, in females).**

At the 700 ppm treatment level, the pup weights of both litters from both generations were significantly decreased ($p<0.05$) at one or more intervals during lactation: F_{1A} pups on lactations days (LD) 7 and 21 (91 and 87% of controls, respectively); F_{1B} pups on LD 21 (90% of controls); F_{2A} pups on LD 21 (91% of controls); and F_{2B} pups on LD 0, 7, and 21 (90, 91, and 91% of controls, respectively). Pup survival, mean number of pups born, and sex ratios at birth were similar between the treated and control groups of both generations. There were no abnormal clinical signs, external abnormalities, or behavioral abnormalities noted in any litter of either generation. **The offspring LOAEL is 700 ppm, based on decreased pup body weights in both litters of both generations. The offspring NOAEL is 250 ppm.**

There were no treatment-related effects on mating, gestation, or fertility indices or mean gestation lengths. **The reproductive LOAEL is undetermined, and the reproductive NOAEL is greater than or equal to 700 ppm.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a 2-generation reproductive study in the rat (OPPTS 870.3800; OECD 416).

5. <u>Additional Information from Literature Sources</u>

There was no additional relevant information from the published literature.

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is low concern for pre- and/or postnatal toxicity resulting from exposure to imidacloprid.

A. Determination of Susceptibility

There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure in developmental studies. There is no quantitative or qualitative evidence of increased susceptibility of rat offspring in the multi-generation reproduction study.

There is evidence of an increased qualitative susceptibility in the rat developmental neurotoxicity study. At the highest dose tested (750 ppm), maternal effects consisted largely of slight decreases in food consumption and body weight gain during early lactation, while pup effects included decreased body weight, decreased motor activity, decreased caudate/putamen width, females only (PNDs 11 and adult), and slight changes in performance in the water maze, males only, at the same dose.

B. Degree of Concern Analysis and Residual Uncertainties

Since there is no evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure, there is no concern and no residual uncertainties for pre-natal toxicity. There is also no concern and no residual uncertainties for pre-/post-natal toxicity in the rat multi-generation reproduction study.

There is evidence of increased qualitative susceptibility in the rat developmental neurotoxicity study, but the concern is low since: **1)** the effects in pups are well-characterized with a clear NOAEL; **2)** the pup effects occur in the presence of maternal toxicity with the same NOAEL for effects in pups and dams; and, **3)** the doses and endpoints selected for regulatory purposes are protective of the pup effects noted at higher doses in the developmental neurotoxicity study. Therefore, there are no residual uncertainties for pre-/post-natal toxicity in this study.

C. Special FQPA Safety Factor(s):

The Special FQPA Safety Factor can be reduced to 1x since there are no residual uncertainties for pre-/post-natal toxicity.

HIARC recommended the Special FQPA Safety Factor **assuming** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. **Recommendation for a Developmental Neurotoxicity Study**

A developmental neurotoxicity study in the rat has been submitted, reviewed and classified as acceptable/nonguideline.

II. HAZARD IDENTIFICATION

1. **Acute Reference Dose (aRfD)** - General Population

Study Selected: Acute Neurotoxicity Study - Rat OPPTS 870.6200a

MRID No.: 43170301

Executive Summary: In an acute neurotoxicity study (MRIDs 43170310, 43285801), groups of Sprague-Dawley rats (18/sex/dose) were given a single oral administration of imidacloprid (97.6% a.i.) in 0.5% methylcellulose with 0.4% Tween 80 in deionized water at 0, 42, 151 or 307 mg/kg. Parameters evaluated included: clinical pathology (6/sex/dose); Functional Observation Battery (FOB) measurements (12/sex/dose); and neuropathology (6/sex/dose). FOB measurements were made approximately 90 minutes post-dosing, and on days 7 and 14. Motor activity measurements were made at approximately 2.5 hours post-dosing.

At 307 mg/kg, 4/18 males and 10/18 females died and both sexes of rats at this dose exhibited decreased number of rears, grip strength (forelimb and hindlimb) and response to stimuli (auditory, touch, or tail pinch) as well as increased gait abnormalities and righting reflex impairments and body temperatures. These symptoms regressed by day 5. At 151 mg/kg, cage side FOB assessments revealed tremors in one male and one female and red nasal staining in one male. On the day of dosing, a dose-related decrease in total session motor activity was observed in males at 151 mg/kg (25% decrease) and 307 mg/kg (73% decrease) and in females at all dose levels with the decreases (25, 48 and 81%, respectively at 42, 151 and 307 mg/kg) reaching statistical significance ($p<0.05$) at 151 and 307 mg/kg dose levels. Decreases in motor activity was seen at all time intervals. Total session locomotor activity was also decreased to about the same percentage difference but statistical significance were not reported. On days 7 and 14, decreases (not statistically significant) were still observed in motor and locomotor activity in surviving high-dose males. **The LOAEL was 42 mg/kg based upon the decrease in motor and locomotor activities observed in females; a NOAEL was not established.**

This study is classified as **acceptable/guideline** and satisfies the requirements for an acute neurotoxicity screening battery in rats (§81-8; 870.6200a).

