

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

**MEMORANDUM**

Date: 4/30/07

Subject: Imidacloprid. Human Health Risk Assessment. Section 3 Requests for Uses on Peanut, Proso Millet, Pearl Millet, Oat, Kava, Globe Artichoke, Caneberries, Wild Raspberry, and Soybeans.

PP#s	6E7116, 6E7108, & 6F7049		
PC Code:	129099	40 CFR:	180.472
DP Num:	337873, 337876, 337879	Decision #s:	365863, 371243, 370491

From: W. Cutchin, Acting Branch Senior Scientist  
Alternative Risk Integration Assessment Team (ARIA)  
Risk Integration Minor Use and Emergency Response Branch (RIMUERB)  
Registration Division (RD) (7505P)

Through: PV Shah, Ph.D., Acting Branch Chief  
Registration Action Branch (RAB1)  
Health Effects Division (HED) (7509P)

To: S. Jackson/D. Rosenblatt, PM Team 05  
RIMUERB/RD (7505P)

The ARIA Team of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that ARIA evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed and registered uses of imidacloprid [1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine] on peanut, proso millet, pearl millet, oat, kava, globe artichoke, caneberries, wild raspberry, and soybeans. A summary of the findings and an assessment of human risk resulting from the registered and proposed tolerances for imidacloprid is provided in this document. The risk assessment, the residue chemistry data review, and the dietary risk assessment were provided by W. Cutchin (ARIA), the occupational/residential exposure assessment by M. Dow (ARIA), and the drinking water assessment by R. Parker of the Environmental Fate and Effects Division (EFED).

## Table of Contents

1.0	Executive Summary .....	4
2.0	Ingredient Profile.....	12
2.1	Summary of Registered/Proposed Uses .....	13
2.2	Structure and Nomenclature .....	16
2.3	Physical and Chemical Properties.....	17
3.0	Hazard Characterization/Assessment.....	17
3.1	Hazard and Dose-Response Characterization.....	17
3.1.1	Dose-response .....	18
3.1.2	FQPA .....	21
3.2	Absorption, Distribution, Metabolism, Excretion (ADME).....	21
3.3	FQPA Considerations.....	22
3.3.1	Adequacy of the Toxicity Data Base.....	23
3.3.2	Evidence of Neurotoxicity .....	23
3.3.3	Developmental Toxicity Studies.....	23
3.3.4	Reproductive Toxicity Study .....	25
3.3.5	Additional Information from Literature Sources .....	26
3.3.6	Pre-and/or Postnatal Toxicity .....	26
3.3.7	Recommendation for a Developmental Neurotoxicity Study .....	27
3.4	Safety Factor for Infants and Children .....	28
3.4.1	Adequacy of the Exposure Data Base .....	28
3.4.2	Safety Factor Conclusion .....	29
3.5	Hazard Identification and Toxicity Endpoint Selection.....	29
3.5.1	Acute Population Adjusted Dose (aPAD) - General Population .....	29
3.5.2	Chronic Population Adjusted Dose (cPAD).....	30
3.5.3	Incidental Oral Exposure (Short- and Intermediate-Term) .....	32
3.5.4	Dermal Absorption .....	33
3.5.5	Dermal Absorption .....	34
3.5.6	Dermal Exposure .....	34
3.5.7	Inhalation Exposure .....	35
3.5.8	Level of Concern for Margin of Exposure.....	36
3.5.9	Recommendation for Aggregate Exposure Risk Assessments .....	37
3.3.10	Classification of Carcinogenic Potential .....	37
3.5.11	Summary of Toxicological Doses and Endpoints for Imidacloprid for Use in Human Risk Assessments.....	39
3.6	Endocrine disruption.....	40
4.0	Public Health and Pesticide Epidemiology Data .....	41
4.1	Incident Reports .....	41
5.0	Dietary Exposure/Risk Characterization .....	41
5.1	Pesticide Metabolism and Environmental Degradation.....	41
5.1.1	Metabolism in Primary Crops and Livestock .....	41
5.1.2	Metabolism in Rotational Crops.....	41
5.1.3	Analytical Methodology .....	42
5.1.4	Environmental Degradation .....	43
5.1.5	Comparative Metabolic Profile .....	43
5.1.6	Toxicity Profile of Major Metabolites and Degradates .....	44
5.1.7	Pesticide Metabolites and Degradates of Concern .....	45
5.1.8	Drinking Water Residue Profile .....	45
5.1.9	Food Residue Profile.....	45
5.1.10	International Residue Limits .....	50
5.2	Dietary Exposure and Risk .....	50
5.3	Anticipated Residue and Percent Crop Treated Information .....	51
6.0	Residential (Non-Occupational) Exposure/Risk Characterization.....	53
6.1	Residential Handler Exposure.....	53
6.2.	Residential Post-application Exposure .....	59

6.3	Combined Residential Exposure .....	65
6.4	Other (Spray Drift, etc.).....	66
7.0	Aggregate Risk Assessments and Risk Characterization .....	66
7.1	Acute Aggregate Risk.....	67
7.2	Short-Term Aggregate Risk .....	67
7.3	Intermediate-Term Aggregate Risk .....	68
7.4	Long-Term Aggregate Risk .....	68
8.0	Cumulative Risk Characterization/Assessment .....	68
9.0	Occupational Exposure/Risk Pathway.....	69
9.1	Short-/Intermediate-/Long-Term Handler Risk.....	69
9.2	Short-/Intermediate-/Long-Term Post-application Risk.....	72
9.3	Restricted Entry Interval (REI) .....	74
10.0	Data Needs and Label Requirements .....	74
10.1	Toxicology .....	74
10.2	Residue Chemistry.....	74
10.3	Occupational and Residential Exposure.....	74
	Attachment 1: Toxicological Effects Tables .....	76
	Attachment 2: Structures of Imidacloprid Metabolites .....	82

## 1.0 Executive Summary

Imidacloprid is a systemic insecticide registered to control soil insects, sucking insects, chewing insects, and termites. It is effective against the larval, nymphal and adult stages. The primary mode of action is the disruption of the nervous system by acting as an inhibitor at nicotinic acetylcholine receptors. Imidacloprid blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in nerve function impairment.

The Interregional Research Project No. 4 (IR-4), on behalf of the Agricultural Experiment Stations of Texas, Missouri, Georgia, Wisconsin, and Hawaii, has submitted a petition for the use of imidacloprid on peanuts; proso and pearl millet; oats; kava; globe artichoke; caneberry, subgroup 13A; and wild raspberry. IR-4 is not requesting a change in the existing tolerance for globe artichokes; the request is for the addition of a soil use to the existing foliar use. Bayer Corp. has also submitted a petition for the use of imidacloprid on soybeans.

### *Hazard Assessment*

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 evidenced as changes in clinical signs and Functional Observation Battery (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, and 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 in the chronic toxicity study. The rabbit appeared to be very sensitive as there was increased mortality in the oral 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. There was no evidence of carcinogenic potential in either the rat chronic toxicity/carcinogenicity or mouse carcinogenicity studies and no concern for mutagenicity. There was no evidence of increased qualitative or quantitative susceptibility of rats or rabbits to *in utero* exposure to imidacloprid and no evidence of qualitative or quantitative increased susceptibility of rat offspring in the reproduction 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 [postnatal days (PNDs) 11 and adult]; and slight changes in performance in the water maze, males only, at the same dose.

On 11/10/93, the Reference Dose (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.

The HED Hazard Identification Assessment Review Committee (HIARC) met on 10/8/02 to select endpoints for risk assessment and to evaluate the potential for increased susceptibility of infants and children from exposure to imidacloprid according to the February 2002 OPP 10X guidance document. This was a re-evaluation of the toxicology database subsequent to the initial evaluation by the HIARC on 9/11/97. The FQPA Safety Factor (SF) was reduced to 1x based on toxicological considerations by the HIARC (TXR # 0051292, 10/31/02), the conservative residue assumptions used in the dietary and residential exposure risk assessments, and the completeness of the residue chemistry and environmental fate databases (evaluated by the risk assessment team).

Risk assessments were conducted for the following specific exposure scenarios listed below. The acute Population-Adjusted Dose (aPAD) was calculated by dividing the acute Point of Departure (aPOD), in this case the Lowest-Observed-Adverse-Effect-Level (LOAEL) by 300 [10X for interspecies extrapolation, 10X for intraspecies variation; and 3X uncertainty factor (UF) for the use of a LOAEL due to the lack of a No-Observed-Adverse-Effect-Level (NOAEL) in the acute neurotoxicity study]. The chronic PAD (cPAD) was calculated by dividing the chronic POD (cPOD), in this case the NOAEL by 100 (10X for interspecies extrapolation, 10X for intraspecies variation). Since the FQPA SF has been reduced to 1X, the aPAD and cPAD are not further adjusted. Since oral studies were selected for all durations of dermal and inhalation exposure, a 7% dermal absorption factor and a 100 % inhalation absorption factor are used in the route-to-route extrapolation. The level of concern for occupational dermal and inhalation exposures are for Margins of Exposure (MOEs) <100. For the occupational exposure assessment, dermal and inhalation exposure estimates can be combined because the same effects (endpoints) were identified for dermal and inhalation exposure from an oral study. The level of concern for residential oral, dermal and inhalation exposures are for MOEs <100. Short-term oral, dermal and inhalation exposure estimates can be aggregated because of the use of the same toxicity endpoint (decreased body weight gain) from the same study (oral rat developmental toxicity study).

<u>Exposure Scenario</u>	<u>Dose</u>	<u>Endpoint</u>	<u>Effect/Study</u>
Acute dietary	LOAEL = 42 mg/kg/day	aPAD = 0.14 mg/kg/day	Decreased motor and locomotor activities/Acute neurotoxicity study in rats
Chronic dietary	NOAEL = 5.7 mg/kg/day	cPAD = 0.057 mg/kg/day	Increased incidence of mineralized particles in the thyroid colloid/Chronic toxicity study in rats
Short-term incidental oral	Oral NOAEL = 10 mg/kg/day	Target MOE = 100 (residential)	Decreased body weight gain and decreased corrected body weight gain in maternal animals/ Developmental toxicity study in rats
Short-term dermal	Oral NOAEL = 10 mg/kg/day	Target MOE = 100 (occupational and residential)	
Short-term inhalation	Oral NOAEL = 10 mg/kg/day	Target MOE = 100 (occupational and residential)	

### *Exposure Assessment*

The petitioners have submitted sample labels for numerous imidacloprid products. The uses on peanuts and kava include both an in-furrow spray on or below seed during or before planting and a foliar use. The peanut and kava seed uses are for a single application at 0.38 pounds active ingredient per acre (lb ai/A). The foliar uses on peanut and kava are for up to 3 applications for a total 0.13 lb ai/A with pre-harvest intervals (PHI) of 14 days for peanut and 7 days for kava. The uses on millet and oats include commercial seed treatment or below seed during or before planting at 0.25 or 0.09 lb ai/100lb seed, respectively. The use on globe artichoke includes both an in-furrow spray on or below seed during or before planting at and a foliar use, both at 0.5 lb ai/A with a 7-day PHI. The labels for caneberries indicate either a foliar application at 0.3 lb ai/A with a 3-day PHI or a drench application 0.5 lb ai/A with a 7-day PHI. Since the previous lower tolerance for caneberries was based using the drench application at the higher rate, the use is supported and may remain on the labels. There is an existing use of imidacloprid on soybean seeds for protection from damage caused by seed corn maggot, to reduce feeding damage caused by soybean aphids and over-wintering bean leaf beetles, and to help suppress the spread of certain viruses, at 2.0-4.0 fl. oz. per hundredweight of seed. The requested foliar use on soybeans is in addition to the current use on soybean seeds for three applications at 0.047 lb ai/A with a maximum total application of 0.14 lb ai/A.

The nature of imidacloprid residues in plants and livestock is adequately understood. The residue of concern in plants and livestock are imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent. Adequate enforcement methods are available for determination of imidacloprid residues of concern in plant (Bayer Gas Chromatography/Mass Spectrometry (GC/MS) Method 00200) and livestock commodities (Bayer GC/MS Method 00191). The method is a common moiety method that uses oxidation of parent and metabolites to 6-chloronicotinic acid (6-CNA) with demonstrated limit of detection (LOD) and limit of quantitation (LOQ) at 0.01 and 0.05 ppm, respectively, in plant commodities. Samples in the submitted peanut crop field trial and processing studies were for analyzed for combined residues of imidacloprid and its metabolites containing 6-chloropyridinyl moiety, all expressed as the parent, using a modification of Bayer GC/MS Method 00200. The LOD and LOQ were calculated as 0.03 ppm and 0.076 ppm for nutmeat; 0.01 ppm and 0.033 ppm, for oil; and 0.02 ppm and 0.062 ppm for meal. For caneberries, total residues of imidacloprid were determined using a working method based on Bayer Method 00200. The lower limit of method validation (LLMV) of the modified method in this study was reported as 0.05 ppm. LODs were estimated as 0.009 ppm, 0.02 ppm and 0.03 ppm for raspberry, marionberry and boysenberry, respectively. The total imidacloprid residue was analyzed in soybean field trial and processing samples by a common moiety method (oxidation to 6-CNA) and quantitated by liquid chromatography with tandem mass spectroscopy detection (LC-MS/MS). The method in these studies, NT-001-P04-01, is based on an earlier method, 00834. The LOQ for imidacloprid in soybean forage, hay, and seed was 0.025 ppm, 0.100 ppm, and 0.05 ppm, respectively. The calculated LODs for soybean forage, hay, and seed were 0.0111 ppm, 0.0382 ppm, and 0.0136 ppm, respectively. The data from the soybean processing study support a method LOQ of 0.050 ppm for each analyte in soybean seed and processed commodities.

Another analytical method was used in the caneberry trial designated as Study No. AAFC03-085R. The method used quantitation by high performance liquid chromatography with mass spectroscopy detector (HPLC/MS). The LLMV in this study was reported as 0.30 ppm. The LOD and LOQ were calculated to be 0.068 ppm and 0.203 ppm, respectively. However, total residues of imidacloprid were determined to be below the LLMV (<0.30 ppm) and/or calculated LOQ (<0.203 ppm) at all PHIs. As the method used could not be validated at the target LOQ (0.05 ppm), the method LLMV was unacceptably high and the residues reported at each PHI were below the LLMV, this residue study is considered scientifically unacceptable. Therefore, the results from this trial should not be used to support the registration of imidacloprid in/on caneberries.

Residues of imidacloprid have previously been shown to be stable in a variety of raw agricultural commodities (RACs) for up to 2 years. Peanut storage stability testing performed after approximately 4.4 years of frozen storage showed no appreciable degradation. There are sufficient storage stability data to support the submitted residue field trials and processing studies. The expected residue levels in the livestock feed items associated with the subject petition were used to recalculate the maximum theoretical dietary burden (MTDB) for livestock. The newly calculated MTDBs are not greater than those calculated previously. Therefore, the proposed uses will not require an increase in livestock tolerances.

Peanut field trials were conducted using a single in-furrow applications at a rate of approximately 0.375 lb ai/A at planting followed by foliar applications made 4 to 6 days apart at a rate of approximately 0.044 lb ai/A for a total of approximately 0.507 lb ai/A. The results from the trials show that the maximum combined residues in nutmeat were 0.40 ppm. Maximum residues in 14-day and 28-day hay samples were 24 ppm. Residues declined in nutmeat to a maximum of 0.14 ppm by 28 days. The submitted studies are adequate in number and geographic diversity and are supported by adequate storage stability data and analytical methodology. However, the residue data as analyzed by the Tolerance/Maximum Residue Limit (MRL) Harmonization Spreadsheet indicates that the requested tolerances on peanut nutmeat and hay are not appropriate. A new Section F requesting imidacloprid tolerances on peanuts at 0.60 ppm and peanut, hay at 35 ppm is required.

No crop-specific data to support the tolerance requests in conjunction with the requested uses for proso millet, pearl millet, oats, kava, and globe artichoke. Since there are identical seed treatment uses with tolerances for most of the cereal grain crop group and a tolerance for indirect or inadvertent residues on the cereal grain crop group, tolerances can be translated to the seed treatment uses on proso millet and pearl millet. ARIA recommends for the proposed tolerances on proso and pearl millet grain at 0.05 ppm. In addition, residues would be expected on the other millet RACs as residues are found on other grain RACs from the same uses. A revised Section F is required for proso millet, forage at 2.0 ppm; proso millet, hay at 6.0 ppm; proso millet, straw at 3.0 ppm; pearl millet, forage at 2.0 ppm; pearl millet, hay at 6.0 ppm; and pearl millet, straw at 3.0 ppm. There are already existing tolerances for the seed treatment use on oats: oats, grain at 0.05 ppm; oats, forage at 2.0 ppm; oats, hay at 6.0 ppm; oats, straw at 3.0 ppm as a result of the same proposed seed treatment use as proposed here. The request for use and tolerance for imidacloprid on oats is not necessary; the requested tolerances should be removed from Section F. Since kava is projected to be part of the root and tuber vegetable crop group 1 in the near

future and the proposed use is identical to that used for root and tuber vegetables, ARIA recommends for the proposed imidacloprid tolerances on kava, leaves at 4.0 ppm and kava, roots at 0.40 ppm. A tolerance of 2.5 ppm has already been established for imidacloprid on globe artichokes as a result of a foliar use. IR-4 is now requesting a use either below the seed row before planting, in-furrow during planting, or by chemigation into the root zone. Comparisons of data on foliar vs. limited soil-applied imidacloprid or the two treatments combined indicate that the foliar treatments clearly drive the magnitude of the resulting residues. Any slight additional residues from soil treatments are expected to be covered by existing tolerances established to reflect foliar application. Therefore, it is unlikely that the residues of imidacloprid from the proposed soil treatment use on globe artichoke will exceed the existing 2.5 ppm tolerance. ARIA recommends for the proposed imidacloprid use on globe artichoke without a change in the existing tolerance.

A previous petition for the use of imidacloprid on caneberries as drench application resulted in a conditional registration and permanent tolerance. In the current petition, imidacloprid was applied to caneberries in three foliar-directed broadcast sprays. The maximum residues observed in caneberries were 0.70 ppm in blackberry, 0.96 ppm in raspberry, 1.7 ppm in marionberry and 1.5 ppm in boysenberry. The residue data as analyzed by the Tolerance/MRL Harmonization Spreadsheet indicates that the requested tolerance on caneberries, crop group 13A at 2.5 ppm is not appropriate. However, since the databases are small for blackberries and raspberries, the fruits are essentially the same size and texture, and in the interest of harmonizing with Canada, ARIA will consider the entire database for caneberries together. The Tolerance/MRL Harmonization Spreadsheet indicates the appropriate tolerance level for the entire database of caneberry residues should be 2.5 ppm. Therefore, ARIA recommends for the proposed tolerance for caneberry, crop group 13A at 2.5 ppm. The petitioner has requested a tolerance for wild raspberry. The crop definition for caneberry, crop group 13A indicates that no separate tolerance is required for wild raspberry and it should be removed from the Section F.

Residue field trials on soybeans were conducted to measure the magnitude of residues in soybeans resulting from the existing pre-plant seed treatment followed by three foliar applications of imidacloprid to the growing soybean plants. The highest imidacloprid residue on soybean forage and hay at 0-day PHI was 8.87 ppm and 24.0 ppm, respectively. The highest imidacloprid residue on soybean seed at a 21-day PHI was 2.04 ppm. The total imidacloprid residue was found to decline significantly on soybean forage with time. In soybean hay, total imidacloprid residue was found to decline significantly at one trial but remained relatively constant at the other. On soybean seed, total imidacloprid residue remained constant with time. The residue data as analyzed by the Tolerance/MRL Harmonization Spreadsheet indicates that the requested tolerance on soybean, forage is appropriate at 8.0 ppm. However, the requested tolerance levels on the other soybean commodities are not appropriate. A new Section F requesting imidacloprid tolerances on soybean, seed at 3.5 ppm, and soybean, hay at 35 ppm is required.