Dose and Endpoint for Establishing aRfD: 42 mg/kg (LOAEL), based upon the decreased in motor and locomotor activities observed in females.

Uncertainty Factor (UF): 300

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate, since these effects were seen following a single dose, and is applicable to the general population, including infants and children and is also protective of developmental effects which may occur in the subpopulation females 13-50. The maternal and developmental effects in the rabbit study, though severe, occurred at higher doses, and this endpoint is adequately protective of those effects. A 3X uncertainty factor for the use of a LOAEL was judged to be adequate (as opposed to a 10X) because: **1)** the LOAEL (42 m/k/d) is comparable to the LOAELs seen in adults in the developmental rat study (30 m/k/d) and the two-generation reproduction study [47/52 m/k/d (male/female)] and in the offspring in the DNT (55 m/k/d); **2)** the extrapolated NOAEL of 14 m/k/d (42/3 = 14) is comparable to the NOAEL of 20 m/k/d established in the offspring in the DNT; and, **3)** the neurotoxic effects in this study showed a good dose response which resulted in minimal effects on motor activity and locomotor activity at the LOAEL.

$$\textbf{Acute RfD (gen. pop'n)} = \frac{42\ \text{(LOAEL) mg/kg}}{300} = \mathbf{0.14\ mg/kg}$$

2. Chronic Reference Dose (cRfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat OPPTS 870.4300

MRID No.: 42256331

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID 42256331), NTN 33893 Technical (Imidacloprid; 94.3-95.3% a.i., batch #180587) was administered to 50 Bor WISW (SPF Cpb) rats/sex/dose in feed at concentrations of 0, 100, 300, or 900 ppm (equivalent to 0, 5.7, 16.9, or 51.3 and 0, 7.6, 24.9, or 73.0 mg/kg bw/day for males and females, respectively) for 24 months. In a supplementary combined chronic/carcinogenicity study (MRID 42256332), NTN 33893 Technical (Imidacloprid; 94.3-95.3% a.i., batch #180587) was administered to 50 Bor WISW (SPF Cpb) rats/sex/dose in feed at concentrations of 0 or 1800 ppm (equivalent to 0 or 102.6 and 0 or 143.7 mg/kg bw/day for males and females, respectively) for 24 months. Both studies included additional groups of ten rats/sex/dose for interim sacrifice at 12 months.

There were no treatment-related effects on mortality, clinical signs, food and water consumption, hematology, clinical chemistry, ophthalmology, or gross pathology. Mean absolute body weights of both sexes were decreased throughout the study at the 1800 ppm dose level (males: up to 12%; females: up to 11% less than controls; $p<0.01$ for both sexes). At 900 ppm, body weights were decreased by up to 5% in males and 8% in females, and cumulative body weight gains were decreased in females by 11.2% and 16.2% at 900 and 1800 ppm, respectively, compared with that of controls.

The significant decreases in absolute liver weights at 1800 ppm are not considered adverse since the decreases in relative liver weights were small and no corroborating gross or histopathologic lesions were noted. The small statistically significant changes in absolute and relative weights of

other organs in male and female rats at 12 or 24 months at 900 and 1800 ppm were not accompanied by either gross or microscopic changes and are not considered adverse. In the interim sacrifice groups, increased incidence of a microscopic thyroid lesion described as mineralized particles in the colloid of isolated follicles were noted in males at 900 and 1800 ppm [10/10 males ($p<0.05$) at both doses vs. 3/10 or 5/10 males in the two control groups]. In the main study groups, the incidence of the same lesion was 12/50, 31/50, 44/50, 46/50 at 100, 300, 900, and 1800 ppm, respectively, in males compared with 2/50 and 12/50 for the two control groups. The incidence of mineralized particles in thyroid colloid in females was 27/50 and 38/50 at 900 and 1800 ppm, respectively, compared with 11/50 and 3/50 for controls ($p<0.01$). In addition, at 1800 ppm colloid aggregation was decreased 100% ($p<0.05$) in males at 12 months and decreased 51% ($p<0.01$) in males and 68% ($p<0.01$) in females at 24 months. At 1800 ppm, a marked decrease occurred in the incidence of nephropathy in both males and females (65 and 92% less than controls, respectively; $p<0.01$), which corresponded to 46-76% ($p<0.01$) decreased urine protein in males and up to a 85% decrease in females. In females, a 44% ($p<0.05$) increase in retinal atrophy and a 65% increase in porphyrin accumulation in the Harderian glands were noted at 1800 ppm.