There are many processed commodities of regulatory interest associated with these petitions among which are millet flour, oat flour, and rolled oats. It has been determined that imidacloprid residues do not concentrate in grain processed commodities; therefore, no imidacloprid tolerances are required on millet and oat processed commodities. The submitted peanut

processing study indicates that imidacloprid residues do not concentrate in peanut oil. The average concentration factor from the two processing studies is higher than the theoretical maximum. The highest average field trial (HAFT) of 0.32 ppm times the theoretical maximum of 2.2X yields an expected residue of 0.704 ppm in peanut meal. Therefore, the requested tolerance is not appropriate; a revised Section F requesting an imidacloprid tolerance on peanut, meal at 0.75 ppm is required. The submitted processing study indicates that imidacloprid residues do not concentrate in soybean meal, hulls, or oil. Therefore, a separate tolerance for imidacloprid residues in soybean meal, hulls, or oil is not required. The processing study indicates that imidacloprid residues will concentrate in aspirated grain fractions. The expected residue is 240 ppm in aspirated grain fractions. The requested tolerance level for imidacloprid residues in aspirated grain fractions is appropriate. However, the Agency does not differentiate soybean from other aspirated grain fractions; therefore, a revised Section F for aspirated grain fractions at 240 ppm is required.

EFED provided revised, Tier 1 estimated drinking water concentrations (EDWCs) for surface water (using FQPA Index Reservoir Screening Tool (FIRST)) for imidacloprid and its degradates (imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin). Revised ground water EDWCs were not estimated because these values have been shown previously to be substantially lower in magnitude than the surface water concentrations. The revised surface water EDWCs for the proposed uses do not exceed the EDWCs provided by EFED in conjunction with the 3/14/03 HED risk assessment for imidacloprid (DP Num: 271770, M. Barrett, 2/25/03). Therefore, the overall highest surface and ground water EDWCs were used in the current risk assessment (DP Num: 311925, R. Parker, 5/16/06). Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.” The surface water values (using FIRST), the acute (peak) and chronic (annual average) EDWCs, based on the citrus use pattern, are 36.0 ppb and 17.2 ppb, respectively.

An unrefined, acute dietary exposure assessment using tolerance-level residues and assuming 100% crop treated (%CT) for all registered and proposed commodities was conducted for the general U.S. population and various population subgroups. Exposure to drinking water was incorporated directly in the dietary assessment using the acute (peak) concentration for surface water generated by the FIRST model, 36.0 ppb. This assessment indicates that the acute dietary exposure estimates are below HED’s level of concern, <100% aPAD, at the 95<sup>th</sup> exposure percentile for the general U.S. population and all other population subgroups. The acute dietary exposure is estimated for the U.S. population at 28% of the aPAD and the most highly exposed population subgroup, children 1-2 years old, at 70% of the aPAD.

A partially refined, chronic dietary exposure assessment (using tolerance-level residues for all registered and proposed commodities, and %CT information for some commodities) was conducted for the general U.S. population and various population subgroups. Exposure to drinking water was incorporated directly into the dietary assessment using the chronic (annual average) concentration for surface water generated by the FIRST model, 17.2 ppb. This assessment concludes that the chronic dietary exposure estimates are below HED’s level of concern (<100% cPAD) for the general U.S. population and all population subgroups. The chronic dietary exposure is estimated for the U.S. population at 13% of the cPAD and the most highly exposed population subgroup, children 1-2 years old, at 38% of the cPAD.

### *Residential*

Imidacloprid is registered for indoor as well as outdoor residential uses on ornamental lawns and turf as well as for use on golf courses, ornamental plantings (*i.e.*, flowering plants, foliage plants, herbaceous perennial plants, and woody plant, shrubs and trees), and as a pre- and post-construction termiticide. Residential handlers may also be exposed to imidacloprid via the use of spot-on treatments for dogs or cats for flea control. ARIA believes that residential pesticide handlers (*i.e.*, persons who might mix, load and, or apply a pesticide material) could be exposed to several formulations that contain imidacloprid. ARIA expects that residential handler exposures will be short-term (*i.e.*, 1-30 days) based upon the pest spectra, sites of application, methods of application, formulations and the retreatment intervals. The pet-treatment scenario resulted in the highest combined MOE for adults (MOE = 400; handler and post-application) and children (MOE = 260; post-application). The turf-treatment scenario resulted in much lower exposures for both adults (MOE = 15,000; handler and post-application) and children (MOE = 1,500; post-application). These MOEs are below HED's level of concern.

### *Aggregate Risk Exposure*

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of imidacloprid (food and drinking water). The acute dietary exposure estimates, which included food and water, are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the general U.S. population (28% of the aPAD) and all other population subgroups. The most highly-exposed population subgroup is children 1-2 years old, at 70% of the aPAD. Therefore, the acute aggregate risk associated with the proposed use of imidacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroup.

Short-term aggregate risk assessments are required for adults as there is potential for both dermal and inhalation handler exposure, and dermal post-application exposure from the residential uses of imidacloprid on turf and pets. In addition, short-term aggregate risk assessments are required for children/toddlers because there is a potential for oral and dermal post-application exposure resulting from the residential uses of imidacloprid on turf and pets. The pet-treatment scenario resulted in the lowest combined MOE for adults (MOE = 400; handler and post-application) and children (MOE = 260; post-application). The turf-treatment resulted in much lower exposures for both adults (MOE = 15,000; handler and post-application) and children (MOE = 1,500; post-application). Therefore, the pet-treatment exposure estimates were aggregated with the chronic dietary (food and water) to provide a worst-case estimate of short-term aggregate risk for the U.S. population and children 1-2 years old (the child population subgroup with the highest estimated chronic dietary food exposure). As the resulting MOEs are greater than 100, the short-term aggregate risks are below HED's level of concern.

An assessment of the intermediate-term aggregate risk for exposure to imidacloprid is not required since, based on the current use patterns, ARIA does not expect exposure durations that would result in intermediate-term exposures.

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of imidacloprid (food and drinking water) and residential uses. However,

due to the use patterns, no chronic residential exposures are expected. The chronic dietary exposure estimates, which included food and water, are below HED's level of concern (<100% cPAD) for the general U.S. population (13% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 38% of the cPAD. Therefore, the chronic aggregate risk associated with the proposed use of imidacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroups.

An assessment of the cancer risk for exposure to imidacloprid is not required.

### *Occupational Exposure*

Imidacloprid products are registered to control aphids, leafhoppers, whiteflies and rednecked cane borer. Some imidacloprid products are not limited to soil applications and may have repeat applications. None of the products may be applied pre-bloom, during bloom or when bees are actively foraging. All of the product labels require applicators and other handlers to wear personal protective equipment (PPE) consisting of long-sleeved shirt, long pants, shoe plus socks and chemical-resistant gloves made of any waterproof material such as barrier laminate, butyl rubber, nitrile rubber, neoprene rubber, natural rubber, polyethylene, polyvinylchloride or viton.

Based primarily on the proposed new use patterns, commercial and private (*i.e.*, grower operators) pesticide handlers are typically expected to have short-term exposures (*i.e.*, 1-30 days). The proposed new use pattern indicates that the most highly exposed occupational pesticide handlers are likely to be mixer/loaders using open-pour loading of liquids or granules, and applicators using airblast sprayers, ground-boom sprayers, high-pressure hand-wand sprayers, backpack sprayers and aircraft. In some cases, HED believes that certain individuals (private growers versus commercial applicators) may perform all three handler activities, that is, mix, load, and apply the material. A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to imidacloprid. All of the pesticide handler exposure scenarios from the proposed new use patterns are above an MOE of 100 and therefore do not exceed HED's level of concern.

Typically there is the possibility for agricultural workers to experience post-application exposures to dislodgeable pesticide residues. Post-application worker exposure is estimated using HED procedure that assumes 20% of the application rate is available as dislodgeable foliar residue on the day of treatment. ARIA does not expect post-application exposures to exceed short-term exposure. Therefore, only short-term exposures are assessed. These estimates are considered to be screening level estimates *i.e.*, conservative (protective). HED's level of concern for dermal exposure is for MOEs <100. In this case, all the MOEs are greater than 100; therefore, post-application dermal exposure is not of concern for agricultural workers. Post-application inhalation exposure is expected to be negligible.

### **Recommendation**

Provided revised Section Fs are submitted as specified in Section 10.2, the residue chemistry and hazard databases support the establishment of the permanent tolerances for the combined

residues of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, in/on the RACs listed below.

Commodity	Recommended Tolerance (ppm)
Peanut	0.45
Peanut, hay	35
Peanut, meal	0.75
Millet, proso, grain	0.05
Millet, proso, forage	2.0
Millet, proso, hay	6.0
Millet, proso, straw	3.0
Millet, pearl, grain	0.05
Millet, pearl, forage	2.0
Millet, pearl, hay	6.0
Millet, pearl, straw	3.0
Kava, roots	0.40
Kava, leaves	4.0
Caneberry, subgroup 13A	2.5
Soybean, seed	3.5
Soybean, forage	8.0
Soybean, hay	35
Aspirated grain fractions	240

## 2.0 Ingredient Profile

Imidacloprid is an insecticide registered for uses on a variety of crops for the control of many insects, including aphids, cucumber beetles and whiteflies (including sweet potato or silverleaf whitefly). Imidacloprid is a member of the pyridylmethanamine class of compounds. Its mode of action is the disruption of the nervous system by acting as an inhibitor at nicotinic acetylcholine receptors. Imidacloprid blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in normal nerve function impairment.

Imidacloprid is also currently registered for use on residential ornamental lawns, golf courses, and ornamental plantings (*i.e.*, flowering plants, foliage plants, herbaceous perennial plants, and woody plant, shrubs and trees). In addition to the outdoor uses, imidacloprid is also registered for use indoors. It should be noted that imidacloprid is registered as a pre- and post-construction termiticide. However, due to the low volatility and short half-life of imidacloprid, coupled with the fact that it is used pre- and post-construction only, HED does not expect there to be potential for long-term exposure to imidacloprid from this use. Therefore, long-term exposure assessment is not warranted.

Tolerances are currently established for the combined residues of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, under 40 CFR §180.472 in/on various plant and livestock commodities. Section 18 Emergency Exemption tolerances with expiration/revocation dates are established in/on plant commodities under 40 CFR §180.472(b), and indirect or inadvertent tolerances are established as a result of application of the pesticide to growing crops and other non-food crops under 40 CFR §180.472(d).

## 2.1 Summary of Registered/Proposed Uses

Tolerances are currently established for the combined residues of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, under 40 CFR §180.472 in/on various plant and livestock commodities. Section 18 Emergency Exemption tolerances with expiration/revocation dates are established in/on plant commodities under 40 CFR §180.472(b), and indirect or inadvertent tolerances are established as a result of application of the pesticide to growing crops and other non-food crops under 40 CFR §180.472(d).

Table 2.1 Summary of Proposed Directions for Use of Imidacloprid.							
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	RTI <sup>1</sup> (days)	PHI (days)	Use Directions and Limitations
Peanuts							
Apply as directed or broadcast spray	Provado <sup>®</sup> 70 [264-823]	0.043	3	0.13	5	14	Use not permitted in CA
Spray band below seed row before planting, in-furrow during planting, chemigation	Gaicho <sup>®</sup> 600 SC [264-828]	0.38	1	0.38	NA	15	Spray band below seed row up to 7 days before planting, Use not permitted in CA
Apply as directed or broadcast spray	Provado <sup>®</sup> 1.6 Flowable [3125-457]	0.043	3	0.13	5	14	Use not permitted in CA
In-furrow spray on or below seed during planting, chemigation	Gaicho <sup>®</sup> 550 SC [264-827]	0.38	1	0.38	NA	15	Use not permitted in CA
In-furrow spray on or below seed during planting, chemigation	Admire <sup>®</sup> 2 Flowable [3125-422]	0.38	1	0.38	NA	15	Use not permitted in CA

**Table 2.1 Summary of Proposed Directions for Use of Imidacloprid.**

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	RTI <sup>1</sup> (days)	PHI (days)	Use Directions and Limitations
<b>Millet</b>							
Seed treatment: commercial or at or immediately before planting	Gaicho <sup>®</sup> 480 [7501-155]	0.25/	1	0.25/ 100 lb seed	NA		Do not graze or feed livestock for 45 days after planting
Seed treatment: commercial or at or immediately before planting	Gaicho <sup>®</sup> 600 Flowable [7501-173]	0.25/ 100 lb seed	1	0.25/ 100 lb seed	NA		Do not graze or feed livestock for 45 days after planting
<b>Oat</b>							
Seed treatment: commercial or at or immediately before planting	Gaicho <sup>®</sup> 480 [7501-155]	0.03-0.09 /100 lb seed	1	0.09/100 lb seed	NA		Do not graze or feed livestock for 45 days after planting
Seed treatment: commercial or at or immediately before planting	Gaicho <sup>®</sup> 600 Flowable [7501-173]	0.03-0.09 /100 lb seed	1	0.09/100 lb seed	NA		Do not graze or feed livestock for 45 days after planting
<b>Vegetable, root and tuber, crop group 1, (except sugarbeets) plus Kava</b>							
Directed or broadcast foliar spray and chemigation	Provado <sup>®</sup> 70 WG [264-823]	0.044	1-3	0.044 (radish) 0.13 (all others)	5	7	Not for use on crops grown for seed. Use not permitted in CA
Spray band below seed row before planting, in-furrow during planting, chemigation	Gaicho <sup>®</sup> 600 SC [264-828]	0.25-0.38	1	0.38	NA	21	Spray band below seed row up to 14 days before planting. Not for use on crops grown for seed. Use not permitted in CA
Directed or broadcast foliar spray	Provado <sup>®</sup> 1.6 Flowable	0.044	1-3	0.044 (radish) 0.13 (all	5	7	Not for use on crops grown for seed. Use not permitted in CA

**Table 2.1 Summary of Proposed Directions for Use of Imidacloprid.**

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	RTI <sup>1</sup> (days)	PHI (days)	Use Directions and Limitations
and chemigation	[3125-457]			others)			
Spray band below seed row before planting, in-furrow during planting, chemigation	Gaicho <sup>®</sup> 550 SC [264-827]	0.16-0.38	1	0.38	NA	21	Spray band below seed row up to 14 days before planting. Not for use on crops grown for seed. Use not permitted in CA
Spray band below seed row before planting, in-furrow during planting, chemigation	Admire <sup>®</sup> 2 Flowable [3125-422]	0.16-0.38	1	0.38	NA	21	Spray band below seed row up to 14 days before planting. Not for use on crops grown for seed. Use not permitted in CA
<b>Globe Artichoke</b>							
Directed or broadcast foliar spray and chemigation	Provado <sup>®</sup> 70 WG [264-823]	0.05-0.13	4	0.5	14	7	
Spray band below seed row before planting, in-furrow during planting, chemigation	Gaicho <sup>®</sup> 600 SC [264-828]	0.25-0.5	1	0.5	NA	7	Use not permitted in CA
Directed or broadcast foliar spray and chemigation	Provado <sup>®</sup> 1.6 Flowable [3125-457]	0.04-0.125	4	0.5	14	7	
Spray band below seed row before planting, in-furrow during planting, chemigation	Gaicho <sup>®</sup> 550 SC [264-827]	0.25-0.5	1	0.5	NA	7	Spray band below seed row up to 14 days before planting. Not for use on crops grown for seed.
Spray band below seed	Admire <sup>®</sup> 2 Flowable	0.25-0.5	1	0.5	NA	7	Spray band below seed row up to 14 days

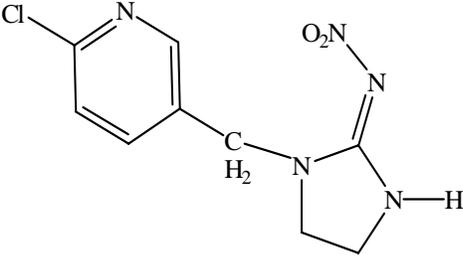
<b>Table 2.1 Summary of Proposed Directions for Use of Imidacloprid.</b>							
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	RTI <sup>1</sup> (days)	PHI (days)	Use Directions and Limitations
row before planting, in-furrow during planting, chemigation	[3125-422]						before planting. Not for use on crops grown for seed.
<b>Caneberries</b>							
Chemigation or basal soil drench.	Admire <sup>®</sup> 2 Flowable [3125-422]	0.25-0.5	1	0.5	NA	7	Do not apply pre-bloom or during bloom or when bees are actively foraging.
Chemigation or basal soil drench.	Gauche <sup>®</sup> 550 SC [264-827]	0.25-0.5	1	0.5	NA	7	Do not apply pre-bloom or during bloom or when bees are actively foraging.
Apply as directed or broadcast spray or chemigation	Provado <sup>®</sup> Pro [264-858]	0.1	1	0.3	7	3	Do not apply during bloom or when bees are actively foraging.
Apply as directed or broadcast spray or chemigation	Provado <sup>®</sup> 70 WG [264-823]	0.1	1	0.3	7	3	Do not apply during bloom or when bees are actively foraging.
Apply as directed or broadcast spray or chemigation	Provado <sup>®</sup> 1.6 Flowable [3125-457]	0.1	1	0.3	7	3	Do not apply pre-bloom or during bloom or when bees are actively foraging.
<b>Soybeans</b>							
Apply as directed or broadcast spray.	Encore <sup>™</sup> [264-783]	0.047	3	0.14	7	7	Do not apply through any type of irrigation system or in enclosed structures.
Apply as directed or broadcast spray.	Trimax <sup>™</sup> Pro [264-855]	0.047	3	0.14	7	7	Do not apply through any type of irrigation system or in enclosed structures.

<sup>1</sup> RTI = retreatment interval; PHI = preharvest interval.

The proposed use directions, including rotational crop restrictions, are all adequate.

## 2.2 Structure and Nomenclature

**Table 2.2 Test Compound Nomenclature.**

Chemical Structure	
Common Name	Imidacloprid
Company experimental name	BAY NTN 33893
IUPAC name	(EZ)-1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine
CAS name	1-[(6-chloro-3-pyridinyl)methyl]-N-nitro-2-imidazolidinimine
CAS #	138261-41-3
End-use products/(EP)	Provado® 1.6F (EPA Reg. No. 264-763) Provado® Pro (EPA Reg. No. 264-858) Admire® 2F (EPA Reg. No. 264-758) Gaucho® 550 SC (EPA Reg. No. 264-827) Gaucho® 600 SC (EPA Reg. No. 264-828) Provado® 70WG (EPA Reg. No. 264-823) Gaucho® 75 ST (EPA Reg. No. 264-959) Gaucho® 480 Flowable (EPA Reg. No. 264-957) Gaucho® 600 Flowable (EPA Reg. No. 264-968) Encore™ (EPA Reg. No. 264-783) Trimax™ Pro (EPA Reg. No. 264-855)

## 2.3 Physical and Chemical Properties

Parameter	Value	Reference
Melting point	144°C	The Pesticide Manual Twelfth Edition (2000)
pH	5 to 11	
Specific gravity	1.54 (@ 23°C)	
Water solubility (g/L at 20°C)	0.61	
Solvent solubility (g/L at 20°C)	Dichloromethane: 55, Isopropanol: 1.2, Toluene: 0.68, n-hexane: < 0.1	
Vapor pressure (mPa at 20°C)	4 x 10 <sup>-7</sup>	
Octanol/water partition coefficient [Log(K <sub>OW</sub> )]	0.57 (21°C)	
UV/visible absorption spectrum	Not provided.	

## 3.0 Hazard Characterization/Assessment

### 3.1 Hazard and Dose-Response Characterization

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 evidenced as changes in 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, and 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 in the chronic toxicity study. The rabbit appeared to be very sensitive as there was increased mortality in the oral 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. There was no evidence of carcinogenic potential in either the rat chronic toxicity/carcinogenicity or mouse carcinogenicity studies and no concern for mutagenicity. There was no evidence of increased qualitative or quantitative susceptibility of rats or rabbits to *in utero* exposure to imidacloprid and no evidence of qualitative or quantitative increased susceptibility of rat offspring in the reproduction 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.

On 11/10/93, 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.

### 3.1.1 Dose-response

*Acute Dietary Endpoint:* The rat acute neurotoxicity study was used to select the dose and endpoint for establishing the aPAD of 0.14 mg/kg/day for the general U.S. population. The LOAEL of 42 mg/kg was based upon the decrease in motor and locomotor activities observed in females. This aPAD is applicable to the general population, including infants and children, and is also protective of developmental effects which may occur in females of reproductive age. 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 300-fold uncertainty factor (3x UF<sub>L</sub>; and 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated in the aPAD. 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 mg/kg) is comparable to the LOAELs seen in adults in the developmental rat study (30 mg/kg/d) and the two-generation reproduction study [47/52 mg/kg/d (male/female)] and in the offspring in the DNT study (55 mg/kg/d); 2) the extrapolated NOAEL of 14 mg/kg ( $42/3 = 14$ ) is comparable to the NOAEL of 20 mg/kg/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. The FQPA SF of 1x is applicable for the acute dietary risk assessment. Thus, the aPAD is 0.14 mg/kg.

*Chronic Dietary Endpoint:* The rat combined chronic toxicity/carcinogenicity study was used to select the dose and endpoint for establishing the cPAD of 0.057 mg/kg/day for the general U.S. population. The NOAEL of 5.7 mg/kg/day was based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day. The mineralized particles are interpreted to be the result of imidacloprid selectively localizing in the thyroid colloid, resulting in increased clumping and basophilia of the colloid. The clumping may result in a decrease in the uptake of organic iodine which can cause a decrease in the production of thyroid hormones (T<sub>3</sub> and T<sub>4</sub>). In addition, this may result in a decrease in the ability of the follicular cells to phagocytize the colloid and release active thyroid hormones. These observations are the best available indicator of thyroid organ toxicity since T<sub>3</sub>, T<sub>4</sub> and TSH were not measured in the rat combined chronic toxicity/carcinogenicity study. A 100-fold uncertainty factor (10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated into the cPAD. The FQPA SF of 1x is applicable for the chronic dietary risk assessment. Thus, the cPAD is 0.057 mg/kg/day.

*Carcinogenicity:* The RfD/Peer Review Committee classified imidacloprid as a “Group E” (no evidence of carcinogenicity for humans) chemical based on adequate studies in two animal species; therefore, a cancer risk assessment is not required.

*Short-Term Incidental Oral Endpoint:* A short-term incidental oral endpoint was selected from the rat developmental toxicity study. The maternal NOAEL of 10 mg/kg/day was chosen based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day. This study and endpoint are appropriate for the population of concern (infants and children) and the route and duration of exposure.

*Intermediate-Term Incidental Oral Endpoint:* An intermediate-term incidental oral endpoint was selected from the rat subchronic neurotoxicity study. The NOAEL of 9.3 mg/kg/day was chosen based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day. This study and endpoint are appropriate for the population of concern (infants and children) and for the route and duration of exposure.

*Dermal Penetration:* Dermal Absorption Factor: 7.2% (this value was rounded to 7% for risk assessment purposes). No dermal absorption study was submitted. The rabbit dermal NOAEL is 1000 mg/kg/day with no systemic effects noted in the 28-day dermal toxicity study. In the developmental toxicity study, the rabbit maternal NOAEL/LOAEL (based on maternal deaths and decreased maternal absolute body weights, body weight gains, and food consumption) is 24/72 mg/kg/day. An upper-bound estimate of dermal absorption (7.2%) was calculated by comparing the maternal LOAEL from the rabbit developmental study (870.3700b) with the NOAEL from the rabbit dermal study (870.3250).

*Short-Term Dermal Endpoint:* A short-term dermal endpoint was selected from the rat developmental toxicity study. The maternal NOAEL of 10 mg/kg/day was chosen based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day. 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 and is at a comparable dose where neurotoxic signs were noted in the rat acute neurotoxicity study. A dermal absorption factor of 7% was applied for route-to-route extrapolation. This dose/endpoint is appropriate for short-term exposure risk assessment.

*Intermediate-term Dermal Endpoint:* An intermediate-term dermal endpoint was selected from the rat subchronic neurotoxicity study. The NOAEL of 9.3 mg/kg/day was chosen based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day. 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 and is at a comparable dose where neurotoxic signs were noted in the rat acute neurotoxicity study. A dermal absorption factor of 7% was applied for route-to-route extrapolation. This dose/endpoint is appropriate for intermediate-term exposure risk assessment.

*Long-term Dermal Endpoint:* A long-term dermal endpoint was selected from the rat combined chronic toxicity/carcinogenicity study. The NOAEL of 5.7 mg/kg/day was based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day. No long-term dermal study was submitted. A dermal absorption factor of 7% was applied for route-to-route extrapolation. This dose/endpoint is appropriate for long-term exposure risk assessment.

*Short-term Inhalation Endpoint:* A short-term inhalation endpoint was chosen from the rat developmental study. The maternal NOAEL of 10 mg/kg/day was chosen based upon decreased body weight gain and decreased corrected body weight gain at the LOAEL of 30 mg/kg/day. 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. This dose/endpoint is appropriate for short-term exposure risk assessment.

*Intermediate-term Inhalation Endpoint:* An intermediate-term inhalation endpoint was chosen from the rat subchronic neurotoxicity study. The NOAEL of 9.3 mg/kg/day was chosen based upon decreased body weight gain at the LOAEL of 63.3 mg/kg/day. This dose and endpoint are appropriate for the duration of exposure. The submitted 4-week 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. This dose/endpoint is appropriate for intermediate-term exposure risk assessment.

*Long-term Inhalation Endpoint:* A long-term inhalation endpoint was selected from the rat combined chronic toxicity/carcinogenicity study. The NOAEL of 5.7 mg/kg/day was based upon an increased incidence of mineralized particles in the thyroid colloid in males at the LOAEL of 16.9 mg/kg/day. No long-term inhalation study was submitted. An inhalation absorption factor of 100% should be applied. This dose/endpoint is appropriate for long-term exposure risk assessment.

*MOE for Occupational/Residential Risk Assessments:* A MOE of 100 is required for short-, intermediate-, and long-term occupational risk assessments for both dermal and inhalation routes of exposure. A MOE of 100 is required for residential risk assessments for all routes of exposure for any duration. For short-/intermediate-/long-term oral, dermal and inhalation exposures, the following route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 7% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs since all of the dermal and inhalation endpoints are based on oral equivalents.

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-term 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).

### **3.1.2 FQPA**

On 10/08/2002, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to imidacloprid according to the February 2002 OPP 10X guidance document. The HIARC concluded that the toxicology database was complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity (TXR NO. 0051292, D. Nixon, 10/31/02). Based on the hazard data, the HIARC recommended the FQPA SF be reduced to 1x. The imidacloprid risk assessment team evaluated the quality of the exposure data; and, based upon these data, recommended that the FQPA SF be reduced to 1x (DP Num: 286101, J. Tyler, 3/4/03).

## **3.2 Absorption, Distribution, Metabolism, Excretion (ADME)**

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-CNA 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-<sup>14</sup>C] imidacloprid and [imidazolidine-4,5-<sup>14</sup>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-<sup>14</sup>C] imidacloprid and WAK 3839 (a metabolite of imidacloprid), 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.

### **3.3 FQPA Considerations**

On 10/08/2002, the HED HIARC evaluated the potential for increased susceptibility of infants and children from exposure to imidacloprid according to the February 2002 OPP 10X guidance document. The HIARC concluded that the toxicology database was complete for FQPA purposes and that there are no residual uncertainties for pre-/post-natal toxicity (TXR NO. 0051292, D. Nixon, 10/31/02). Based on the hazard data, the HIARC recommended the FQPA SF be reduced to 1x. The imidacloprid risk assessment team evaluated the quality of the exposure data; and, based upon these data, recommended that the FQPA SF be reduced to 1x (DP Num: 286101, J. Tyler, 3/4/03).

The 300-fold UF (3x UF<sub>L</sub>; and 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated in the aPAD. 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 mg/kg) is comparable to the LOAELs seen in adults in the developmental rat study (30 mg/kg/d) and the two-generation reproduction study [47/52 mg/kg/d (male/female)] and in the offspring in the DNT study (55 mg/kg/d); 2) the extrapolated NOAEL of 14 mg/kg (42/3 = 14) is comparable to the NOAEL of 20 mg/kg/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 (DP Num: 286101, J. Tyler, 3/4/03).

### 3.3.1 Adequacy of the Toxicity Data Base

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

### 3.3.2 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

### 3.3.3 Developmental Toxicity Studies

#### 3.3.3.1 Rat

In a developmental toxicity study (MRID 42256338) NTN 33893 Technical (Imidacloprid; 94.2% ai, 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).

### 3.3.3.2 Rabbit

In a developmental toxicity study (MRID 42256339) NTN 33893 Technical (Imidacloprid; 95.3% ai, 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 1 fetus (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).

### 3.3.4 Reproductive Toxicity Study

In a 2-generation reproduction study (MRID 42256340) NTN 33893 Technical (Imidacloprid; 95.3% ai, 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<sub>0</sub> males, 0, 8.8, 22.1, or 62.8 mg/kg bw/day, respectively, for F<sub>0</sub> females, 0, 6.4, 16.5, or 47.3 mg/kg bw/day, respectively, for F<sub>1</sub> males, and 0, 7.2, 18.9, or 52.3 mg/kg bw/day, respectively, for F<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> males and females had decreased body weight gains during premating (10 and 12% less than controls, respectively), and F<sub>1</sub> 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<sub>1A</sub>, F<sub>1B</sub>, F<sub>2A</sub>, and F<sub>2B</sub> 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<sub>1</sub> 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 pre-mating weight gain by F<sub>0</sub> males and females and F<sub>1</sub> females and decreased gestational weight gain by F<sub>1</sub> 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<sub>1A</sub> pups on lactations days (LD) 7 and 21 (91 and 87% of controls, respectively); F<sub>1B</sub> pups on LD 21 (90% of controls); F<sub>2A</sub> pups on LD 21 (91% of controls); and F<sub>2B</sub> 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).

### **3.3.5 Additional Information from Literature Sources**

There was no additional relevant information from the published literature.

### **3.3.6 Pre-and/or Postnatal Toxicity**

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

#### **3.3.6.1 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.

### **3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility**

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.

### **3.3.7 Recommendation for a Developmental Neurotoxicity Study**

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

In a developmental neurotoxicity study (MRID 45537501), imidacloprid (98.2-98.4% ai, 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 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 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.

### **3.4 Safety Factor for Infants and Children**

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

HIARC recommended the FQPA SF 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.

#### **3.4.1 Adequacy of the Exposure Data Base**

The imidacloprid risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

The dietary food exposure assessment utilizes proposed tolerance level or higher residues and 100% CT information for all commodities. By using these screening-level assessments, exposures/risks will not be underestimated.

The dietary drinking water assessment (Tier 1 estimates) utilizes values generated by model and

associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

The residential exposure assessment utilizes: activity specific transfer coefficients and chemical-specific turf transferable residue (TTR) studies for the post-application scenario. The refined residential assessment is based on reliable data and is unlikely to underestimate exposure/risk.

### **3.4.2 Safety Factor Conclusion**

There is a complete toxicity database for imidacloprid and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. There is no evidence of susceptibility following *in utero* and/or postnatal exposure in the developmental toxicity studies in rats or rabbits, and in the 2-generation rat reproduction study. There are no residual uncertainties concerning pre- and postnatal toxicity and no neurotoxicity concerns. The assessments are based on reliable data and will not underestimate exposure/risk. Based on these data and conclusions, the FQPA SF can be reduced to 1X.

## **3.5 Hazard Identification and Toxicity Endpoint Selection**

### **3.5.1 Acute Population Adjusted Dose (aPAD) - 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% ai) 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 aPAD: 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.

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

### 3.5.2 Chronic Population Adjusted Dose (cPAD)

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% ai, 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% ai, 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 cPAD: 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.

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

### 3.5.3 Incidental Oral Exposure (Short- and Intermediate-Term)

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% ai, 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.

### 3.5.4 Dermal Absorption

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.

### 3.5.5 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.

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

### 3.5.6 Dermal Exposure

#### 3.5.7.1 Dermal 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.

#### 3.5.6.2 Dermal Intermediate-Term (1 - 6 Months) Exposure

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.

### **3.5.6.3 Dermal Long-Term (> 6 Months) Exposure**

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

MRID No.: 42256331

Executive Summary: See Chronic PAD

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.

## **3.5.7 Inhalation Exposure**

### **3.5.7.1 Inhalation 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: 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.

### **3.5.7.2 Inhalation Intermediate-Term (1- 6 Months) Exposure**

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.

### **3.5.7.3 Inhalation Long-Term (> 6 Months) Exposure**

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

MRID No.: 42256331

Executive Summary: See Chronic PAD

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.

### **3.5.8 Level of Concern for Margin of Exposure**

<b>Table 3.5.8 Summary of Levels of Concern for Risk Assessment.</b>			
<b>Route</b>	<b>Short-Term (1-30 Days)</b>	<b>Intermediate-Term (1 - 6 Months)</b>	<b>Long-Term (&gt; 6 Months)</b>
<b>Occupational (Worker) Exposure</b>			
<b>Dermal</b>	100	100	100
<b>Inhalation</b>	100	100	100
<b>Residential Exposure</b>			
<b>Dermal</b>	100	100	100
<b>Inhalation</b>	100	100	100

Oral	100	100	100
------	-----	-----	-----

### 3.5.9 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).

### 3.3.10 Classification of Carcinogenic Potential

#### 3.3.10.1 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.

#### 3.3.10.2 Carcinogenicity Study in Mice

MRID No. 42256335

Executive Summary: In a carcinogenicity study (MRID 42256335) NTN 33893 Technical (Imidacloprid; 95.0-95.3% ai, 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.

### 3.5.10.3 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).

### 3.5.11 Summary of Toxicological Doses and Endpoints for Imidacloprid for Use in Human Risk Assessments.

Table 3.5.11 Summary of Toxicological Dose and Endpoints for Imidacloprid for Use in Human Health Risk Assessment <sup>1</sup> .			
Exposure Scenario	Dose Used in Risk Assessment, UF	*FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>all populations</u>	LOAEL = 42 mg/kg/day UF = 300 <sup>2</sup> Acute PAD = 0.14 mg/kg	FQPA SF = 1X aPAD = $\frac{aPOD}{FQPA SF}$ = 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 <u>all populations</u>	NOAEL = 5.7 mg/kg/day UF = 100 Chronic PAD = 0.057 mg/kg/day	FQPA SF = 1X cPAD = $\frac{cPOD}{FQPA SF}$ = 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%) <sup>3</sup>	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%) <sup>3</sup>	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.

**Table 3.5.11 Summary of Toxicological Dose and Endpoints for Imidacloprid for Use in Human Health Risk Assessment<sup>1</sup>.**

<b>Exposure Scenario</b>	<b>Dose Used in Risk Assessment, UF</b>	<b>*FQPA SF and Level of Concern for Risk Assessment</b>	<b>Study and Toxicological Effects</b>
Long-Term Dermal (> 6 months)	oral study NOAEL = 5.7 mg/kg/day (dermal absorption rate = 7.2%) <sup>3</sup>	<b>LOC for MOE = 100</b> (Occupational) <b>LOC for MOE = 100</b> (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.
Short-Term Inhalation (1-30 days)	oral study NOAEL = 10 mg/kg/day (inhalation absorption rate = 100%)	<b>LOC for MOE = 100</b> (Occupational) <b>LOC for MOE = 100</b> (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%)	<b>LOC for MOE = 100</b> (Occupational) <b>LOC for MOE = 100</b> (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%)	<b>LOC for MOE = 100</b> (Occupational) <b>LOC for MOE = 100</b> (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)	no evidence of carcinogenicity for humans	Not applicable	No evidence of carcinogenicity in rats and mice.

<sup>1</sup> UF = uncertainty factor, NOAEL = no-observed adverse-effect level, LOAEL = lowest-observed adverse-effect level, PAD = population-adjusted dose (a = acute, c = chronic) POD = point of departure, MOE = margin of exposure, LOC = level of concern.

<sup>2</sup> A 300-fold uncertainty factor (3x UF<sub>L</sub>; and 10x for interspecies extrapolation and 10x for intraspecies variation) was incorporated in the aPOD. 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 mg/kg) is comparable to the LOAELs seen in adults in the developmental rat study (30 mg/kg/d) and the two-generation reproduction study [47/52 mg/kg/d (male/female)] and in the offspring in the DNT study (55 mg/kg/d); 2) the extrapolated NOAEL of 14 mg/kg (42/3 = 14) is comparable to the NOAEL of 20 mg/kg/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 (DP Num: 286101, J. Tyler, 3/4/03).

<sup>3</sup> A dermal absorption factor of 7% was used for risk assessment purposes.

### 3.6 Endocrine disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator

may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, imidacloprid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

#### **4.0 Public Health and Pesticide Epidemiology Data**

##### **4.1 Incident Reports**

According to OPPs Incident Data System there are a number of unconfirmed incidents regarding imidacloprid. The State of California sent a report in 1999 of 56 cases involving imidacloprid the majority of which involved pesticide mixtures. In only one case was imidacloprid considered the cause of the illness (a kennel worker splashed a drop in his eye which began burning and had a corneal abrasion) [Personal Communication from Dr. Jerome Blondell to J. Tyler (e-mail 10/31/02)].

#### **5.0 Dietary Exposure/Risk Characterization**

##### **5.1 Pesticide Metabolism and Environmental Degradation**

###### **5.1.1 Metabolism in Primary Crops and Livestock**

Data concerning the metabolism of imidacloprid in apples, potatoes, tomatoes, eggplant, cottonseed, field corn, tobacco, ruminants, and poultry have been submitted and reviewed in conjunction with PP#3F4169/3H5655 (DP Num: 185148, F. Griffith, 9/20/93; DP Num: 200233, F. Griffith, 6/8/94; and DP Num: 217632, F. Griffith, 2/29/96). The results of the aforementioned plant and livestock metabolism studies were presented to the HED Metabolism Assessment Review Committee (MARC) on 6/22/93 (F. Griffith, 6/18/93). The nature of imidacloprid residues in plants and livestock is adequately understood. The residue of concern in plants and livestock is imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, as specified in 40 CFR §180.472.

###### **5.1.2 Metabolism in Rotational Crops**

No rotational crop data were submitted in conjunction with the proposed uses. The nature of the imidacloprid residue in rotational crops has been adequately characterized and identified. The identified residue in rotational crops is nearly identical to that identified in the primary crops, and

the regulable residues in rotated crops are imidacloprid and its metabolites containing the 6-chloropyridinyl moiety. According to the proposed use labels, treated areas may be replanted with any crop specified on the labels or with any crop for which a tolerance exists for imidacloprid. However, a 12-month plant-back interval should be observed for crops not listed on the labels and for those crops for which no tolerances for imidacloprid have been established. Also, cover crops for soil building or erosion control may be planted any time, but do not graze or harvest for food or feed (PP# 6F4682 & 0E6106; DP Num: 224074 & 263729; MRID: 43939401, 43939402, & 45051401; Y. Donovan; 7/12/00).

### 5.1.3 Analytical Methodology

Adequate enforcement methods are available for determination of imidacloprid residues of concern in plant (Bayer GC/MS Method 00200) and livestock commodities (Bayer GC/MS Method 00191). These methods have undergone successful EPA petition method validations (PMVs), and the registrant has fulfilled the remaining requirements for additional raw data, method validation, independent laboratory validation (ILV), and an acceptable confirmatory method (high-performance liquid chromatography/ultraviolet (HPLC/UV) Method 00357) (DP Num: 187911, 6/18/93; DP Num: 202113, 6/1/94; DP Num: 200233, 6/8/94; DP Num: 213252, 6/8/95; and DP Num: 221591, 12/18/95; F. Griffith). The LOD and LOQ for the GC/MS Method 00200 are 0.01 and 0.05 ppm, respectively, in plant commodities.