The LOAEL for NTN 33893 in rats is 300 ppm (16.9 mg/kg bw/day for males, 24.9 mg/kg bw/day for females), based on thyroid toxicity (increased incidence of mineralized particles in thyroid colloid) in males. The NOAEL is 100 ppm (5.7 mg/kg bw/day for males, 7.6 mg/kg bw/day for females).

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on thyroid toxicity and decreased body weights in both sexes.

When considered together, these chronic toxicity/carcinogenicity studies in the rat are classified **Acceptable/Guideline** and satisfy the guideline requirements for a chronic toxicity/carcinogenicity study in the rat [OPPTS 870.4300; OECD 453].

Dose and Endpoint for Establishing cRfD: 5.7 mg/kg/day (NOAEL), based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day.

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor: This study and endpoint are appropriate for the route and duration of exposure. The NOAEL is the lowest in the database for chronic effects and is protective of all populations.

$$\textbf{Chronic RfD} = \frac{5.7\ \text{(NOAEL) mg/kg/day}}{100} = \mathbf{0.057\ mg/kg}$$

3. Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: Developmental Toxicity Study - Rat OPPTS 670.3700a

MRID No.: 42256338

Executive Summary: In a developmental toxicity study (MRID 42256338) NTN 33893 Technical (Imidacloprid; 94.2% a.i., batch# PT. 17001/87) was administered to 25 mated female HSD(SD) rats/dose by gavage at dose levels of 0, 10, 30, or 100 mg/kg bw/day from gestation days (GD) 6 through 15, inclusive. On GD 21, dams were sacrificed and subjected to cesarean section, and all fetuses were weighed, sexed, and examined externally. Approximately one-half of the fetuses were examined for visceral alterations, and the remaining one-half of the fetuses were examined for skeletal alterations.

There were no deaths or treatment-related clinical signs. At the 10 mg/kg bw/day treatment level, body weight gain was transiently decreased during GD 6-11 (81% of controls; n.s), then increased during GD 11-16 and 16-21 (8 and 10%, respectively; n.s.). At the 30 mg/kg bw/day treatment level, body weight gains were decreased for the GD 6-11 and 6-16 intervals (76 and 89% of controls, respectively; n.s.). At the 100 mg/kg bw/day treatment level, body weight gains were decreased throughout dosing and for the post-dosing interval as well (57 and 87% of controls, respectively; n.s.). The mean corrected (for gravid uterine weight) GD 6-21 body weight gains of the mid- and high-dose groups were also decreased (71 and 53% of controls, respectively; $p<0.01$ for the high-dose group only). Food consumption (g/animal/day) by the high-dose group was decreased throughout treatment and increased during the post-dosing interval (27.2% less than controls, 20.5% greater than controls, respectively), while food consumption by the low- and mid-dose groups were decreased only during GD 6-11 (9.5 and 10.0% less than controls, respectively; $p<0.01$); however, the decreases noted for the low- and mid-dose groups were not considered treatment-related because similar decreases were not present when food consumption was evaluated on a g/kg bw/day basis. There were no treatment-related effects on intrauterine parameters. **The maternal toxicity LOAEL for imidacloprid in HSD(SD) rats is 30 mg/kg bw/day, based on decreased body weight gain and decreased corrected body weight gain. The maternal toxicity NOAEL is 10 mg/kg/day.**

There were no treatment-related effects on fetal deaths or resorptions, numbers of viable fetuses per litter, or fetal weights, sex ratios, or external or visceral structural alterations. Wavy ribs were observed in 2/158 (1/25), 1/155 (1/25), 0/153 (0/24), and 7/149 (4/25) fetuses (litters) of the control, low-, mid-, and high-dose groups, respectively, and were considered treatment-related. **The developmental toxicity LOAEL for imidacloprid in HSD(SD) rats is 100 mg/kg bw/day, based on a slight increase in the incidence of wavy ribs. The developmental toxicity NOAEL is 30 mg/kg bw/day.**

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirements for a developmental toxicity study in the rat (OPPTS 870.3700a; OECD 414).

Dose and Endpoint for Risk Assessment: 10 mg/kg/day (Maternal NOAEL), based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day.

Comments about Study/Endpoint: The endpoint of concern is appropriate for the population of concern (infants and children) and the duration of exposure.

4. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: Subchronic Neurotoxicity Study - Rat OPPTS 870.6200b

MRID No.: 43286401
Executive Summary: Four groups of 12/sex Fischer strain rats were dosed as control, 150, 1000 or 3000 ppm imidacloprid (technical 98% purity, corresponding to 9.3, 63.3 or 196 in males and 10.5, 69.3 or 213 in females mg/kg/day imidacloprid) for 13 weeks in a subchronic neurotoxicity screen study. 6 additional rats/ sex/dose were also assessed for clinical chemistry and hematology (MRID No.: 43286401).

The LOAEL for neurotoxicity is > 3000 ppm (196/213 mg/kg/day, M/F).