Bayer GC/MS Method 00200 is a common moiety method that uses a 3:1 methanol/1% sulfuric acid extraction, filtering through Celite/filter paper, XAD-4 resin column clean-up, oxidation of parent and metabolites to 6-CNA by refluxing in a 32% sodium hydroxide (NaOH) solution combined with a 5% potassium permanganate (KMnO<sub>4</sub>) solution, extracted 3 times with methyl t-butyl ether, then N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSFTA) derivatization for 1 hour, and determination by capillary GC/MS selective ion monitoring at m/z 214, 216, 170, and 140.

Samples in the submitted peanut crop field trial and processing studies were for analyzed for combined residues of imidacloprid and its metabolites containing 6-chloropyridinyl moiety, all expressed as the parent, using a modification of Bayer GC/MS Method 00200. The LOD and LOQ were calculated as 0.03 ppm and 0.076 ppm for nutmeat; 0.01 ppm and 0.033 ppm, for oil; and 0.02 ppm and 0.062 ppm for meal.

For caneberries, total residues of imidacloprid (including the metabolites containing the 6-chloropicolyl moiety) were determined using working methods based on the gas chromatographic Bayer Method 00200 - Reformatted (Report Number 102624-R1) with GC/MS. In IR-4 PR No. 08257, minor modifications to the reference analytical method did not affect the validity of the method for the determination of total residues of imidacloprid in/on caneberries. The LLMV of the modified method in this study was reported as 0.05 ppm. LODs were estimated as 0.009 ppm, 0.02 ppm and 0.03 ppm for raspberry, marionberry and boysenberry, respectively. The method is valid for the determination of total imidacloprid residues in caneberries

Also in the caneberry Study No. AAFC03-085R, the method was modified to allow quantitation by HPLC/MS. The LLMV in this study was reported as 0.30 ppm. The LOD and LOQ were calculated to be 0.068 ppm and 0.203 ppm, respectively. Concurrent recoveries in raspberry samples ranged from 60.9% to 86.2% (n=6) when samples were fortified at the LLMV. Total residues of imidacloprid were determined to be below the LLMV (<0.30 ppm) and/or calculated LOQ (<0.203 ppm) at all PHIs. As the modified method used could not be validated at the target LOQ (0.05 ppm), the method LLMV was unacceptably high and the residues reported at each PHI were below the LLMV, this residue study is considered scientifically unacceptable. Therefore, the results from this study should not be used to support the registration of imidacloprid in/on caneberries.

The total imidacloprid residue (imidacloprid + *des* nitro imidacloprid + hydroxyl imidacloprid + olefin imidacloprid + 6-chloronicotinic acid) was analyzed in soybean samples by a common moiety method (oxidation to 6-chloronicotinic acid) and quantitated by using isotopically-labeled internal standards and LC-MS/MS. The method in this study, NT-001-P04-01, is based on an earlier method, 00834. The LOQ for imidacloprid in soybean forage, hay, and seed was 0.025 ppm, 0.100 ppm, and 0.05 ppm, respectively. The calculated LOD for soybean forage, hay, and seed were 0.0111 ppm, 0.0382 ppm, and 0.0136 ppm, respectively. The data from the soybean processing study support a method LOQ of 0.050 ppm for each analyte in soybean seed and processed commodities. The method is adequate for data collection purposes.

These data indicate that the GC/MS method, Bayer Method 00200, and HPLC/MS method, NT-001-P04-01, are adequate for determining residues of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, in/on the commodities associated with the proposed uses.

Bayer Corporation previously submitted adequate multiresidue method (MRM) recovery data for imidacloprid and the metabolites 5-hydroxy imidacloprid, imidacloprid olefin, *des* nitro imidacloprid and 6-CNA through Food and Drug Administration (FDA) Protocols A through E (DP Num: 187911, 6/18/93; DP Num: 193027, 7/15/93; DP Num: 200233, 6/8/94; and 194206, 6/22/94; F. Griffith). Imidacloprid and its metabolites were not recoverable by these methods. The results of the MRM testing for imidacloprid were forwarded to FDA for inclusion in the Pesticide Analytical Method Volume I (PAM I) (DP Num: 193005, F. Griffith, 7/15/93).

#### **5.1.4 Environmental Degradation**

In a meeting on 12/18/02, the HED MARC recommended that for surface water risk assessment, degradates of concern should be parent and the three degradates: imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin (DP Num: 28740, J. Tyler, 1/13/03).

#### **5.1.5 Comparative Metabolic Profile**

In a rat metabolism study, 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 two major evident routes of biotransformation. The first included an oxidative cleavage of the parent compound to give 6-CNA and its glycine conjugate.

Dechlorination of this metabolite formed the 6-CNA 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-<sup>14</sup>C] imidacloprid and [imidazolidine-4,5-<sup>14</sup>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).

Imidacloprid is metabolized in plants by three pathways as follows: 1) hydroxylation of the dihydroimidazole ring of imidacloprid to form the 4-hydroxy, 5-hydroxy, and dihydroxy imidacloprid followed by the loss of water to form the olefin; 2) reduction and loss of the nitro group on the dihydroimidazole ring to form the nitrosimino imidacloprid, then the guanidine imidacloprid, and finally the urea imidacloprid; and 3) bridge cleavage of the C-N bond to form the 6-chloropicolyl alcohol (6-CPA) which rapidly forms the glucoside and the 6-CNA, and dihydroimidazole. All residues are determined as 6-CNA, then converted to imidacloprid equivalents.

Imidacloprid is metabolized in ruminants by 3 pathways as follows: 1) hydroxylation of the dihydroimidazole ring of imidacloprid to form 4-hydroxy, 5-hydroxy, plus the glucuronide conjugates of each monohydroxy metabolite, and the dihydroxy imidacloprid followed by the loss of water to form the olefin imidacloprid; 2) reduction and loss of the nitro group on the dihydroimidazole ring to form aminoguanidine imidacloprid, then the guanidine imidacloprid and finally the urea imidacloprid; and 3) opening of the dihydroimidazole ring with loss of the ethyl group and subsequent oxidation. The first step is forming the nitroguanidine imidacloprid, next the ring open guanidine which can also form both the guanidine imidacloprid and the dihydroxy guanidine imidacloprid. This metabolite can form picolylic urea, and picolylic amine which is oxidized to 6-CNA which then can conjugate with glycine. The identified residues in ruminants are imidacloprid and its metabolites that contain the 6-chloropyridinyl moiety. All residues are determined as 6-CNA, then converted to imidacloprid equivalents.

Imidacloprid is metabolized in poultry by 3 pathways as follows: 1) hydroxylation of the dihydroimidazole ring of imidacloprid to form 4-hydroxy, 5-hydroxy and the dihydroxy imidacloprid followed by loss of water to form the olefin; 2) reduction and loss of the nitro group on the dihydroimidazole ring to form the dihydroxyguanidine imidacloprid; and 3) opening of the dihydroimidazole ring with the loss of the ethyl group and subsequent oxidation. The first step is forming the nitroguanidine imidacloprid, next the ring open guanidine imidacloprid which can also form from both the dihydroxy guanidine imidacloprid and the guanidine imidacloprid. This metabolite can form picolylic amine which is oxidized to 6-CNA. The identified residues in poultry are imidacloprid and its metabolites which contain the 6-chloropyridinyl moiety. All residues are determined as 6-CNA, then converted to imidacloprid equivalents.

#### **5.1.6 Toxicity Profile of Major Metabolites and Degradates**

Little information is available on the toxicity of the major imidacloprid metabolites. The 6-CNA metabolite formed in plants and animals appears to be also formed in the rat, and is, therefore, part of the total toxic exposure for these animals. It is unlikely to be more toxic than the parent

### 5.1.7 Pesticide Metabolites and Degradates of Concern

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Imidacloprid and its metabolites containing the 6-chloropyridinyl moiety	Imidacloprid and its metabolites containing the 6-chloropyridinyl moiety
	Rotational Crop		
Livestock	Ruminant		
	Poultry		
Drinking Water		Imidacloprid and degradates: imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin	Not Applicable

The structures of imidacloprid metabolites can be seen in Attachment 2.

### 5.1.8 Drinking Water Residue Profile

In a meeting on 12/18/02, the HED MARC recommended that for surface water risk assessment, degradates of concern should be parent and the three degradates: imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin (DP Num: 28740, J. Tyler, 1/13/03). EFED provided revised, Tier 1 EDWCs for surface water (using FIRST) for imidacloprid and its degradates (imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin) for the proposed uses only. Revised ground water EDWCs were not estimated because these values have been shown previously to be substantially lower in magnitude than the surface water concentrations. The revised surface water EDWCs for the proposed uses do not exceed the EDWCs provided by EFED in conjunction with the 3/14/03 HED risk assessment for imidacloprid (DP Num: 271770, M. Barrett, 2/25/03). Therefore, the overall highest surface and ground water EDWCs were used in the current risk assessment (DP Num: 311925, R. Parker, 5/16/06).

Chemical	Surface Water (µg/L)		Groundwater (µg/L)
	Acute	Chronic	Acute and Chronic
<b>Revised EDWCs<sup>1</sup></b>			
Imidacloprid total residues <sup>2</sup>	Tree nuts – 35.9	Tree nuts and coffee – 15.3	Not provided.
<b>Previously-calculated EDWCs<sup>3</sup></b>			
Imidacloprid total residues <sup>2</sup>	Citrus – <b>36.0</b>	Citrus – 17.2	2.09

1. Memo, R. Parker, 5/16/06; DP# 311925.

2. Imidacloprid and its degradates (imidacloprid urea, imidacloprid guanidine, and imidacloprid olefin).

3. Memo, M. Barrett, 2/25/03; DP# 271770.

### 5.1.9 Food Residue Profile

IR-4, on behalf of the Agricultural Experiment Stations of Texas, Missouri, Georgia, Wisconsin,

and Hawaii, has submitted a petition for the use of imidacloprid on peanuts; proso and pearl millet; oats; kava; globe artichoke; caneberry, subgroup 13A; and wild raspberry. IR-4 is not requesting a change in the existing tolerance for globe artichokes; the request is for the addition of a soil use to the existing foliar use. Bayer Corp. has also submitted a petition for the use of imidacloprid on soybeans. Imidacloprid (1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine) is an insecticide registered for uses on a variety of crops for the control of aphids, cucumber beetles and whiteflies (including sweet potato or silverleaf whitefly).

In conjunction with these petitions, tolerances have been requested for the combined residues of the insecticide imidacloprid (1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine) and its metabolites containing the 6-chloropyridinyl moiety, all expressed as 1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine.

The petitioners have submitted sample labels for numerous imidacloprid products. The uses on peanuts and kava include both an in-furrow spray on or below seed during or before planting and a foliar use. The peanut and kava seed use is for a single application at 0.38 pounds active ingredient per acre (lb ai/A). The foliar uses on peanut and kava are for up to 3 applications for a total 0.13 lb ai/A with PHIs of 14 days for peanut and 7 days for kava. The uses on millet and oats include commercial seed treatment or below seed during or before planting at 0.25 or 0.09 lb ai/100lb seed, respectively. The use on globe artichoke includes both an in-furrow spray on or below seed during or before planting at and a foliar use, both at 0.5 lb ai/A with a 7-day PHI. These use directions are adequate.

The labels for caneberries indicate either a foliar application at 0.3 lb ai/A with a 3-day PHI or a drench application 0.5 lb ai/A with a 7-day PHI. Since the previous lower tolerance for caneberries was based using the drench application at the higher rate, the use is supported may remain on the labels.

There is an existing use of imidacloprid on soybean seeds for protection from damage caused by seed corn maggot, to reduce feeding damage caused by soybean aphids and over-wintering bean leaf beetles, and to help suppress the spread of certain viruses, at 2.0-4.0 fl. oz. per hundredweight of seed. The requested foliar use on soybeans is in addition to the current use on soybean seeds for three applications at 0.047 lb ai/A with a maximum total application of 0.14 lb ai/A. These use directions are adequate.

The nature of imidacloprid residues in plants and livestock is adequately understood. The residue of concern in plants and livestock is imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent.

Adequate enforcement methods are available for determination of imidacloprid residues of concern in plant (Bayer GC/MS Method 00200) and livestock commodities (Bayer GC/MS Method 00191). These methods have undergone successful EPA PMVs. Bayer GC/MS Method 00200 is a common moiety method that uses oxidation of parent and metabolites to 6-CNA with demonstrated LOD and LOQ at 0.01 and 0.05 ppm, respectively, in plant commodities. Previously submitted MRM recovery data for imidacloprid and the metabolites 5-hydroxy imidacloprid, imidacloprid olefin, des nitro imidacloprid and 6-CNA indicate that these residues were not recoverable by these methods.

Samples in the submitted peanut crop field trial and processing studies were for analyzed for combined residues of imidacloprid and its metabolites containing 6-chloropyridinyl moiety, all expressed as the parent, using a modification of Bayer GC/MS Method 00200. The LOD and LOQ were calculated as 0.03 ppm and 0.076 ppm for nutmeat; 0.01 ppm and 0.033 ppm, for oil; and 0.02 ppm and 0.062 ppm for meal.

For caneberries, total residues of imidacloprid were determined using a working method based on Bayer Method 00200. The LLMV of the modified method in this study was reported as 0.05 ppm. LODs were estimated as 0.009 ppm, 0.02 ppm and 0.03 ppm for raspberry, marionberry and boysenberry, respectively. Another analytical method was used in the caneberry trial designated as Study No. AAFC03-085R. The method used quantitation by high performance liquid chromatography with mass spectroscopy detector (HPLC/MS). The LLMV in this study was reported as 0.30 ppm. The LOD and LOQ were calculated to be 0.068 ppm and 0.203 ppm, respectively. However, total residues of imidacloprid were determined to be below the LLMV (<0.30 ppm) and/or calculated LOQ (<0.203 ppm) at all PHIs. As the method used could not be validated at the target LOQ (0.05 ppm), the method LLMV was unacceptably high and the residues reported at each PHI were below the LLMV, this residue study is considered scientifically unacceptable. Therefore, the results from this trial should not be used to support the registration of imidacloprid in/on caneberries.

The total imidacloprid residue was analyzed in soybean field trial and processing samples by a common moiety method (oxidation to 6-CNA) and quantitated by LC-MS/MS. The method in these studies, NT-001-P04-01, is based on an earlier method, 00834. The LOQ for imidacloprid in soybean forage, hay, and seed was 0.025 ppm, 0.100 ppm, and 0.05 ppm, respectively. The calculated LODs for soybean forage, hay, and seed were 0.0111 ppm, 0.0382 ppm, and 0.0136 ppm, respectively. The data from the soybean processing study support a method LOQ of 0.050 ppm for each analyte in soybean seed and processed commodities. The method is adequate for data collection purposes.

Residues of imidacloprid have previously been shown to be stable in a variety of RACs for up to 2 years. In addition, analysis of samples from the <sup>14</sup>C-imidacloprid plant metabolism studies for corn, cotton, apples, and potatoes showed no loss of imidacloprid and its major metabolites during a period of 2 years of frozen storage. The maximum storage interval for field-treated samples in the peanut studies was approximately 4 years (1489 days for nutmeat, 1506 days for oil, 1662 days for hay, and 1534 days for meal). Storage stability testing performed after approximately 4.4 years of frozen storage (1600 days for both nutmeat and oil, 1609 days for hay, and 1595 days for meal) showed no appreciable degradation. Caneberries were stored

frozen for up to 87 days. Concurrent storage stability studies with marionberries indicated that residues were stable when frozen for up to 75 days. The soybean field trial samples analyzed in this study were held in frozen storage for a maximum of 15 months (450 days) prior to extraction. Soybean aspirated grain fractions and the processed commodities of soybean seed were analyzed within 3.1 months (95 days) of production.

The expected residue levels in the livestock feed items associated with the subject petition were used to recalculate the MTDB for livestock. The newly calculated MTDBs are not greater than those calculated previously. Therefore, the proposed uses will not require an increase in livestock tolerances.

Twelve peanut field trials were conducted using a single in-furrow applications at a rate of approximately 0.375 lb ai/A at planting followed by foliar applications made 4 to 6 days apart at a rate of approximately 0.044 lb ai/A for a total of approximately 0.507 lb ai/A. In addition to peanuts and hay harvested 13 to 15 days PHI, each commodity was harvested at 21 and 28 days at the 98-TX17 trial for decline determination. The results from the trials show that the maximum combined residues in nutmeat were 0.40 ppm. Maximum residues in 14-day and 28-day hay samples were 24 ppm. Residues declined in nutmeat to a maximum of 0.14 ppm by 28 days. The submitted studies are adequate in number and geographic diversity and are supported by adequate storage stability data and analytical methodology. However, the residue data as analyzed by the Tolerance/MRL Harmonization Spreadsheet indicates that the requested tolerances on peanut nutmeat and hay are not appropriate. A new Section F requesting imidacloprid tolerances on peanuts at 0.60 ppm and peanut, hay at 35 ppm is required.

No crop-specific data to support the tolerance requests in conjunction with the requested uses for proso millet, pearl millet, and oats. There are existing tolerances for residues of imidacloprid on barley, grain; corn, field, grain; corn, pop, grain; corn, sweet, kernel plus cob with husks removed; oats, grain; rye, grain; sorghum, grain; and wheat, grain all at 0.05 ppm. In addition, there is a tolerance for indirect or inadvertent combined residues of imidacloprid on grain, cereal, group 15 also at 0.05 ppm. Since there are identical seed treatment uses with tolerances for most of the cereal grain crop group and a tolerance for indirect or inadvertent residues on the cereal grain crop group, tolerances can be translated to the seed treatment uses on proso millet and pearl millet. ARIA recommends for the proposed tolerances on proso and pearl millet grain at 0.05 ppm. In addition, residues would be expected on the other millet RACs as residues are found on other grain RACs from the same uses. A revised Section F is required for proso millet, forage at 2.0 ppm; proso millet, hay at 6.0 ppm; proso millet, straw at 3.0 ppm; pearl millet, forage at 2.0 ppm; pearl millet, hay at 6.0 ppm; and pearl millet, straw at 3.0 ppm.

As noted above, there are already existing tolerances for the seed treatment use on oats: oats, grain at 0.05 ppm; oats, forage at 2.0 ppm; oats, hay at 6.0 ppm; oats, straw at 3.0 ppm as a result of the same proposed seed treatment use as proposed here. The request for use and tolerance for imidacloprid on oats is not necessary; the requested tolerances should be removed from Section F.

No crop-specific data were submitted to support the tolerance requests in conjunction with the requested use for kava. Since kava is projected to be part of the root and tuber vegetable crop

group 1 in the near future and the proposed use is identical to that used for root and tuber vegetables, ARIA recommends for the proposed imidacloprid tolerances on kava, leaves at 4.0 ppm and kava, roots at 0.40 ppm.

No new crop-specific data to support the tolerance requests in conjunction with the requested use on globe artichoke. A tolerance of 2.5 ppm has already been established for imidacloprid on globe artichokes as a result of a foliar use. IR-4 is now requesting a use either below the seed row before planting, in-furrow during planting, or by chemigation into the root zone. Comparisons of data on foliar vs. limited soil-applied imidacloprid or the two treatments combined indicate that the foliar treatments clearly drive the magnitude of the resulting residues. Any slight additional residues from soil treatments are expected to be covered by existing tolerances established to reflect foliar application. Therefore, it is unlikely that the residues of imidacloprid from the proposed soil treatment use on globe artichoke will exceed the existing 2.5 ppm tolerance. ARIA recommends for the proposed imidacloprid use on globe artichoke without a change in the existing tolerance.

A previous petition for the use of imidacloprid on caneberries as drench application 0.5 lb ai/A with a 7-day PHI resulted in a conditional registration and permanent tolerance at 0.05 ppm. The registration was conditional until the submission of additional crop field trial data. Residue data have now been submitted. A total of ten trials were conducted in the U.S. and Canada. Imidacloprid was applied to caneberries in three foliar-directed broadcast sprays at a rate of 0.10 to 0.11 lb ai/A/application at 6 to 11-day retreatment intervals (RTIs) for total application rates of 0.30 to 0.31 lb ai/A. Crops were harvested 2-4 days after the last application (DALA). The maximum residues observed in caneberries were 0.70 ppm in blackberry, 0.96 ppm in raspberry, 1.7 ppm in marionberry and 1.5 ppm in boysenberry. The residue data as analyzed by the Tolerance/MRL Harmonization Spreadsheet indicates that the requested tolerance on caneberries, crop group 13A at 2.5 ppm is not appropriate. The commodities blackberry, marionberry, and boysenberry are considered cultivars of blackberries while raspberries are separate. The Tolerance/MRL Harmonization Spreadsheet indicates appropriate tolerance levels of 3.5 ppm and 1.3 ppm for blackberries and raspberries, respectively. However, since the databases are small for blackberries and raspberries, the fruits are essentially the same size and texture, and in the interest of harmonizing with Canada, ARIA will consider the entire database for caneberries together. The Tolerance/MRL Harmonization Spreadsheet indicates the appropriate tolerance level for the entire database of caneberry residues should be 2.5 ppm. Therefore, ARIA recommends for the proposed tolerance for caneberry, subgroup 13A at 2.5 ppm.

The petitioner has requested a tolerance for wild raspberry. The crop definition for caneberry, crop group 13A indicates that no separate tolerance is required for wild raspberry and it should be removed from the Section F.

Bayer Corp. submitted a total of 21 crop residue field trials on soybeans. The trials were conducted to measure the magnitude of residues in soybeans resulting from the existing pre-plant seed treatment followed by three foliar applications of imidacloprid to the growing soybean plants. The soybean seeds were treated at a nominal rate of 0.125 lb ai/100 lb seed prior to planting. The growing soybean plants were subsequently treated with three foliar broadcast

applications of imidacloprid at a target rate of 0.047 lb ai/A. Total imidacloprid application rates (seed + foliar) ranged from 0.201 to 0.275 lb ai/A. The highest imidacloprid residue on soybean forage and hay at 0-day PHI was 8.87 ppm and 24.0 ppm, respectively. The highest imidacloprid residue on soybean seed at a 21-day PHI was 2.04 ppm. The total imidacloprid residue was found to decline significantly on soybean forage with time. In soybean hay, total imidacloprid residue was found to decline significantly at one trial but remained relatively constant at the other. On soybean seed, total imidacloprid residue remained constant with time. The residue data as analyzed by the Tolerance/MRL Harmonization Spreadsheet indicates that the requested tolerance on soybean, forage is appropriate at 8.0 ppm. However, the requested tolerance levels on the other soybean commodities are not appropriate. A new Section F requesting imidacloprid tolerances on soybean, seed at 3.5 ppm, and soybean, hay at 35 ppm is required.

There are many processed commodities of regulatory interest associated with these petitions among which are millet flour, oat flour, and rolled oats. It has been determined that imidacloprid residues do not concentrate in grain processed commodities; therefore, no imidacloprid tolerances are required on millet and oat processed commodities.

The submitted peanut processing study indicates that imidacloprid residues do not concentrate in peanut oil. Therefore, a separate tolerance for imidacloprid residues in peanut oil is not required. The average of the two processing studies indicates that imidacloprid residues will concentrate at 2.5X in peanut meal  $((1.9+3.1)/2)$ . However, this is higher than the theoretical maximum of 2.2X. The HAFT of 0.32 ppm times the theoretical maximum of 2.2X yields an expected residue of 0.704 ppm in peanut meal. Therefore, the requested tolerance for imidacloprid residues in peanut meal at 0.9 ppm is not appropriate. ARIA recommends for the establishment of an imidacloprid tolerance on peanut, meal at 0.75 ppm. A revised Section F requesting an imidacloprid tolerance on peanut, meal at 0.75 ppm is required.

The submitted processing study indicates that imidacloprid residues do not concentrate in soybean meal, hulls, or oil. Therefore, a separate tolerance for imidacloprid residues in soybean meal, hulls, or oil is not required. The processing study indicates that imidacloprid residues will concentrate at 160X in aspirated grain fractions. The HAFT of 1.50 ppm for soybean seed at the proposed application rate and PHI times the empirical concentration value of 160X yields an expected residue of 240 ppm in aspirated grain fractions. The requested tolerance for imidacloprid residues in aspirated grain fractions is appropriate. However, the Agency does not differentiate soybean from other aspirated grain fractions; therefore, a revised Section F for aspirated grain fractions at 240 ppm is required.

#### **5.1.10 International Residue Limits**

There are no established Canadian or Mexican MRLs for the proposed uses. There is an established Codex MRLs for the sum of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, expressed as imidacloprid, in/on cereal grain at 0.05 ppm. Therefore, there are no harmonization issues for these petitions.

## **5.2 Dietary Exposure and Risk**

Acute Dietary Exposure Results and Characterization: An unrefined, acute dietary exposure assessment using tolerance-level residues and assuming 100 %CT for all registered and proposed commodities was conducted for the general U.S. population and various population subgroups. Exposure to drinking water was incorporated directly in the dietary assessment using the acute (peak) concentration for surface water generated by the FIRST model. This assessment indicates that the acute dietary exposure estimates are below HED’s level of concern, <100% aPAD, at the 95<sup>th</sup> exposure percentile for the general U.S. population and all other population subgroups. The acute dietary exposure is estimated for the U.S. population at 28% of the aPAD and the most highly exposed population subgroup, children 1-2 years old, at 70% of the aPAD.

Chronic Dietary Exposure Results and Characterization: A partially refined, chronic dietary exposure assessment (using tolerance-level residues for all registered and proposed commodities, and %CT information for some commodities) was conducted for the general U.S. population and various population subgroups. Exposure to drinking water was incorporated directly into the dietary assessment using the chronic (annual average) concentration for surface water generated by the FIRST model. This assessment concludes that the chronic dietary exposure estimates are below HED’s level of concern (<100% cPAD) for the general U.S. population and all population subgroups. The chronic dietary exposure is estimated for the U.S. population at 13% of the cPAD and the most highly exposed population subgroup, children 1-2 years old, at 38% of the cPAD.

Population Subgroup	Acute Dietary <sup>1</sup> (95 <sup>th</sup> Percentile)		Chronic Dietary <sup>2</sup>	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.038804	28	0.007485	13
All Infants (< 1 year old)	0.078749	56	0.016051	28
Children 1-2 years old	<b>0.097651</b>	<b>70</b>	<b>0.021658</b>	<b>38</b>
Children 3-5 years old	0.072627	52	0.016268	29
Children 6-12 years old	0.046044	33	0.010035	18
Youth 13-19 years old	0.029223	21	0.005964	11
Adults 20-49 years old	0.026397	19	0.005883	10
Adults 50+ years old	0.025483	18	0.006008	11
Females 13-49 years old	0.026228	19	0.005647	10

1. aPAD of 0.14 mg/kg/day applies to the general U.S. population and all population subgroups.  
2. cPAD of 0.057 mg/kg/day applies to the general U.S. population and all population subgroups.

### 5.3 Anticipated Residue and Percent Crop Treated Information

No anticipated residue information was used in the dietary exposure assessments. The %CT information used in the chronic assessment is presented in Table 5.3

Crop	Pounds of Active Ingredient	Percent of Crop Treated	Maximum Percent of Crop Treated
Apples	10,000	30	45
Artichokes	<500	5	15
Beans, Green	2,000	5	10
Beets (NCFAP '97)	<500	15	-
Blueberries	<500	10	15
Broccoli	9,000	35	55
Brussels Sprouts *	<500	55	60
Cabbage	3,000	20	25
Cantaloupes	8,000	30	50
Carrots	<500	<1	<2.5
Cauliflower	4,000	40	60
Celery	1,000	5	15
Cherries	<500	5	7
Chicory *	<500	-	-
Collards	<500	10	15
Corn	100,000	<1	<2.5
Cotton	30,000	5	10
Cucumbers	1,000	5	7
Eggplant	<500	45	50
Grapefruit	2,000	5	10
Grapes	20,000	30	35
Greens, Turnip	<500	10	15
Honeydew	1,000	10	15
Hops (NCFAP '97)	4,000	90	-
Kale	<500	30	35
Lemons	1,000	<1	5
Lettuce	40,000	60	80
Nectarines *	<500	-	-
Olives *	<500	-	-
Onions	1,000	<1	<2.5
Oranges	10,000	5	10
Parsley (NCFAP '97)	<500	35	-
Peaches	<500	5	25
Pears	2,000	10	20
Pecans	9,000	10	15
Peppers	9,000	25	35
Potatoes	60,000	35	40
Pumpkins	1,000	5	15
Sod (NCFAP '97)	<500	5	-
Spinach	1,000	20	30
Squash	2,000	10	25
Strawberries	2,000	10	15
Sugar Beets	<500	<1	<2.5
Sweet Corn	<500	<1	<2.5
Tangerines	<500	10	15

Tobacco	10,000	20	25
Tomatoes	20,000	15	35
Walnuts	<500	<1	<2.5
Watermelons	4,000	10	10

<sup>1</sup> Checking our available usage databases, we found no usage data for the following crops: dairy cattle for milk, limes, mustard greens, wheat, soybeans, apricots, plums, dry beans, snap beans, and processed and green peas. For your calculations, you may use <1%, for each crop, for both typical average and likely maximum (DP Num: 311925, R. Parker, 5/16/06).

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

### 6.1 Residential Handler Exposure

Imidacloprid is registered for use on residential ornamental lawns and turf as well as for use on golf courses. It is registered for use on ornamental plantings (*i.e.*, flowering plants, foliage plants, herbaceous perennial plants, and woody plant, shrubs and trees). It is registered for indoor as well as outdoor residential uses. It is registered as a pre- and post-construction termiticide.

The Office of Pesticide Programs' Reference Files System (REFS) (7 MAY 02) indicates that there are 82 registered products (excluding Section 18 registrations) that contain imidacloprid. With the use of the Pesticide Product Label System (PPLS), HED determined the use patterns of each product in terms of pesticide handlers. HED believes that residential pesticide handlers (*i.e.*, persons who might mix, load, and/or apply a pesticide material) could be exposed to several formulations that contain imidacloprid. See Table 6.1 for a summary of residential handler use patterns. HED expects that residential handlers will be exposed to short-term (*i.e.*, 1-30 days) exposures based upon the pest spectra, sites of application, methods of application, formulations and the RTI intervals, if applicable.

Site	Formulation	Application Rate	Number of Applications	Comments
Lawns & Turf Ornamental Plantings	Granular 0.62 %	0.4 lb ai/A	1/yr	applied with broadcast by push-type "drop" or rotary spreader
flowers, ground covers shrubs, house plants	Ready-to Use Pump Sprayer 0.012 % 24 fl.oz.	"spray till point of run-off"	"as needed" 7 - 14 day intervals	
Indoor & Outdoor Residential Potted Plants	Plant "spikes" 0.8 oz (20 g) 10 two gram spikes 2.5 %	one package will treat 4-5 eight inch pots	efficacious for 8 weeks	formulation contains fertilizer and Bitrex. Not for use on edible plants/herbs etc.
Potting medium for indoor or	0.015 % ready to use potting		efficacious 4 months	Used as medium for new seedlings or as additional

<b>Table 6.1 Summary of Residential “Handler” Use Patterns</b>				
<b>Site</b>	<b>Formulation</b>	<b>Application Rate</b>	<b>Number of Applications</b>	<b>Comments</b>
outdoor plant containers	medium - largest container 19 lb 3 oz			medium when transplanting to larger containers. Label directs use of rubber gloves. Medium contains sphagnum, bark, perlite, vermiculite, limestone and fertilizers
Lawns, trees, shrubs, flowers	liquid concentrate 0.70 % 32 fl oz	0.001098 lb ai/5000 ft <sup>2</sup>	“repeat if needed” in 7 - 14 days	For use on out-door, non-food residential plants Assumed applied via compressed air or garden hose-end sprayer
Trees & Shrubs	liquid concentrate 2.95 % one gallon = largest container size	depends on plant stem size. One gallon treats 20 “medium” trees or 42 “average” shrubs	1/yr	Applied to soil by pouring dilute from a bucket or a watering can around bases of plant “stems”/trunks
Cats & Dogs	ready to use liquid 9.1 %, max = 5 ml for large dogs > 55 lb	max rate = 5.0 ml for dogs > 55 lb	1/mo if needed	Packaged in “dropper” vials. The end cap is removed and one half the contents dropped between the scapulae and one half on the lumbrosacral region. No rubbing or other contact is directed.

There are numerous granular products that contain imidacloprid alone or with some combination of lawn/garden fertilizer. An example is Merit<sup>®</sup> 0.62 G Insecticide (EPA Reg No 3125-416) which contains 0.62 % imidacloprid. The maximum rate of application for these products is 0.4 lb ai/A.

There are one or two Ready-To-Use products that contain imidacloprid alone or in combination with another active. Merit<sup>®</sup> RTU (EPA Reg No 3125-501) is the single active product and contains 24 fluid ounces of product of which 0.012% is imidacloprid.

Another formulation that might be handled by a residential handler is potted plant spikes that contain 2.5 % imidacloprid. A product is Merit<sup>®</sup> 2.5 PR (EPA Reg No 3125-531).

There is a potting medium mixture for use with indoor or outdoor potted plants. Merit<sup>®</sup> PM plus fertilizer (EPA Reg No 3125-532) is an example and contains 0.015 % imidacloprid.

Imidacloprid is formulated alone or in combination with other actives as a concentrate for dilution and use in either pump sprayers or garden hose-end sprayers. Merit® + Tempo concentrate (EPA Reg No 3125-505) is a product that contains 2.94 % imidacloprid.

Merit® 2.94 TLC (EPA Reg No3125-554) is designed to be used as a soil drench application using a bucket or watering can to pour the diluted product around trees or shrubs. It also contains 2.94 % active ingredient.

And finally, residential handlers may be exposed to imidacloprid via the use of one of the Advantage® products such as Advantage® 110 (EPA Reg. No 11556-121) which are spot-on treatments for dogs or cats for flea control.

The various types of products intended for residential use (*i.e.*, application) as discussed above, are intended for control of different pests. Therefore, HED believes that it is highly unlikely that a residential handler would be concurrently exposed to more than one formulation containing imidacloprid at any given time (*i.e.*, apply a granular, then apply a topical flea control product, then apply a RTU product).

There are numerous products such as gel baits for cockroach control, numerous products intended for commercial ornamental, lawn and turf pest control, commercially applied products for ant control, products used as preservatives for wood products, building materials, textiles and plastics. All of these types of products are intended for use by commercial applicators of one type or other; and, therefore, will not be addressed in terms of residential pesticide handler.

There are termiticide products. Since termiticide applications are done by professional applicators, residential “handler” assessment is not necessary. Further, since the pre and post-construction use as a termiticide is subsoil and since the vapor pressure of imidacloprid is  $1.5 \times 10^{-9}$  mm Hg at 20°C, HED believes there is no residential post-application inhalation exposure.

### 6.1.1 Resident-applicator Granular Push-type Spreader

The resident-applicator using push-type spreader to apply granules is assessed using HED’s SOPs for Residential Exposure Assessments (81 DEC 97) in conjunction with unit exposures developed by the Outdoor Residential Exposure Task Force (ORETF) and cited as HED Science Advisory Council for Exposure (ExpoSAC) policy in a memorandum by G. Bangs (Memo, G. Bangs, MRID 449722-01, 30 APRIL 01). The dermal unit exposure for an applicator wearing short pants and short-sleeved shirt plus shoes and socks = 0.68 mg ai/lb handled. The inhalation unit exposure is 0.00091 mg ai/lb handled. Dermal absorption is 7%. The rate of application is taken from Merit® 0.62 G insecticide (Reg. No. 3125-416). Therefore:

$$0.68 \text{ mg ai/lb handled} * 0.4 \text{ lb handled/A} * 0.5 \text{ A/day} * 0.07 \div 70 \text{ kg bw} = 0.000136 \text{ mg ai/kg bw/day}_{\text{dermal}}$$

$$0.00091 \text{ mg ai/lb handled} * 0.4 \text{ lb handled/A} * 0.5 \text{ A/day} \div 70 \text{ kg bw} = 0.0000026 \text{ mg ai/kg bw/day}_{\text{inhalation}}$$

Dermal + Inhalation exposure = 0.000139 mg ai/kg bw/day

MOE = NOAEL/Dose = 10 mg ai/kg bw/day/0.000139 mg ai/kg bw/day = 72,150.

### 6.1.2 Resident-applicator Ready To Use

Merit<sup>®</sup> RTU is 0.012 % imidacloprid in a 24 fl. oz. trigger pump spray bottle. Exposure is not formally assessed here. HED expects that exposure from use of the entire contents (*i.e.*, 24 fl.oz.) will not exceed the exposure associated with the use of a garden hose-end sprayer and which is assessed later in this document.

### 6.1.3 Resident-applicator Potted Plant Spikes

Merit<sup>®</sup> 2.5 PR consists of 10 two gram “spikes” of which 2.5 % is imidacloprid. Plant “spikes” are actually semi-solid cylindrically shaped objects about the diameter of a lead pencil and about an inch long. They are composed of a mixture of imidacloprid, fertilizers/plant nutrients and decomposable bonding materials. There are no specific unit exposure data relative to this use pattern therefore HED uses the PHED “hand” unit exposure for an applicator applying granular bait by hand. HED believes that use of the hand applied granular unit exposure overestimates the exposure actually experienced from the use of plant “spikes.” Essentially only the tips of one or two fingers and one thumb are necessary to push “spikes” into potting soil. HED assumes that the entire package is used at one time. One package of 10 “spikes” will treat 4 - 5 eight inch plant pots. The label directs a user to “push spikes down into the soil...” Since the vapor pressure of imidacloprid is  $1.5 \times 10^{-9}$  mm Hg at 20°C, HED believes inhalation exposure in this case is negligible. So, 10 two gram “spikes” equal 20 g product of which 2.5% is imidacloprid = 0.5 g ai ( $0.5 \text{ g ai} \div 453.6 \text{ g/lb} = 0.0011 \text{ lb ai}$ ). The unit exposure for the hand is 356 mg ai/lb handled and is for a “gloved” (*i.e.*, “protected”) hand. The unit exposure is back-calculated to account for 90% protection of a gloved hand and the ungloved unit exposure is 3,560 mg ai/lb handled. Exposure is then estimated as:

$3,560 \text{ mg ai/lb handled} * 0.0011 \text{ lb ai handled/day} * 7\% \text{ Derm. Abs.} \div 70 \text{ kg bw} = 0.00392 \text{ mg ai/kg bw/day}$ . MOE = NOAEL/DOSE  $\therefore 10 \text{ mg ai/kg bw/day} \div 0.00392 \text{ mg ai/kg bw/day} = 2,600$  which is believed to be a conservative (*i.e.*, highly protective) estimate of risk.

### 6.1.4 Resident-applicator/Plant Potting Medium

Merit<sup>®</sup> PM plus fertilizer (Reg. No. 3125-532) is a plant potting medium for use in indoor or outdoor containers. It contains 0.015% imidacloprid. The largest container net weight is 19.19 lb of which 0.015% is imidacloprid = 0.00288 lb ai. HED assumes that one large container is used per day. As with the assessment of plant “spikes” above, HED utilizes the SOP unit exposure value for hands for residential applicator applying granular bait by hand. The hand unit exposure is corrected to equate to an “ungloved” (*i.e.*, “unprotected”) hand. Estimated exposure is:

$3,560 \text{ mg ai/lb handled} * 0.00288 \text{ lb handled/day} * 7\% \text{ D.A.} \div 70 \text{ kg bw} = 0.01 \text{ mg ai/kg bw/day.}$

$\text{MOE} = \text{NOAEL/DOSE} \therefore 10 \text{ mg ai/kg bw/day} \div 0.1 \text{ mg ai/kg bw/day} = 1,000.$

### 6.1.5 Resident-applicator using Garden Hose-end Sprayer

Merit<sup>®</sup> Concentrate Insecticide (Reg. No. 3125-500) contains 2.94% imidacloprid and is a liquid concentrate for dilution and use in pump up sprayers or garden hose-end sprayers. HED policy indicates a larger area per day may be treated with a hose-end sprayer which results in possible contact with more active ingredient per day. Therefore, exposure from a hose-end sprayer is assessed versus that of a compressed air sprayer.