Systemic effects include body weight gain decrease over the first four weeks for the 1000 (22% males, 18% females) and 3000 (50% males, 25% females) ppm dose groups and decreased terminal body weight for both sexes with an associated decrease in forelimb grip strength especially in males. The LOAEL for systemic effects is 1000 ppm (63.3/69.3 mg/kg/day, M/F) based on decreased body weight gain and the NOAEL is 150 ppm (9.3/10.5 mg/kg/day, M/F).

Classification: MINIMUM. The study did not demonstrate a LOAEL for neurotoxicity. The study satisfies the guideline requirement for a series 82-7 subchronic neurotoxicity screen study in rodents.

Dose and Endpoint for Risk Assessment: 9.3 mg/kg/day (NOAEL), based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day.

Comments about Study/Endpoint: The endpoint of concern is appropriate for the population of concern (infants and children) and the duration of exposure. Also, this study did evaluate neurotoxicity parameters and no neurotoxicity was noted in the presence of systemic toxicity (decreased body weight gain) that was observed in other oral studies of similar duration.

5. Dermal Absorption

Dermal Absorption Factor: No dermal absorption study was submitted. Using a ratio of the maternal LOAEL from the developmental rabbit study and the NOAEL from the rabbit dermal toxicity study, one can derive a dermal absorption factor of 7.2% as an upper-bound estimate.

$$\frac{\text{Dev. Rabbit LOAEL}}{\text{Dermal Tox. NOAEL}} = \frac{72 \text{ mg/kg/day}}{1000 \text{ mg/kg/day}} = 7.2\%$$

6. Dermal Exposure: Short-Term (1- 30 days) Exposure

Study Selected: Developmental Toxicity Study - Rat OPPTS 670.3700a

MRID No.: 42256338

Executive Summary: See Short-term Incidental Oral

Dose and Endpoint for Risk Assessment: 10 mg/kg/day (Maternal NOAEL), based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day.

Comments about Study/Endpoint: A 21-day dermal study in rabbits was submitted with no systemic effects noted up to 1000 mg/kg/day; however, the dermal study did not evaluate FOB and other neurological parameters. Since there are neurotoxic effects noted in both adult and offspring rats via the oral route that were not evaluated in the dermal study, the HIARC chose an oral endpoint for this risk assessment to adequately protect against neurotoxicity via dermal exposure. The chosen endpoint is from a study of the appropriate duration of exposure. A dermal absorption factor of 7.2% should be applied for route-to-route extrapolation.

7. Dermal Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: Subchronic Neurotoxicity Study - Rat OPPTS 870.6200b

MRID No.: 43286401

Executive Summary: See Intermediate-term Incidental Oral

Dose and Endpoint for Risk Assessment: 9.3 mg/kg/day (NOAEL), based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day.

Comments about Study/Endpoint: A 21-day dermal study in rabbits was submitted with no systemic effects noted up to 1000 mg/kg/day; however, the dermal study did not evaluate FOB and other neurological parameters. Since there are neurotoxic effects noted in both adult and offspring rats via the oral route that were not evaluated in the dermal study, the HIARC chose an oral endpoint for this risk assessment to adequately protect against neurotoxicity via dermal exposure. The chosen endpoint is from a study of the appropriate duration of exposure. A dermal absorption factor of 7.2% should be applied for route-to-route extrapolation.

8. Dermal Exposure Long-Term (> 6 Months)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat OPPTS 870.4300

MRID No.: 42256331

Executive Summary: See Chronic RfD

Dose and Endpoint for Risk Assessment: 5.7 mg/kg/day (NOAEL), based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day.

Comments about Study/Endpoint: No long-term dermal study was submitted. The chosen endpoint is from a study of the appropriate duration of exposure. A dermal absorption factor of 7.2% should be applied for route-to-route extrapolation.

9. Inhalation Exposure: Short -Term (1- 30 days)

Study Selected: Developmental Toxicity Study - Rat OPPTS 670.3700a

MRID No.: 42256338

Executive Summary: See Short-term Incidental Oral

Dose and Endpoint for Risk Assessment: 10 mg/kg/day (Maternal NOAEL), based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day.

Comments about Study/Endpoint: This dose and endpoint are appropriate for the duration of exposure. The submitted 28-day inhalation study (MRID 42273001) did not test up to the limit dose and no systemic toxicity was observed up to the highest dose tested 0.191 mg/L. Also FOB and other neurological parameters were not evaluated. An inhalation absorption factor of 100% should be applied.

10. Inhalation Exposure: Intermediate-Term (1- 6 Months)

Study Selected: Subchronic Neurotoxicity Study - Rat OPPTS 870.6200b

MRID No.: 43286401

Executive Summary: See Intermediate-term Incidental Oral

Dose and Endpoint for Risk Assessment: 9.3 mg/kg/day (NOAEL), based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day.