The unit density of this product is 1.6 g/ml (pers. comm. D. Kenny, Registration Division, 25 OCT 02). Using a conversion factor (Oil & Colour Chemists Assoc. [www.occa.org.uk](http://www.occa.org.uk)) g/ml are converted to lb/gal by multiplying by 0.09978. Thus,  $1.6 \text{ g/ml} * 0.09978 = 0.1596 \text{ lb/gal}$  of which 2.94 % is imidacloprid or 0.00469 lb/gal imidacloprid.

$0.00469 \text{ lb/gal} \div 128 \text{ fl oz/gal} = 0.0000366 \text{ lb ai/fl oz.}$  The maximum rate of application is 6 fl oz/1000 ft<sup>2</sup> therefore

$0.0000366 \text{ lb ai/fl oz} * 6 \text{ fl oz/1000 ft}^2 = 0.0002196 \text{ lb ai/1000 ft}^2.$  HED SOPs assume 0.5 acre treated per day (rounded to 22,000 square feet treated per day); therefore, 0.0048312 lb ai will be applied per day. The unit exposure value for a residential handler using open-pour mixing/loading for a garden hose-end sprayer is 11 mg/lb handled (dermal) and 0.013 mg/lb handled (inhalation) (Memo, G. Bangs, MRID 449722-01; 30 APR 01; Summary of HED's Reviews of ORETF Chemical Handler Exposure Studies). Thus, exposure is estimated as:

$11.0 \text{ mg ai/lb handled} * 0.0002196 \text{ lb ai/1000 ft}^2 * 22,000 \text{ ft}^2/\text{day} * 7\% \text{ dermal absorption} \div 70 \text{ kg bw} = 0.000053 \text{ mg ai/kg bw/day}$  for dermal.

$0.016 \text{ mg ai/lb handled} * 0.0002196 \text{ lb ai/1000 ft}^2 * 22,000 \text{ ft}^2/\text{day} \div 70 \text{ kg bw} = 0.0000011 \text{ mg ai/kg bw/day.}$

Dermal + inhalation = 0.0000541 mg ai/kg bw/day. MOE = NOAEL/Dose ∴

$10 \text{ mg ai/kg bw/day} \div 0.0000541 \text{ mg ai/kg bw/day} = 185,000$

### 6.1.6 Resident-applicator/Soil Drench Using Bucket or Watering Can

Merit<sup>®</sup> 2.94 TLC is a liquid concentrate intended for use as a systemic soil drench application using a pale or watering can. The largest product container is 3.78 liter and HED assumes that equates to 3780 grams of which 2.94% is imidacloprid, or 111 g ai. HED assumes the contents of one container are used per day which will treat 20 medium trees or 42 average-sized shrubs. The total 111 g ai = 0.245 lb ai. The unit exposures are taken from the Residential SOPs with

dermal = 2.9 mg/lb handled and inhalation = 0.0012 mg/lb handled. The unit exposures are for a residential handler using liquid, open pour mixing. Exposure is estimated as:

$$2.9 \text{ mg ai/lb handled} * 0.245 \text{ lb handled/day} * 7\% \text{ dermal absorption} \div 70 \text{ kg bw} \\ = 0.0007 \text{ mg ai/kg bw/day (dermal)}$$

$$0.0012 \text{ mg ai/lb handled} * 0.245 \text{ lb handled/day} \div 70 \text{ kg bw} = 0.0000042 \text{ mg ai/kg bw/day.}$$

Dermal + inhalation = 0.0007 and with MOE = NOAEL/DOSE, 10 mg ai/kg bw/day  $\div$  0.0007 = 14,000.

The MOE is > 100 therefore this use is not of concern to HED.

### 6.1.7 Resident-applicator of Pet Spot-On

HED believes that imidacloprid applied as label directed will result in negligible handler exposure. A handler uses a dropper to deliver 2.5 ml to two spots (total volume = 5 ml, equal to 500 mg/dog) on a dog's back. There should be no contact with any material and if there is contact, HED believes it would be minimal. There are neither chemical specific data nor any applicable surrogate data with which to assess this method of application. There is an unpublished study (see residential post-application exposure to treated pets [Fichtel, M. and R. Krebber. 27 MAR 1996, Imidacloprid (Bay t 7391) - Stroke Test in Dogs after Topical Application of Imidacloprid Spot-on 10%; Bayer Animal Health Development AH-D ID: 16051]) designed to measure possible post-application exposure. Data were collected from 15 beagle dogs which were each treated with 500 mg of Imidacloprid 10% Spot-on per animal. The study used cotton-glove dosimeter hand-wipes of the treated areas over 24 hours. Summary data are:

#### (mg imidacloprid/glove +/- SEM)

10 min	24.9 +/- 6.4
1 hr	17.3 +/- 3.3
12 hr	3.9 +/- 1.1
24 hr	2.7 +/- 0.7

The total dose from the four sampling times over 24 hours is 48.8 mg imidacloprid. This is derived from purposeful stroking of a treated animal, on the treatment loci. HED herein uses the data from sampling at ten minutes post-application and assumes that a pesticide handler would not receive a greater dose if applied according to label directions than what was measured via cotton glove dosimetry from purposeful stroking of treatment loci. Cotton glove dosimeters are highly sorbent and in this case, dermal absorption is 7%. Therefore, an estimate of exposure is:

$$24.9 \text{ mg ai/day} * 7\% \text{ dermal absorption} \div 70 \text{ kg bw} = 0.025 \text{ mg ai/kg bw/day}$$

$$\text{MOE} = \text{NOAEL/DOSE where } 10 \text{ mg ai/kg bw/day} \div 0.025 \text{ mg ai/kg bw/day} = 400$$

Since MOEs for residential handlers are > 100 they do not exceed HED's level of concern.

<b>Table 6.1.7 Summary of Residential Handler Exposures and Risks</b>		
<b>Activity</b>	<b>Exposure/Dose mg ai/kg bw/day</b>	<b>MOE</b>
Granular/push-type spreader application	Dermal + inhalation 0.0000139	72,150
Ready to Use Trigger Pump Spray	negligible see hose end spray	
Potted Plant Spikes	Dermal (inhalation negligible) 0.00392	2,600
Plant Potting Medium	Dermal (inhalation negligible) 0.01	1,000
Garden Hose-end Spray	Dermal + Inhalation 0.0000541	185,000
Soil Drench - Water Can/Bucket	Dermal + Inhalation 0.0007	14,000
Pet Spot-On	Dermal (inhalation negligible) 0.025	400

## 6.2. Residential Post-application Exposure

As noted earlier, HED conducted a “Non-Occupational/Residential Exposure Assessment for Imidacloprid - Turf and Pet Uses” (Memo, Y. Donovan, DP 268562, 22 JAN 01). The 22 JAN 01 memo by Donovan, cites an HED review of a study (“memo of 11/14/96, L. Lasota, DP Barcode D223275, MRID# 43923901”) of imidacloprid foliar dislodgeable residues from turf as well as passive monitoring of dermal and inhalation exposure measured during the course of prescribed “jazzercise” activities. The accepted study provides compound specific turf transferable residue data as well as dermal transfer factors relative for use in assessing non-occupational, post-application, dermal exposures. The 2001 Donovan memo did not utilize the study data as no dermal or inhalation toxicological endpoints were identified at that time. In the current assessment, where applicable, data and information from the 1996 LaSota memo are utilized to estimate dermal, post-application exposures. The half life of imidacloprid at the three study locations was 2.0 day in Florida, 0.9 day in New Jersey, and 1.1 day in Kansas. Due to residential application practices and the half-lives observed in the turf transferable residue study, HED believes post-application exposures will be short-term (1-30 days) and therefore assessment of intermediate-term residential post-application exposure is not necessary and not presented here. See Table 6.2 for a summary of residential post-application exposures and risks.

<b>Table 6.2 Summary Residential Post-Application Exposures and Risks</b>
---

Activity	Exposure (Dose) mg ai/kg bw/day	MOE	COMBINED MOE <sup>1</sup>
Toddler oral hand to mouth from contacting treated turf	0.0059	1,700	1,500
Toddler oral - ingestion of granules	0.12	350	N/A
Toddler incidental oral ingestion of treated soil	0.02	500,000	N/A
Toddler incidental oral from contacting treated pet	10 min hand wipe data = 0.11 1 hr hand wipe data = 0.08 12 hr hand wipe data = 0.017 24 hr hand wipe data = 0.012	3,600 5,200 23,000 33,000	255 261 271 272
Toddler dermal - pet “hug”/contacting treated pet	0.036	275	See pet incidental oral
Adult dermal post applic turf contact	0.00053	19,000	N/A
Adult combined dermal exposure = application + post-application	0.0000162 0.00053	72150 19,000	15,000 <sup>2</sup>
Toddler dermal post applic turf contact	0.001	10,000	See hand to mouth turf
Adult golfer post app turf contact	0.00016	62,500	N/A
Child golfer post app turf contact	0.000272	37,000	N/A

<sup>1</sup> Combined MOEs are presented for toddler oral + dermal exposure to treated turf, and oral + dermal exposure to a treated pet. Combined MOEs are expressed as:  $1 / ((1/\text{MOE}_{\text{DERMAL}}) + (1/\text{MOE}_{\text{ORAL}}))$

<sup>2</sup> Combined MOEs are presented for an adult who applies the material to his/her lawn and then experiences post-application exposure. MOEs combined from different sources of exposure (*i.e.*, application + post-application) are expressed as:  $1 / ((1/\text{MOE}_{\text{applicator}}) + (1/\text{MOE}_{\text{post-application}}))$

Children’s short-term oral hand-to-mouth turf exposure was assessed by Donovan (JAN 01) using HED standard operating procedures. The oral daily dose estimated was 0.0059 mg ai/kg bw/day.  $\text{MOE} = \text{NOAEL} \div \text{Average Daily Dose}$ . Using the short-term incidental oral NOAEL identified by the HIARC (10 August 02) of 10 mg ai/kg bw/day, the MOE for short-term oral hand-to-mouth (*i.e.*, incidental oral exposure from contacting treated turf grass) is  $10 \text{ mg ai/kg bw/day} \div 0.0059 \text{ mg ai/kg bw/day} = 1700$ .

Children’s Incidental Oral Ingestion of Granules was assessed by Donovan (JAN 01) using SOPs and the estimated Average Daily Oral Dose was 0.12 mg ai/kg bw/day. Using the LOAEL of 42 mg ai/kg bw/day acute dietary endpoint identified by HIARC, the MOE for incidental ingestion of granules is  $42 \text{ mg ai/kg bw/day} \div 0.12 \text{ mg ai/kg bw/day} = 350$ . Use of a LOAEL to calculate MOE requires an uncertainty factor of 300. Since the MOE is 350, this is not a risk of concern to HED.

Children Incidental Oral Ingestion of Pesticide Treated Soil may be estimated using HED SOPs for Residential Exposure Assessments (18 DEC 97) which state that:  $PDR_t$  for incidental ingestion of soil =  $SR_t * IgR * CF1$

where:  $PDR_t$  = potential dose rate on day "t" (mg/day)  
 $SR_t$  = soil residue on day "t" (ug/g)  
 $IgR$  = ingestion rate of soil (mg/day) (100 mg/day)  
 $CF1$  = weight unit conversion factor to convert the ug of residues on the soil to grams to provide units of mg/day (1E-6 g/ug)

and:  $SR_t = AR * F * (1-D)_t * CF2 * CF3 * CF4$

where:  $AR$  = application rate (lb ai/acre) (0.4 lb ai/A)  
 $F$  = fraction of ai available in uppermost cm of soil (fraction/cm) (1.0/cm)  
 $D$  = fraction of residue that dissipates daily  
 $t$  = post-application day on which exposure is being assessed (day zero)  
 $CF2$  = weight unit conversion factor to convert the lbs ai in the application rate to ug for the soil residue value (4.54E+8 ug/lb)  
 $CF3$  = area unit conversion to convert the surface area units (acre) in the application rate to  $cm^2$  for the  $SR$  value (2.47E-8 acre/ $cm^2$ )  
 $CF4$  = volume to weight unit conversion factor to convert the volume units ( $cm^3$ ) to weight units for the  $SR$  value (0.67  $cm^3$ /g soil)

Therefore  $0.4 \text{ lb ai/A} * 1.0/\text{cm} * (1-0)^0 * 4.54 \times 10^8 \text{ ug/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2 * 0.67 \text{ cm}^3/\text{g soil} = 3.0 \text{ ug/g soil and}$

$3.0 \text{ ug/g soil} * 100 \text{ mg/day} * 1 \times 10^{-6} \text{ g/ug} = 0.0003 \text{ mg/day} \div 15 \text{ kg body wt} = 0.00002 \text{ mg ai/kg bw/day}$  average daily oral dose from incidental oral ingestion of pesticide treated soil.

$MOE = 10 \text{ mg ai/kg bw/day} \div 0.00002 \text{ mg ai/kg bw/day} = 500,000.$

Toddler incidental oral ingestion from touching a treated pet may be assessed using HED SOPs for Residential Exposure Assessments (18 DEC 97) 9.2.2 "Postapplication Potential Dose Among Toddlers from Incidental Nondietary Ingestion of Pesticide Residues on Pets from Hand-to-Mouth Transfer." The SOPs utilize certain assumptions in lieu of chemical-specific data.

In this case, there is an unpublished study (Fichtel, M. and R. Krebber. 27 MAR 1996, Imidacloprid (Bay t 7391) - Stroke Test in Dogs after Topical Application of Imidacloprid Spot-on 10%; Bayer Animal Health Development AH-D ID: 16051) which was designed to determine residues that persons with close physical contact to a treated animal might experience. **UNTIL FORMALLY NOTIFIED OTHERWISE, THE STUDY SHOULD BE CONSIDERED PROPRIETARY AND SUBJECT TO DATA COMPENSATION.** The study used cotton gloves as dosimeters. Sixteen beagle dogs received a 500 mg dose (as would a dog receiving a maximum treatment dose from Advantage 110 Flea Adulticide (Reg. No. 11556-121), one half of which was administered between the scapulae (shoulders) and one half on the rump (lumbosacral

region) according to label directions. Samples were taken from each treatment site separately (*i.e.*, shoulders separately from rump area) and consisted of 30 strokes, one per second at about 20 cm per stroke such as not to overlap the treated areas. A new dosimeter glove was used for each “site” change and for each dog. Residues were analyzed after extraction with acetonitrile using HPLC with UV detector (recovery rates of 83-94%).

Summary results:

(mg imidacloprid/glove +/- SEM)

10 min	24.9 +/- 6.4
1 hr	17.3 +/- 3.3
12 hr	3.9 +/- 1.1
24 hr	2.7 +/- 0.7

The dosimetry data are used in conjunction with the SOPs, that is to say, using the SOPs but substituting measured dislodgeable residues for the otherwise assumed 20 % of administered dose. Further, the HED ExpoSAC believes that it is likely there would be one event per day. Therefore the resulting MOEs are calculated as follows:

10 min post-application:  $24.9 \text{ mg ai}/6000 \text{ cm}^2 * 0.5 (=50 \% \text{ saliva extraction factor}) * 20 \text{ cm}^2/\text{event} * 1 \text{ event}/\text{day} \div 15 \text{ kg bw} = 0.00276$ . MOE = NOAEL  $\div$  DOSE or  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.00276 \text{ mg ai}/\text{kg bw}/\text{day} = 3,600$ .

1 hr post-application:  $17.3 \text{ mg ai}/6000 \text{ cm}^2 * 0.5 (= 50 \% \text{ saliva extraction factor}) * 20 \text{ cm}^2/\text{event} * 1 \text{ event}/\text{day} \div 15 \text{ kg bw} = 0.0019 \text{ mg ai}/\text{kg bw}/\text{day}$ . MOE = NOAEL  $\div$  DOSE or  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.0019 \text{ mg ai}/\text{kg bw}/\text{day} = 5,200$ .

12 hr post-application:  $3.9 \text{ mg ai}/6000 \text{ cm}^2 * 0.5 (= 50 \% \text{ saliva extraction factor}) * 20 \text{ cm}^2/\text{event} * 1 \text{ event}/\text{day} \div 15 \text{ kg bw} = 0.000433 \text{ mg ai}/\text{kg bw}/\text{day}$ . MOE = NOAEL  $\div$  DOSE or  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.000433 \text{ mg ai}/\text{kg bw}/\text{day} = 23,000$ .

24 hr post-application:  $2.7 \text{ mg ai}/6000 \text{ cm}^2 * 0.5 (= 50 \% \text{ saliva extraction factor}) * 20 \text{ cm}^2/\text{event} * 1 \text{ event}/\text{day} \div 15 \text{ kg bw} = 0.0003$ . MOE = NOAEL  $\div$  DOSE or  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.0003 \text{ mg ai}/\text{kg bw}/\text{day} = 33,000$ .

The data indicate that imidacloprid rapidly biologically disperses from the specific application loci. HED believes it is unlikely that a toddler would consistently “stroke” a pet exactly on the application loci. This assessment addresses the maximum dose that would be applied to a large dog. A toddler is expected to more likely touch areas of a pet to which imidacloprid has not dispersed (immediately upon treatment) such as the sides of shoulders or flanks. The use of highly absorbent cotton gloves as dosimeters, is expected to result in over-estimation of actual dermal exposure. In the case of imidacloprid, the dermal absorption is 7%.

It is unlikely that a toddler could absorb the “dose” measured by absorption to a cotton glove purposefully moved directly over the point of treatment, essentially at the time of treatment.

Cotton is much more absorptive than human skin and the surface area of an adult hand is much greater than that of a toddler.

HED believes that the MOEs > 100, based upon the study data, are conservative *i.e.*, overestimate the actual exposure and risk. This use is therefore, not of concern to HED.

Toddler Dermal Exposure From Touching Treated Pet (pet hug) may be estimated according to the Residential SOPs as follows:

$$D = (((AR * F_{AR}) / SA_{pet}) * (1 - DR)^t * SA_{hug} * (1 \text{ mg}/1000\mu\text{g})) * DA$$

where:

D	= dose from dermal pet contact (mg/day);
AR	= application rate or amount applied to animal in a single treatment (mg ai/animal);
F <sub>AR</sub>	= fraction of the application rate available for dermal contact as transferable residue (20%)
SA <sub>pet</sub>	= surface area of a treated dog (5,986cm <sup>2</sup> /animal);
t	= time after application (days);
DR	= fractional dissipation rate per day (5% per day/100); and
SA <sub>hug</sub>	= surface area of a child hug (1,875cm <sup>2</sup> contact/hug).
DA	= Dermal absorption factor (7%)

In this case actual compound specific study data are used in place of the expression (AR\*F<sub>AR</sub>) which is the assumption that 20% of the application rate is available as dislodgeable residue. The ExpoSAC believes it is appropriate to use the dislodgeable residues from the 10 min post-application observations in the dog wipe study. Therefore, the estimate of exposure and risk are expressed as:

$$24.9 \text{ mg ai} \div 5986 \text{ cm}^2/\text{surface area dog} * (1 - DR)^{0\text{day}} * 1875 \text{ cm}^2/\text{surface area child hug} * 7 \% DA \div 15 \text{ kg bw} = 0.036 \text{ mg ai/kg bw/day. MOE} = \text{NOAEL}/\text{DOSE} \therefore 10 \text{ mg ai/kg bw/day} \div 0.036 \text{ mg ai/kg bw/day} = 275.$$

The MOE is > 100 and is therefore does exceed HED's level of concern.

Adult and toddler dermal post-application exposure to treated turf is assessed using SOPs which indicate that Potential Dose Rate (PDR) = Dislodgeable Foliar Residue (DFR) \* Transfer Coefficient (TC) \* hours/day \* 0.001 mg/μg ÷ body weight (70 kg for adult, 15 kg for toddler).