Comments about Study/Endpoint: This dose and endpoint are appropriate for the duration of exposure. The submitted 28-day inhalation study (MRID 42273001) did not test up to the limit dose and no systemic toxicity was observed up to the highest dose tested 0.191 mg/L. Also FOB and other neurological parameters were not evaluated. An inhalation absorption factor of 100% should be applied.

11. Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: Combined Chronic Toxicity/Carcinogenicity - Rat OPPTS 870.4300

MRID No.: 42256331

Executive Summary: See Chronic RfD

Dose and Endpoint for Risk Assessment: 5.7 mg/kg/day (NOAEL), based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day.

Comments about Study/Endpoint: No long-term inhalation study was submitted. The chosen endpoint is of the appropriate duration of exposure. An inhalation absorption factor of 100% should be applied.

12. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	100	100	100
Dermal	100	100	100
Inhalation	100	100	100

The MOEs for dermal and inhalation exposures may be combined for occupational exposure risk assessment because oral equivalent doses were used for these routes of exposure.

13. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows:

For short- and intermediate-exposure, oral and dermal and inhalation endpoints can be aggregated because of the use of oral equivalents and a common endpoint (decreased body weight gain).

For long-term exposure, oral and dermal and inhalation endpoints can be aggregated because of the use of oral equivalents and a common endpoint (thyroid toxicity).

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 42256331

Executive Summary: See Chronic RfD

Discussion of Tumor Data At the doses tested, there was no treatment related increase in tumor incidence when compared to controls.

Adequacy of the Dose Levels Tested Dosing was considered adequate based on thyroid toxicity and decreased body weights in both sexes.

2. Carcinogenicity Study in Mice

MRID No. 42256335

Executive Summary: In a carcinogenicity study (MRID 42256335) NTN 33893 Technical (Imidacloprid; 95.0-95.3% a.i., batch #180587) was administered to 50 B6C3F1 mice/sex/dose in the diet at dose levels of 0, 100, 330, or 1000 ppm (equivalent to 0, 20, 66, or 208 mg/kg bw/day for males and 0, 30, 104, or 274 mg/kg bw/day for females) for 24 months. In a supplementary study to determine the maximum tolerated dose (MRID 42256336), the same test material was administered to 60 B6C3F1 mice/sex/dose in the diet at dose levels of 0 or 2000 ppm (equivalent to 0 or 414 mg/kg bw/day for males and 0 or 424 mg/kg bw/day for females) for 24 months. Both studies included additional groups of 10 animals/sex/dose for evaluation at a 12 month interim sacrifice.

There were no treatment-related deaths in either study. Increased incidences of "squeaking or twittering" were noted only at 2000 ppm; however, the significance of this finding is unclear. There were no treatment-related effects on hematological or clinical chemistry parameters, or gross and histopathology, including tumors. At 2000 ppm, absolute body weights were decreased in both sexes from week 13 through the end of the study (males: 74-87% of controls; females 79-89% of controls; $p<0.01$ for both). Cumulative body weight gain for the first year of the study was decreased for males and females of the 2000 ppm group and males of the 1000 ppm group (33, 45, and 85% of their respective controls). At 2000 ppm, males had decreased food consumption on most days throughout the first half of the study and on some days during the second half as well (63-90% of controls; $p<0.05$ or $p<0.01$), and females had reduced food

consumption throughout the entire study (53-69% of controls; p<0.01), with reduced food efficiency, as well (24% less than controls). There were also sporadic non-statistically significant decreases in food consumption noted at the 1000 ppm dose level: males during week 104 (87% of controls) and females during weeks 1, 52, 78, and 104 (81-90% of controls). Water intake was decreased in females from the 1000 ppm group and both males and females of the 2000 ppm group (10, 29, and 38% less than their respective controls). Treatment-related effects on organ weights were noted at 2000 ppm and included the following: decreased absolute lung, liver, spleen, and kidney weights, and increased relative brain weight in both sexes at both interim and final sacrifice; increased relative testes weight at both interim and final sacrifices; decreased absolute adrenal weight in both sexes at interim sacrifice and females only at final sacrifice; decreased relative liver weight in both sexes at interim sacrifice and females only at terminal sacrifice; decreased absolute ovary weight at final sacrifice only; increased relative spleen weight in males at interim sacrifice; and decreased relative spleen weight in females at interim and final sacrifice. The organ weight changes were not considered toxicologically important due to lack of corresponding gross or microscopic changes. **The systemic toxicity LOAEL for imidacloprid in B6C3F1 mice is 2000 ppm (equivalent to 414 mg/kg bw/day for males and 424 mg/kg bw/day for females), based on decreased body weights, food consumption, and water intake. The NOAEL is 1000 ppm (equivalent to 208 mg/kg/bw/day for males, 274 mg/kg bw/day for females).**

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate when the two studies were combined, based on decreased body weights, food consumption, and water intake.

This carcinogenicity study in the mouse is classified **Acceptable/Guideline** and satisfies the guideline requirements for a carcinogenicity study in the mouse (OPPTS 870.4200b; OECD 451).