DFR and TC are utilized from the study reviewed and found acceptable by L. LaSota (Memo 14 NOV 1996, DP 223276, MRID 439239-01). The combined arithmetic mean of imidacloprid transferable residues from three study locations was 79.8 ng/cm<sup>2</sup> and was determined using the turf roller technique. The study was conducted at an application rate of 0.5 lb ai/A and the maximum label rate for commercial application to residential lawns and turf is 0.4 lb ai/A. Data were collected as soon as sprays had dried. The TCs were determined using "inner" and "outer"

whole body dosimeters to simulate the use of a sleeveless shirt, short pants and shoes and adjusted to simulate 4 hours of foliar contact/day. The TC for adults is 3,343 cm<sup>2</sup>/hr and 1,397 cm<sup>2</sup>/hr for toddlers.

$0.064 \mu\text{g}/\text{cm}^2 * 3.343 \text{ cm}^2/\text{hr} * 0.001 \text{ mg}/\mu\text{g} * 2 \text{ hr}/\text{day} * 7 \% \text{ dermal absorption} \div 70 \text{ kg bw} = 0.00053 \text{ mg ai}/\text{kg bw}/\text{day}$  for adults.  $\text{MOE} = 10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.00053 \text{ mg ai}/\text{kg bw}/\text{day} = 23,000$  for adults.

$0.064 \mu\text{g}/\text{m}^2 * 1,397 \text{ cm}^2/\text{hr} * 0.001 \text{ mg}/\mu\text{g} * 2 \text{ hr}/\text{day} * 7 \% \text{ dermal absorption} \div 15 \text{ kg bw} = 0.001 \text{ mg ai}/\text{kg bw}/\text{day}$ .  $\text{MOE} = 10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.001 \text{ mg ai}/\text{kg bw}/\text{day} = 12,000$  for toddlers.

Adult and Adolescent Golfer Post-Application Dermal Exposure may be estimated using the convention stated in ExpoSAC draft Policy regarding “Golfer Exposure Assessment For Adults and Children” (24 August 2000). The draft policy states that adult and adolescent golfer dermal post-application exposure may be calculated as

$\text{DE}_{(t)} (\text{mg ai}/\text{kg bw}/\text{day}) = (\text{TTR}_{(t)} (\mu\text{g}/\text{cm}^2)) * \text{TC} (\text{cm}^2/\text{hr}) * \text{hr}/\text{day}/1000 \mu\text{g}/\text{mg} * \text{BW} (\text{body weight (kg)})$

Where:

$\text{DE}_{(t)}$  = dermal exposure at time (t) attributable to golfing on previously treated turf (mg ai/kg bw/day).  
 $\text{TTR}_{(t)}$  = turf transferable residue at time t ( $\mu\text{g}/\text{cm}^2$ )  
 TC = Transfer Coefficient (500 cm<sup>2</sup>/hr)  
 Hr = exposure period (4 hours)  
 BW = body weight (kg) (70 kg for adult; adjusted (multiplied) by a factor of 1.7 for child golfers)) A BW of 60 kg is utilized if the toxicological endpoint is derived from a developmental study and there are fetal effects.

Therefore,

$\text{DE} = 0.064 \mu\text{g}/\text{cm}^2 * 500 \text{ cm}^2/\text{hr} * 4 \text{ hr}/\text{day}/1000\mu\text{g}/\text{mg} * 7 \% \text{ dermal absorption} \div 70 \text{ kg bw} = 0.00016 \text{ mg ai}/\text{kg bw}/\text{day}$ .

$\text{MOE}$  for adult golfer is  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.00016 \text{ mg ai}/\text{kg bw}/\text{day} = 76,000$ .

The adult dose level is adjusted by a factor of 1.7 to estimate child golfer exposure therefore  $0.00016 \text{ mg ai}/\text{kg bw}/\text{day} * 1.7 = 0.000272 \text{ mg ai}/\text{kg bw}/\text{day}$ .

$\text{MOE}$  for child golfer is  $10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.000272 = 42,000$

Post-application exposure was estimated for residential handlers who might apply imidacloprid to a lawn and then experience post-application exposure. See Summary Table 6.3 for combined  $\text{MOE}$  for application exposure + post-application exposure. “Residential” post-application exposure was not assessed for the use of plant spikes or for the potting medium. HED believes

that it is highly unlikely for adults and toddlers to experience post-application exposure to plant spikes or potting medium after their initial use *i.e.*, application.

HED believes that the estimates of exposure and risk that result from the use of the SOPs are Tier I, screening level estimates. HED also believes that whenever appropriate study data are available, the data should be utilized in lieu of the Tier I estimates based solely on the SOPs. The SOPs resulted in MOEs < 100 for 1) Toddler incidental oral ingestion of granules; 2) for toddler incidental hand-to-mouth oral ingestion from touching a treated pet; and 3) for toddler dermal post-application exposure from “hugging” a treated pet. When study data are used for assessing exposures from a treated pet, the MOEs are > 100 and are not of concern to HED. HED suggests that toddler incidental oral ingestion of granules be compared to all other residential post-application exposures, to residential handler exposures and to commercial handler exposures and that it is likely a conservative over-estimate of risk and therefore not of concern to HED. All other residential post-application exposures and risks resulted in MOEs > 100 and are therefore not of concern to HED.

### 6.3 Combined Residential Exposure

FQPA requires that all exposures that could reasonably be expected to occur on the same day be combined and compared to the appropriate toxicity endpoint. The residential scenarios that can reasonably be expected to occur on the same day for toddlers/children are listed in Table 6.3.

<b>Table 6.3 Exposure Potential for Adult and Child Short-term Aggregate Risk Estimates</b>					
<b>Exposure Scenario</b>		<b>Exposure (Dose) mg ai/kg bw/day</b>	<b>MOE</b>	<b>Combined Exposure (Dose) mg ai/kg bw/day</b>	<b>COMBINED MOE<sup>1</sup></b>
Toddler - Treated Turf	Oral hand-to-mouth post-application exposure from contacting treated turf	0.0059	1,700	0.00692	1,500
	Incidental oral post-application exposure from ingestion of treated soil	0.00002	500,000		
	Dermal post-application exposure from contacting turf	0.001	10,000		
Toddler - Treated Pet	Incidental oral post-application exposure from contacting treated pet	0.00276	3,600	0.03876	260
	Dermal post-application exposure from pet “hug”/ contacting treated pet	0.036	280		
Adult - Treated Turf	Handler dermal and inhalation exposure from applying imidacloprid using granular/push-type spreader	0.0000139	72,000	0.000669	15,000
	Dermal post-application exposure from contacting treated turf	0.00053	19,000		

Table 6.3 Exposure Potential for Adult and Child Short-term Aggregate Risk Estimates					
Exposure Scenario		Exposure (Dose) mg ai/kg bw/day	MOE	Combined Exposure (Dose) mg ai/kg bw/day	COMBINED MOE <sup>1</sup>
Adult - Treated Pet	Handler dermal and inhalation exposure from applying imidacloprid to pet with pet spot-on	0.025	400 <sup>2</sup>		
	Dermal post-application exposure from contacting treated pet				

<sup>1</sup> Combined MOEs are presented for toddler oral + dermal exposure to treated turf, and oral + dermal exposure to a treated pet. Combined MOEs are expressed as:  $MOE_{\text{DERMAL}} + MOE_{\text{ORAL}}$ . Combined MOEs are presented for an adult who applies the material to his/her lawn and then experiences post-application exposure. MOEs combined from different sources of exposure (*i.e.*, application + post-application) are expressed as:  $MOE_{\text{applicator}} + MOE_{\text{post-application}}$ .

2. HED believes handler exposure will be negligible. However, the results from an unpublished study (see residential post-application exposure to treated pets) were used to measure possible post-application exposure. HED herein used the data from sampling at ten minutes post-application and assumes that a pesticide handler would not receive a greater dose if applied according to label directions than what was measured via cotton glove dosimetry from purposeful stroking of treatment loci (see Section 6.1.6 Residential Handler of this risk assessment).

#### 6.4 Other (Spray Drift, etc.)

Spray drift is often a potential source of exposure to residents nearby to agricultural spraying operations. This is particularly the case with aerial operations, but to a lesser extent, could also be a potential source of exposure from ground application methods. As indicated in this assessment, imidacloprid can be directly applied to residential turf. The rates of application to residential turf are generally equal to or greater than the agricultural rates of application. The resulting MOEs are not of concern to HED. Therefore, based on this assessment, HED believes that it is unlikely that there is higher potential for risk of exposure to spray drift from agricultural uses of this chemical than have been assessed for direct residential applications.

#### 7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, ARIA must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, ARIA considers both the route and duration of exposure. In the case of imidacloprid aggregate risk assessments were performed for acute (food + drinking water), short-term aggregate exposure (food + drinking water + residential), and chronic aggregate exposure (food + drinking water). Intermediate- and long-term aggregate risk assessments were not performed because, based on the current and proposed use patterns, ARIA does not expect residential exposure durations that would result in intermediate- or long-term exposures. A cancer aggregate risk assessment was not performed

because imidacloprid is not carcinogenic. All potential exposure pathways were assessed in the aggregate risk assessment.

Rather than using back-calculated drinking water levels of comparison (DWLOCs), estimates of pesticide residues in drinking water were incorporated directly into the dietary exposure analysis to assess aggregate acute and chronic risk. In the past, EPA has not directly combined pesticide exposure estimates from drinking water with pesticide exposures from food because EPA was concerned that combining high-end modeling values for drinking water with more realistic food exposure data might be confusing. Although EPA retains this concern, it is now outweighed by the advantages of using EPA's current aggregate exposure assessment models, Lifeline™ and DEEM™. Advances in these models allow EPA to incorporate actual water consumption data and body weight data in assessing exposure to pesticides in drinking water as well as conduct probabilistic assessments for food, water, and residential exposures to pesticides. These more sophisticated exposure assessments are not possible under the DWLOC approach.

### **7.1 Acute Aggregate Risk**

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of imidacloprid (food and drinking water). The dermal, inhalation, and incidental oral exposures resulting from short-term residential applications are assessed separately. The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the general U.S. population (28% of the aPAD) and all other population subgroups (see Table 5.2). The most highly-exposed population subgroup is children 1-2 years old, at 70% of the aPAD. Therefore, the acute aggregate risk associated with the proposed use of imidacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroups.

### **7.2 Short-Term Aggregate Risk**

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to imidacloprid residues from food, drinking water, and residential pesticide uses. High-end estimates of the residential exposure are used in the short-term assessment, and average values are used for food and drinking water exposures.

Short-term aggregate risk assessments are required for adults as there is potential for both dermal and inhalation handler exposure, and dermal post-application exposure from the residential uses of imidacloprid on turf and pets. In addition, short-term aggregate risk assessments are required for children/toddlers because there is a potential for oral and dermal post-application exposure resulting from the residential uses of imidacloprid on turf and pets. The short-term residential exposure potential from the turf and pet uses for adults and children/toddlers can be found in Table 6.2. The pet-treatment scenario resulted in the highest combined MOE for adults (MOE = 400; handler and post-application) and children (MOE = 260; post-application). The turf-treatment resulted in much lower exposures for both adults (MOE = 15,000; handler and post-application) and children (MOE = 1,500; post-application). Therefore, the pet-treatment exposure estimates were aggregated with the chronic dietary (food) to provide a worst-case estimate of short-term aggregate risk for the U.S. population and children 1-2 years old (the child

population subgroup with the highest estimated chronic dietary food exposure) (see Table 5.2). As the MOEs are greater than 100, the short-term aggregate risks are below HED's level of concern.

<b>Table 7.2 Short-Term Aggregate Risk Calculations for Imidacloprid.</b>						
Population Subgroups	Short-Term Scenario					
	NOAEL (mg/kg/day)	Level of Concern <sup>1</sup>	Max Exposure <sup>2</sup> (mg/kg/day)	Average Dietary Exposure (mg/kg/day)	Residential Exposure <sup>3</sup> (mg/kg/day)	Aggregate MOE (dietary and residential) <sup>4</sup>
US Population	10	100	0.1	0.007485	0.025	310
Children 1-2 years old	10	100	0.1	0.021658	0.03876	170

<sup>1</sup> The level of concern (target MOE) includes 10X for interspecies extrapolation and 10X for intraspecies variation.  
<sup>2</sup> Maximum Exposure (mg/kg/day) = NOAEL/Target MOE  
<sup>3</sup> Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. The pet-treatment scenario resulted in the lowest combined residential MOE for adults (handler and post-application) and children (post-application). The combined MOEs for the pet-use scenario were used to calculate the short-term risk [see Table 11 of HED human health risk assessment dated 3/4/03 (Memo, J. Tyler *et al.*; D286101)].  
<sup>4</sup> Aggregate MOE = [NOAEL ÷ (Avg Dietary Exposure + Residential Exposure)]

### 7.3 Intermediate-Term Aggregate Risk

An assessment of the intermediate-term aggregate risk for exposure to imidacloprid is not required.

### 7.4 Long-Term Aggregate Risk

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of imidacloprid (food and drinking water) and residential uses. However, due to the use patterns, no chronic residential exposures are expected. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only. The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (13% of the cPAD) and all population subgroups (see Table 5.2). The most highly exposed population subgroup is children 1-2 years old, at 38% of the cPAD. Therefore, the chronic aggregate risk associated with the proposed use of imidacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroups.

### 7.5 Cancer Risk

An assessment of the cancer risk for exposure to imidacloprid is not required.

### 8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to imidacloprid and any other substances and imidacloprid does not appear to produce a toxic

metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that imidacloprid has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

## 9.0 Occupational Exposure/Risk Pathway

The current request is for registration of additional formulations (*i.e.*, end-use products). They are summarized as follows.

<b>Product</b>	<b>Application Rate lb ai/A</b>	<b>Preharvest Interval</b>	<b>Application Method</b>	<b>Application Interval</b>
Admire <sup>®</sup> 2 Flowable Insecticide; Reg. No. 264-758; 2.0 lb ai/gal liquid flowable	0.25 - 0.5 (maximum 0.5 lb ai/A/season)	7 days	chemigation or basal soil drench	NA
Gauche <sup>®</sup> 550 SC Insecticide; Reg. No. 264-827; 4.6 lb ai/gal soluble concentrate liquid	0.25-0.5 (maximum 0.5 lb ai/A/season)	7 days	chemigation or basal soil drench	NA
Provado <sup>®</sup> Pro Insecticide; Reg. No. 264-858; 1.6 lb ai/gal liquid	0.1 (maximum 0.3 lb ai/A/season)	3 days	foliar	7 days
Provado <sup>®</sup> 70 WG Insecticide; Reg. No. 264-823; 70 % ai water dispersible granule	0.1 (maximum 0.3 lb ai/A/season)	3 days	foliar	7 days
Provado <sup>®</sup> 1.6 Flowable Insecticide; Reg. No. 264-763; 1.6 lb ai/gal flowable liquid	0.1 (maximum 0.3 lb ai/A/season)	3 days	foliar	7 days

Admire<sup>®</sup> and Gauche<sup>®</sup> are listed to control aphids, leafhoppers, whiteflies and rednecked cane borer. They suppress foliage feeding thrips. The 3 Provado<sup>®</sup> products are listed to control aphids, leafhoppers and thrips. The Provado<sup>®</sup> products are not limited to soil applications and may have repeat applications. None of the products may be applied pre-bloom, during bloom or when bees are actively foraging. All of the product labels require applicators and other handlers to wear PPE consisting of long-sleeved shirt, long pants, shoe plus socks and chemical resistant gloves made of any waterproof material such as barrier laminate, butyl rubber, nitrile rubber, neoprene rubber, natural rubber, polyethylene, polyvinylchloride or viton.

A number of ORE assessments have been conducted for the proposed uses of imidacloprid (DP Num: 337875, M. Dow, 4/17/07 & DP Num: 337878, M. Dow, 4/17/07). The assessment with the worst case occupational exposure is discussed here (DP Num: 281610, 281612, & 281614, M. Dow, 2/26/07).

## 9.1 Short-/Intermediate-/Long-Term Handler Risk

Based primarily on the proposed new use patterns, commercial and private (*i.e.*, grower operators) pesticide handlers are typically expected to have short-term exposures (*i.e.*, 1 - 30 days). The acreages involved with caneberry crops are relatively small as compared to such field crops as cotton, corn or soybean. However, the ExpoSAC asserts that there is a possibility that commercial handlers might be exposed to intermediate-term exposures (1-6 months).

The proposed new use pattern indicates that the most highly exposed occupational pesticide handlers are likely to be mixer/loaders using open-pour loading of liquids or granules, and applicators using airblast sprayers, ground-boom sprayers, high-pressure hand-wand sprayers, backpack sprayers and aircraft. Chemigation in the form of drip or low pressure trickle irrigation is also mentioned as a method of application.

ARIA believes that a “loader” (*i.e.*, applicator in this sense) for chemigation will not likely be exposed more than a loader supporting aerial operations. Chemigation typically involves preparation of minibulk containers which have siphon tubes attached to the irrigation equipment. An individual preparing irrigation equipment to include pesticide application is believed to experience exposure similar to that of a mixer/loader using open-pour loading technique. Therefore, a “chemigator” is not assessed, with the assumption that the work activity is represented by that of a mixer/loader supporting aerial operations. Chemigation includes the soil injection and drip irrigation methods of application used for caneberries.

In some cases, HED believes that certain individuals (private growers versus commercial applicators) may perform all three handler activities, that is, mix, load, and apply the material. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the PHED Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of PPE for each aspect of the job without requiring an applicator to wear unnecessary PPE that may be required for a mixer/loader (e.g., chemical-resistant gloves may only be necessary during the pouring of a liquid formulation).

On 8 October 2002, the HIARC met to discuss the adequacy of the toxicological database relative to imidacloprid. During that meeting a number of toxicological endpoints relative to the current assessment were identified. Short and intermediate term dermal and inhalation endpoints were identified as well as short and intermediate term incidental oral endpoints. The short-term dermal, inhalation and incidental oral endpoints are 10 mg ai/kg bw/day based on a developmental rat study. The effects were reduced body weight gains. The intermediate-term dermal, inhalation and incidental oral endpoints are 9.3 mg ai/kg bw/day and were identified from a sub-chronic neurotoxicity study in the rat. The effects were reduced body weight gains.

The HIARC identified a 7% dermal absorption factor for use in assessing dermal exposures. An MOE  $\geq$  than 100 is adequate to protect pesticide handlers. Table 9.1 contains a summary of estimated exposures and risks to occupational pesticide handlers from the proposed use patterns.