Discussion of Tumor Data At the doses tested, there was no treatment related increase in tumor incidence when compared to controls.

Adequacy of the Dose Levels Tested Dosing was considered adequate when the two studies were combined, based on decreased body weights, food consumption, and water intake in both sexes.

3. Classification of Carcinogenic Potential

Imidacloprid has been classified as a Group E chemical, no evidence of carcinogenicity for humans, by the HED RfD/Peer Review Committee (11/10/93).

IV MUTAGENICITY

The HIARC concluded that there is no concern for mutagenicity resulting from exposure to imidacloprid. Several mutagenicity studies are available. The results from these studies indicate that imidacloprid is not mutagenic in bacterial or mammalian *in vitro* systems. Imidacloprid was clastogenic in two *in vitro* cytogenetic studies with human lymphocytes and CHO cells, but negative in other

cytogenetic assays with CHO cells. Imidacloprid was also negative in unscheduled DNA, *in vivo* mouse micronucleus, and other mutagenicity studies. Overall, the data suggest that imidacloprid is negative for mutagenicity. The acceptable studies satisfy the 1991 mutagenicity guideline requirements.

Mutagenicity Study Summaries	
Study Type and Classification	Reported Results
Gene Mutation - Ames MRID 42256341 Acceptable	Negative for inducing reverse mutation in bacteria exposed to doses up to 5000 ug/plate.
Gene Mutation - Mammalian cell MRID 42256342 Acceptable	Negative for inducing forward mutation in CHO (mammalian) cells treated up to 1222 ug/ml
Gene Mutation - Ames MRID 42256343 Acceptable	Negative up to 12,500 ug/plate
Chromosome Aberration - *in vivo* MRID 42256344 Acceptable	Negative for chromosome breakage up to 2000 ug/ml
Chromosome Aberration - *in vitro* MRID 42256345 Acceptable	Positive at 500 ug/ml - S9 and 1300 ug/ml +S9, both toxic doses
Sister Chromatid Exchange *in vivo* MRID 42256346 Acceptable	Negative up to 2000 ug/ml
Chromosome Aberration - Mouse Micronucleus Test MRID 42256347 Unacceptable	Negative, but only tested up to 80 mg/kg
Chromosome Aberration - *in vivo* MRID 42256348 Unacceptable	Negative, but only tested up to 80 mg/ml
Other genotoxicity MRID 42256349 Acceptable	Positive at 500 ug/ml -S9 and 2000 ug/ml +S9, both toxic doses
Sister Chromatid Exchange *in vitro* MRID 47256350 Acceptable	Negative at toxic doses of 400 ug/ml -S9 and 1250 ug/ml +S9
Rec-Assay - Bacterial MRID 41156351 Acceptable	Negative up to 5000 ug
DNA Repair MRID 42256352 Acceptable	Negative up to 750 ug/ml, a toxic dose
Other genotoxicity MRID 42256353 Acceptable	Negative for crossing-over in yeast up to 10,000 ug

Gene mutation - Ames MRID 42256363 Acceptable	Negative up to 5500 ug/plate
Gene mutation- Mammalian cell MRID 42256364 Acceptable	Negative up to 2000 ug/ml
Gene mutation- Mammalian cell MRID 42256365 Acceptable	Negative up to 2000 ug/ml
Chromosome Aberration - Mouse Micronucleus Test MRID 42256366 Acceptable	Negative up to 50 mg/kg IP, toxic dose
Chromosome Aberration - Mouse Micronucleus Test MRID 42256367 Unacceptable	Negative up to 80 mg/kg IP, a non-toxic dose
Chromosome Aberration - Mouse Micronucleus Test MRID 42256368 Unacceptable	Negative up to 100 mg/kg PO, a non-toxic dose
Chromosome Aberration - Mouse Micronucleus Test MRID 42256369 Acceptable	Negative up to 160 mg/kg PO, toxic dose
Chromosome Aberration - *in vitro* MRID 42256370 Acceptable	Negative up to 1000 ug/ml
Chromosome Aberration - *in vitro* MRID 42256371 Acceptable	Negative up to 1000 ug/ml
DNA Repair MRID 42256372 Acceptable	Negative up to 1333 ug/ml

V HAZARD CHARACTERIZATION

Imidacloprid is a systemic chloro-nicotinyl insecticide that disrupts the nervous system at nicotinic acetylcholine receptors. The toxicology database for imidacloprid is basically complete. The HIARC did request a 28-day inhalation study to characterize the direct effects of imidacloprid on the pulmonary system and any systemic effects via the inhalation route. Imidacloprid has low acute toxicity via the dermal and inhalation routes and moderate acute toxicity via the oral route. It is not an eye or dermal irritant and is not a dermal sensitizer.

The nervous system is the primary target organ of imidacloprid. Nervous system effects on clinical signs and FOB assessments were seen in rat acute and subchronic neurotoxicity studies. These effects included decreased motor and locomotor activities, tremors, gait abnormalities, increased righting reflex impairments and body temperature, decreased number of rears and response to stimuli and decreases in forelimb and hindlimb grip strength. Also, in the rat developmental neurotoxicity study, a decrease in the caudate/putamen width was noted in female pups. Retinal atrophy was seen in high-dose females in the rat combined chronic toxicity/carcinogenicity study. No nervous system effects were noted in the mouse carcinogenicity or the reproduction and developmental studies or in the rabbit dermal or rat inhalation studies.

The dog was less sensitive to the effects of imidacloprid. No effects were noted up to the highest dose tested. The rabbit appeared to be very sensitive as there was increased mortality in the developmental study at the highest dose tested. Increased incidence of mineralized particles in the thyroid colloid was noted in the rat combined chronic toxicity/carcinogenicity study. Body weight decrements were noted in the rat and/or mouse chronic and carcinogenicity studies, the rat subchronic neurotoxicity study, and the developmental, developmental neurotoxicity and reproduction studies. No effects were observed in the rabbit dermal or rat inhalation studies.

Long-term dietary administration of imidacloprid did not result in an overall treatment-related increase in incidence of tumor formation in rats or mice. The RfD/Peer Review Committee classified imidacloprid as a "Group E" chemical, no evidence of carcinogenicity for humans, by all routes of exposure based upon lack of evidence of carcinogenicity in rats and mice.

Imidacloprid was clastogenic in two *in vitro* cytogenetic studies with human lymphocytes and CHO cells, but negative in other cytogenetic assays with CHO cells. Imidacloprid was also negative in unscheduled DNA, *in vivo* mouse micronucleus, and other mutagenicity studies. Overall, the data suggest that imidacloprid is negative for mutagenicity.

Oral rat developmental studies showed no increased susceptibility of the fetus to imidacloprid *in utero*. Maternal toxicity resulted in decreased body weight gain and decreased corrected body weight gain. An increase in the incidence of wavy ribs in fetuses was noted at the same dose where maternal toxicity was observed. No increased susceptibility of the fetus was noted *in utero* in the oral rabbit developmental study. Developmental effects included abortion, total litter resorptions, increased postimplantation loss due to increased late resorptions, decreased fetal weights, and very low incidences of skeletal alterations, including fused, asymmetric, missing, and/or abnormally ossified sternebrae, and/or shortened tail. Maternal toxic effects in the rabbit included maternal deaths and decreased maternal absolute body weights, body weight gain, and food consumption. Parental and offspring toxicity included body weight

decrements at similar dosages in the rat multi-generation reproduction study. There was no increased susceptibility following pre/post natal exposure to rats in this study. There was evidence of an increased qualitative susceptibility in the rat developmental neurotoxicity study. At the highest dose tested, maternal effects consisted largely of slight decreases in food consumption and body weight gain during early lactation, while pup effects included decreased body weight, decreased motor activity, decreased caudate/putamen width, females only (PNDs 11 and adult), and slight changes in performance in the water maze, males only, at the same dose.

Methylene-labeled imidacloprid was rapidly absorbed with approximately 90% of the administered dose being eliminated within 24 hours and 96% within 48 hours. There were no biologically significant differences between sexes, dose levels, or route of administration. Urinary excretion was the major route of elimination (70-80% of recovered radioactivity), with a lesser amount eliminated in feces (17-25% of recovered radioactivity). Biliary excretion was a major contributor to fecal radioactivity (36.6% vs. 4.8% of recovered radioactivity in bile-fistulated animals). Total tissue burden after 48 hours accounted for only approximately 0.5% of the recovered radioactivity, with major sites of accumulation being the liver, kidney, lung, skin, and plasma and minor sites being the brain and testes. Maximum plasma concentration occurred between 1.1 and 2.5 hours, and elimination half-lives (calculated from two exponential terms) were 3 and 26-118 hours. There were two major evident routes of biotransformation. The first included an oxidative cleavage of the parent compound to give 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxynicotinic acid and its mercapturic acid derivative. The second included the hydroxylation of imidazolidine followed by elimination of water of the parent compound to give NTN 35884.

In a comparison between [Methylene-^{14}C] Imidacloprid and [Imidazolidine-4,5-^{14}C] Imidacloprid, the rates of excretion were similar; however, the renal portion was higher with the imidazolidine-labeled test material (90% vs. 75% of recovered radioactivity for methylene-labeled test material. The imidazolidine-labeled test material also demonstrated higher accumulation in the tissues (approximately 1% of recovered radioactivity), with the major sites of accumulation being the liver, kidney, lung, and skin, and the minor sites being brain and muscle.

In a comparison between [Methylene-^{14}C] Imidacloprid and WAK 3839, there were no significant differences in the absorption, distribution, and excretion of the total radioactivity. More radioactivity was found in the tissues of the animals receiving imidacloprid at the 1.0 and 150.0 dose levels (respectively 0.9% and 3.4% vs. 0.2% of administered radioactivity for the WAK 3839 group). The major sites of accumulation of WAK 3839 included lung, renal fat, liver, and kidney, with minor sites being the testis and brain. WAK 3839 was formed during pretreatment (chronic oral dosing) of imidacloprid; however, the proposed metabolic pathways of the two compounds were different.

VI DATA GAPS / REQUIREMENTS

The HIARC recommended that a 28-day inhalation study in rats with FOB and other neurological assessments be conducted because of the concern for exposure via the inhalation route. However, per HED SOP2002.01, a waiver for this study may be granted for an active ingredient that is in Toxicity Category IV for inhalation provided an extrapolated inhalation MOE (based on an oral NOAEL) exceeds a MOE of 1000. Since Imidacloprid is in Toxicity Category IV, the decision to grant a waiver will depend on the MOE attained during risk characterization/risk assessment.

VII ACUTE TOXICITY

Acute Toxicity of Imidacloprid

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	42055331	LD_{50} = 424 mg/kg (M) LD_{50} > 450 mg/kg (F)	II
81-2	Acute Dermal	42055332	LD_{50} > 5000 mg/kg	IV
81-3	Acute Inhalation	42256317	LC_{50} > 5.33 m/L	IV
81-4	Primary Eye Irritation	42055334	Not an eye irritant	IV
81-5	Primary Skin Irritation	42055335	Not a dermal irritant	IV
81-6	Dermal Sensitization	42055336	Not a dermal sensitizer	N/A

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Imidacloprid

Exposure Scenario	Dose Used in Risk Assessment, UF	* Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	LOAEL = 42 mg/kg/day UF = 300 **Acute RfD** = 0.14 mg/kg	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = 0.14 mg/kg	Acute neurotoxicity - rat LOAEL = 42 mg/kg, based upon the decrease in motor and locomotor activities observed in females.
Chronic Dietary all populations	NOAEL= 5.7 mg/kg/day UF = 100 **Chronic RfD** = 0.057 mg/kg/day	FQPA SF = 1X **cPAD** = chr RfD / FQPA SF = 0.057 mg/kg/day	Combined chronic tox/carcinogenicity - rat LOAEL = 16.9 mg/kg/day, based upon increased incidence of mineralized particles in thyroid colloid in males.
Short-Term Oral (1-30 days)	oral study NOAEL= 10 mg/kg/day	**LOC for MOE** = 100 (Residential, includes the FQPA SF)	Developmental toxicity - rat Maternal LOAEL = 30 mg/kg/day, based upon decreased body weight gain and corrected body weight gain.
Intermediate-Term Oral (1- 6 months)	oral study NOAEL= 9.3 mg/kg/day	**LOC for MOE** = 100 (Residential, includes the FQPA SF)	Subchronic neurotoxicity - rat LOAEL = 63.3 mg/kg/day, based upon decreased body weight gain.
Short-Term Dermal (1-30 days)	oral study NOAEL= 10 mg/kg/day (dermal absorption rate = 7.2%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Developmental toxicity - rat Maternal LOAEL = 30 mg/kg/day, based upon decreased body weight gain and corrected body weight gain.
Intermediate-Term Dermal (1-6 months)	oral study NOAEL= 9.3 mg/kg/day (dermal absorption rate = 7.2%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Subchronic neurotoxicity - rat LOAEL = 63.3 mg/kg/day, based upon decreased body weight gain.
Long-Term Dermal (> 6 months)	oral study NOAEL= 5.7 mg/kg/day (dermal absorption rate = 7.2%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Combined chronic tox/carcinogenicity - rat LOAEL = 16.9 mg/kg/day, based upon increased incidence of mineralized particles in thyroid colloid in males.

(Table continues, footnotes follow)

Exposure Scenario	Dose Used in Risk Assessment, UF	* Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Inhalation (1-30 days)	oral study NOAEL= 10 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Developmental toxicity - rat Maternal LOAEL = 30 mg/kg/day, based upon decreased body weight gain and corrected body weight gain.
Intermediate-Term Inhalation (1- 6 months)	oral study NOAEL= 9.3 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Subchronic neurotoxicity - rat LOAEL = 63.3 mg/kg/day, based upon decreased body weight gain.
Long-Term Inhalation (> 6 months)	oral study NOAEL= 5.7 mg/kg/day (inhalation absorption rate = 100%)	**LOC for MOE** = 100 (Occupational) **LOC for MOE** = 100 (Residential, includes the FQPA SF)	Combined chronic tox/carcinogenicity - rat LOAEL = 16.9 mg/kg/day, based upon increased incidence of mineralized particles in thyroid colloid in males.
Cancer (oral, dermal, inhalation)	Group E	Not applicable	No evidence of carcinogenicity in rats and mice.

[1] UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern

* ***NOTE:*** The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.