<b>Table 9.1 Estimated Handler Exposure and Risk from the Proposed New Use Patterns for Imidacloprid</b>					
Unit Exposure <sup>1</sup> mg ai/lb handled	Applic. Rate <sup>2</sup>	Units Treated <sup>3</sup> Per Day	Average Daily Dose <sup>4</sup> mg ai/kg bw/day	COMBINED MOE <sup>5</sup>	
				ST	IT
Mixer/Loader - Liquid - Open Pour					
Dermal: SLNG 2.9 HC SLWG 0.023 HC Inhal 0.0012 HC	0.5 lb ai/A	350 A	Dermal: No Gloves 0.51 With Gloves 0.004 Inhal 0.003	NG 20 WG 1400	NG 18 WG 1300
Mixer/Loader - Open Pour - Granules					
Dermal: SLNG 0.0084 LC SLWG 0.0069 MC Inhal 0.0017 HC	0.1 lb ai/A	350 A	Dermal: No Gloves 0.00029 With Gloves 0.00024 Inhal 0.00085	NG 8800 WG 9200	NG 8200 WG 8500
Applicator - Aerial (Pilots not required to wear protective gloves)					
Dermal: SLNG 0.005 HC Inhal 0.000068 MC	0.5 lb ai/A	350	Dermal: No Gloves 0.00088 Inhal 0.00017	NG 9500	NG 8900
Applicator - Ground-boom - Open-cab					
Dermal: SLNG 0.014 HC SLWG 0.014 MC Inhal 0.00074 HC	0.5 lb ai/A	80 A	Dermal: NG 0.00056 WG 0.00056 Inhal 0.00042	NG 10,000 WG 10000	NG 9500 WG 9500
Applicator - Air-blast - Open Cab					
Dermal: SLNG 0.36 HC SLWG 0.24 HC Inhal 0.0045 HC	0.5 lb ai/A	40 A	Dermal: No Gloves 0.0072 With Gloves 0.0048 Inhal 0.0013	NG 1200 WG 1600	NG 1100 WG 1500
Mix/Load/Applicator - High Pressure Hand-wand					
Dermal SLNG no data SLWG 2.5 LC Inhal 0.12 LC	0.5 lb ai/A	20 A	Dermal: No Gloves no data With Gloves 0.025 Inhal 0.017	NG no data WG 240	NG no data WG 220
Mixer/Loader/Applicator - Backpack - Liquid - Open Pour					
Dermal:	0.5 lb ai/A	1 A	Dermal:	NG	NG

Table 9.1 Estimated Handler Exposure and Risk from the Proposed New Use Patterns for Imidacloprid						
Unit Exposure <sup>1</sup> mg ai/lb handled		Applic. Rate <sup>2</sup>	Units Treated <sup>3</sup> Per Day	Average Daily Dose <sup>4</sup> mg ai/kg bw/day	COMBINED MOE <sup>5</sup>	
					ST	IT
SLNG	no data			No Gloves - no data	no data	no data
SLWG	2.5 LC			With Gloves 0.0013	WG	WG
Inhal	0.03 LC			Inhal 0.00021	6600	6200

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. SLNG = Dermal Single Layer Work Clothing No Gloves; SLWG = Dermal Single Layer Work Clothing With Gloves; Inhal. = Inhalation. Units = mg ai/pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.

2. Applic. Rate. = Taken from Sections A & B (proposed labeling) of IR-4 submission

3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000; Policy 9.1 indicates a worker may spray 40 gallons/day with a backpack sprayer. The labeling for tree nuts indicates 50 gal/A by ground equipment. It is assumed that a backpack sprayer might treat 1 acre/day. From previous assessments it was assumed that a high-pressure handwand can treat 20 A/day.

4. Average Daily Dose = Unit Exposure \* Applic. Rate \* Units Treated \* 0.07 (7 % dermal absorption) ÷ Body Weight (70 kg).

5. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. Short-term dermal and inhalation NOAEL = 10 mg ai/kg bw/day and are identified from developmental study in the rat where maternal effects (↓body weight gain) were observed. MOEs are "combined" that is, Dermal + Inhalation, since the toxicological effects are the same and are identified from the same study. Intermediate-term NOAEL = 9.3 mg ai/kg bw/day. ST = Short-term combined MOE; IT = Intermediate-term combined MOE. NG = No gloves. WG = With gloves.

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to imidacloprid. Therefore, the proposed new use patterns do not exceed HED's level of concern.

## 9.2 Short-/Intermediate-/Long-Term Post-application Risk

Typically there is the possibility for agricultural workers to experience post-application exposures to dislodgeable pesticide residues. There were no chemical-specific data with which to estimate post-application exposure of agricultural workers to dislodgeable residues of imidacloprid. Therefore, theoretical estimates of exposure, based on surrogate studies, have been conducted. The ExpoSAC (SOP 003.1, Rev. 7 Aug. 2000, Regarding Agricultural Transfer Coefficients; Amended ExpoSAC Meeting notes - 13 Sept 01) lists a number of possible post-application agricultural activities relative to caneberries that might result in pesticide exposure to agricultural workers. TCs expressed as cm<sup>2</sup>/hr are identified for each of the post-application, agricultural activities. The TCs are derived from data in surrogate exposure studies conducted during the various activities listed.

The highest (*i.e.*, most conservative) TC relative to caneberries is 1,100 cm<sup>2</sup>/hr (personal communication J. Dawson, ExpoSAC meeting minutes 7 August 2003). The transfer coefficients used in this assessment are from an interim transfer coefficient SOP developed by HED's ExpoSAC using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (policy # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF,

from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Post-application worker exposure is estimated using HED procedure that assumes 20% of the application rate is available as dislodgeable foliar residue on the day of treatment. HED does not expect post-application exposures to exceed short term exposure. Therefore, only short term exposures are assessed.

However, the HED ExpoSAC directs that there may be intermediate-term exposures (1-6 months) to agricultural workers. The following convention is used to estimate post-application exposures to agricultural workers.

$PDR_t = DFR_t * CF1 * Tc * ET$  where:

$PDR_t$  = potential dose rate on day "t" (mg/day)

$DFR_t$  = dislodgeable foliar residue on day "t" ( $\mu\text{g}/\text{cm}^2$ )

$CF1$  = weight unit conversion factor to convert  $\mu\text{g}$  units in DFR value to mg for the daily dose (0.001 mg/ $\mu\text{g}$ )

$Tc$  = transfer coefficient ( $\text{cm}^2/\text{hr}$ ) (In this case 1,100  $\text{cm}^2/\text{hr}$ ; ExpoSAC Policy 003.1 Rev. 7 Aug. 2000; amended 7 August 2003 ExpoSAC meeting Notes).

$ET$  = Exposure Time (hrs) (8)

and

$DFR_t = AR * F * (1-D)^t * CF2 * CF3$  where:

$AR$  = Application rate (lb ai/A) (0.5 lb ai/A)

$F$  = fraction of ai on foliage available as dislodgeable residue (unitless) (20.0 %)

$D$  = fraction of residue that dissipates daily (unitless) (10.0 %)

$t$  = post-application day on which exposure is being assessed

$CF2$  = weight unit conversion factor to convert the lbs ai in the application rate to  $\mu\text{g}$  for the DFR value ( $4.54\text{E}8 \mu\text{g}/\text{lb}$ )

$CF3$  = Area unit conversion factor to convert the surface area units ( $\text{ft}^2$ ) in the application rate to  $\text{cm}^2$  for the DFR value ( $1.08\text{E}-3 \text{ft}^2/\text{cm}^2$  or  $2.47\text{E}-8 \text{acre}/\text{cm}^2$  if the application rate is per acre).

$$\therefore DFR = 0.5 \text{ lb ai/A} * 0.20 * (1-0)^0 * 4.54\text{E}8 \mu\text{g ai/lb} * 2.47\text{E}-8\text{A}/\text{cm}^2 = 1.121 \mu\text{g}/\text{cm}^2$$

$$PDR = 1.121 \mu\text{g}/\text{cm}^2 * 0.001 \text{ mg}/\mu\text{g} * 1,100 \text{ cm}^2/\text{hr} * 8 \text{ hr}/\text{day} = 9.86 \text{ mg ai}/\text{day} * 0.07 (\% \text{ dermal absorption}) \div 70 \text{ kg bw} = 0.00986 \text{ mg ai}/\text{kg bw}/\text{day}$$

$MOE = \text{NOAEL} \div PDR$

$$\therefore 10 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.00986 \text{ mg ai}/\text{kg bw}/\text{day} = 1014 = \text{Short Term MOE}$$

$$\text{and } 9.3 \text{ mg ai}/\text{kg bw}/\text{day} \div 0.0269 \text{ mg ai}/\text{kg bw}/\text{day} = 943 = \text{Intermediate Term MOE.}$$

These estimates are considered to be screening level estimates *i.e.*, conservative (protective). ARIA's level of concern for dermal exposure is for MOEs <100. In this case, MOEs are greater than 100 therefore post-application dermal exposure is not of concern for agricultural workers. Post-application inhalation exposure is expected to be negligible.

### **9.3 Restricted Entry Interval (REI)**

Imidacloprid is classified in Toxicity Category IV for acute dermal, acute inhalation, primary eye irritation and primary skin irritation therefore the interim Worker Protection Standard REI of 12 hours is sufficient to protect workers from excessive exposure.

## **10.0 Data Needs and Label Requirements**

### **10.1 Toxicology**

None.

### **10.2 Residue Chemistry**

A new Section F requesting imidacloprid tolerances on peanuts at 0.60 ppm and peanut, hay at 35 ppm is required.

The request for use and tolerance for imidacloprid on oats is not necessary; the request should be removed from Section F.

A revised Section F is required for proso millet, forage at 2.0 ppm; proso millet, hay at 6.0 ppm; proso millet, straw at 3.0 ppm; pearl millet, forage at 2.0 ppm; pearl millet, hay at 6.0 ppm; and pearl millet, straw at 3.0 ppm.

No separate tolerance is required for wild raspberry and it should be removed from the Section F.

A revised Section F requesting an imidacloprid tolerance on peanut, meal at 0.75 ppm is required.

A revised Section F requesting imidacloprid tolerances on soybean, seed at 3.5 ppm, and soybean, hay at 35 ppm is required.

A revised Section F for aspirated grain fractions at 240 ppm is required.

### **10.3 Occupational and Residential Exposure**

None.

References:

HIARC, TXR NO. 0051292, D. Nixon, 10/31/02  
MARC, DP Num: 28740, J. Tyler, 1/13/03  
Dietary Exposure: DP Num: 337874, 337877, & 337880, W. Cutchin, 4/2/07  
Chemistry Chapter: DP Num: 332757, 333517, & 334153, W. Cutchin, 4/11/07  
ORE: DP Num: 281610, 281612, & 281614, M. Dow, 2/26/07  
EFED Water: DP Num: 311925, R. Parker, 5/16/06  
DP Num: 337875, M. Dow, 4/17/07  
DP Num: 337878, M. Dow, 4/17/07  
PP#s: 3E6564, 3E6561, 3E6738, 3E6760, 5E6920, 5E6921, 5E6922, & 5E6923, DP Num:  
322225, 322249, 322250, 322251, 322253, 322257, 322255, & 322260, J. Tyler, 6/15/06  
PP#s: 2E6409, 1E6254, 2E6506, 2E6406, 2E6435, 0E6203, 2E6414, 1E6237, 2E6458, 1E6074,  
1E6225, 1E6268, 2E6421, 2E6417, & 2E6403, DP Num: 286101, 284746, 282414, 280766,  
278760, 286722, 280447, & 285741, J. Tyler, 3/4/03  
PP#s: 3F4169 & 3H5655; DP Num: 185148, F. Griffith, 9/20/93; DP Num: 200233, F. Griffith,  
6/8/94; and DP Num: 217632, F. Griffith, 2/29/96  
PP# 6F4682 & 0E6106; DP Num: 224074 & 263729; MRID: 43939401, 43939402, &  
45051401; Y. Donovan; 7/12/00

## Attachment 1: Toxicological Effects Tables

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	42055331	LD <sub>50</sub> = 424 mg/kg (M) LD <sub>50</sub> > 450 mg/kg (F)	II
81-2	Acute Dermal	42055332	LD <sub>50</sub> > 5000 mg/kg	IV
81-3	Acute Inhalation	42256317	LC <sub>50</sub> > 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

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rats)	NA	NA
870.3150 90-Day oral toxicity (nonrodents)	NA	NA
870.3200 21/28-Day dermal toxicity (rabbits)	42256329 (1990) Acceptable/guideline 0 or 1000 mg/kg/day 6 hr/day, 5 d/week	NOAEL = 1000 mg/kg/day (HDT) LOAEL = not identified
870.3250 90-Day dermal toxicity	NA	NA
870.3465 4-Week inhalation toxicity (rat)	42273001 (1989) Acceptable/guideline 0, 0.0055, 0.035, or 0.191 mg/L/day, 6 hr/day, 5 d/week for 4 weeks	NOAEL = 0.191 mg/L/day (HDT) LOAEL = not identified
870.3700a Prenatal developmental	42256338 (1992) Acceptable/guideline	<b>Maternal</b> NOAEL = 10 mg/kg/day LOAEL = 30 mg/kg/day based on decreased body weight

<b>Table A.2 Toxicity Profile of Imidacloprid Technical.</b>		
<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
toxicity (rats)	F: 0, 10, 30, or 100 mg/kg/day	gain and decreased corrected body weight gain. <b>Developmental</b> NOAEL = 30 mg/kg/day LOAEL = 100 mg/kg/day based on a slight increase in the incidence of wavy ribs.
870.3700b Prenatal developmental toxicity (rabbits)	42256339 (1992) Acceptable/guideline F: 0, 8, 24, or 72 mg/kg/day	<b>Maternal</b> NOAEL = 24 mg/kg/day LOAEL = 72 mg/kg/day based on maternal deaths and decreased maternal absolute body weights, body weight gains, and food consumption. <b>Developmental</b> NOAEL = 24 mg/kg/day LOAEL = 72 mg/kg/day based on abortion, total litter resorptions, increased postimplantation loss due to increased late resorptions, decreased fetal weights, and very low incidences of skeletal alterations.
870.3800 Reproduction and fertility effects (rats)	42256340 (1990) Acceptable/guideline 0, 100, 250, or 700 ppm F <sub>0</sub> (M/F): 0, 8.1/8.8, 20.1/22.1, or 56.7/62.8 mg/kg/day F <sub>1</sub> (M/F): 0, 6.4/7.2, 16.5/18.9, or 47.3/52.3 mg/kg/day	<b>Parental/Systemic</b> NOAEL = 16.5 mg/kg/day LOAEL = 47.3 mg/kg/day based on decreased pre-mating weight gain by F <sub>0</sub> males and females and F <sub>1</sub> females and decreased gestational weight gain by F <sub>1</sub> females. <b>Reproductive</b> NOAEL = 47.3 mg/kg/day (HDT) LOAEL = not identified <b>Offspring</b> NOAEL = 16.5 mg/kg/day LOAEL = 47.3 mg/kg/day based on decreased pup body weights in both litters of both generations.
870.4100a Chronic toxicity (rodents)	NA; see 870.4300	NA
870.4100b Chronic toxicity (dogs)	42273002 (1989) Acceptable/guideline 0, 200, 500, or 1250/2500 ppm M/F: 0, 6.1, 15, or 41 (first 16 wks.), then 72 mg/kg/day	NOAEL = 72 mg/kg/day (HDT) LOAEL = not identified
870.4200a Carcinogenicity (rats)	NA; see 870.4300	NA
870.4200b Carcinogenicity (mice)	42256335 (1991) Acceptable/guideline with 42256336 0, 100, 330, or 1000 ppm M: 0, 20, 66, or 208 mg/kg/day F: 0, 30, 104, or 274 mg/kg/day 42256336 (1991)	NOAEL = Males: 208 mg/kg/day; Females: 274 mg/kg/day LOAEL = Males: 414 mg/kg/day; Females: 424 mg/kg/day based on decreased body weights, food consumption and water intake. <b>No evidence of carcinogenicity.</b>

<b>Table A.2 Toxicity Profile of Imidacloprid Technical.</b>		
<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
	0 or 2000 ppm M: 0 or 414; F: 0 or 424 mg/kg/day	
870.4300 Combined Chronic/carcinogenicity (rats)	42256331 (1989) Acceptable/guideline with 42256332 0, 100, 300, or 900 ppm M: 0, 5.7, 16.9, or 51.3 mg/kg/day F: 0, 7.6, 24.9, or 73.0 mg/kg/day 42256332 (1991) 0 or 1800 ppm M: 0 or 102.6; F: 0 or 143.7 mg/kg/day	NOAEL = Males: 5.7 mg/kg/day; Females: 7.6 mg/kg/day LOAEL = Males: 16.9 mg/kg/day; Females: 24.9 mg/kg/day based on thyroid toxicity (increased incidence of mineralized particles in thyroid colloid) in males. <b>No evidence of carcinogenicity.</b>
870.5100 Bacterial reverse mutation	42256341 Acceptable/guideline	Negative for inducing reverse mutation in bacteria exposed to doses up to 5000 ug/plate.
870.5100 Bacterial reverse mutation	42256343 Acceptable/guideline	Negative up to 12,500 ug/plate.
870.5100 Bacterial reverse mutation	42256363 Acceptable/guideline	Negative up to 5500 ug/plate.
870.5300 <i>In vitro</i> mammalian cell gene mutation	42256342 Acceptable/guideline	Negative for inducing forward mutation in Chinese Hamster Ovary (CHO) (mammalian) cells treated up to 1222 ug/mL.
870.5300 <i>In vitro</i> mammalian cell gene mutation	42256364 Acceptable/guideline	Negative up to 2000 ug/mL.
870.5300 <i>In vitro</i> mammalian cell gene mutation	42256365 Acceptable/guideline	Negative up to 2000 ug/mL.
870.5375 <i>In vitro</i> mammalian chromosome abberation (HL)	42256345 Acceptable/guideline	Positive at 500 ug/mL - S9 and 1300 ug/mL +S9, both cytotoxic doses
870.5375 <i>In vitro</i> mammalian chromosome abberation (CHV79)	42256370 Acceptable/guideline	Negative up to 1000 ug/mL.
870.5375	42256371	Negative up to 1000 ug/mL.

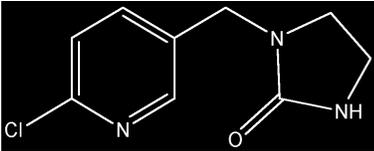
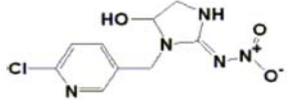
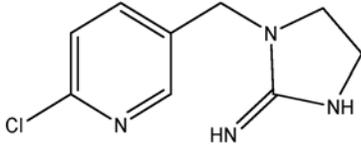
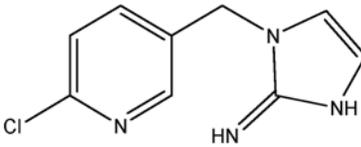
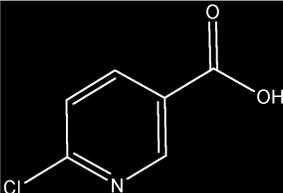
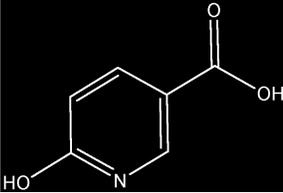
<b>Table A.2 Toxicity Profile of Imidacloprid Technical.</b>		
<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
<i>In vitro</i> mammalian chromosome abberation (CHO)	Acceptable/guideline	
870.5380 Mammalian germ cell chromosome abberation (mouse)	42256348 Unacceptable/guideline	Negative, but only tested up to 80 mg/ml.
870.5385 Mammalian bone marrow chromosome aberration (chinese hamster)	42256344 Acceptable/guideline	Negative for chromosome breakage up to 2000 ug/mL.
870.5395 Mammalian micronucleus (mouse)	42256347 Unacceptable/guideline	Negative, but only tested up to 80 mg/kg.
870.5395 Mammalian micronucleus (mouse)	42256366 Acceptable/guideline	Negative up to 50 mg/kg IP, toxic dose.
870.5395 Mammalian micronucleus (mouse)	42256367 Unacceptable/guideline	Negative up to 80 mg/kg IP, a non-toxic dose.
870.5395 Mammalian micronucleus (mouse)	42256368 Unacceptable/guideline	Negative up to 100 mg/kg PO, a non-toxic dose.
870.5395 Mammalian micronucleus (mouse)	42256369 Acceptable/guideline	Negative up to 160 mg/kg PO, toxic dose.
870.5500 DNA damage/repair <i>REC</i> assay	41156351 Acceptable/guideline	Negative up to 5000 ug/disc, the limit of solubility, with or without activation.
870.5550 Unscheduled DNA synthesis (RPH)	42256352 Acceptable/guideline	Negative up to 750 ug/mL, a cytotoxic dose.
870.5575 Mitotic gene conversion	42256353 Acceptable/guideline	Negative for crossing-over in yeast cells exposed with/without activation to precipitating levels of test article (5,000-10,000 ug/mL).
870.5550 Unscheduled DNA synthesis (RPH)	42256372 Acceptable/guideline	Negative up to cytotoxic doses (1333 ug/mL).
870.5900	42256349	Positive at 500 ug/mL -S9 and 2000 ug/mL +S9, both

<b>Table A.2 Toxicity Profile of Imidacloprid Technical.</b>		
<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
<i>In vitro</i> sister chromatid exchange (CHO)	Acceptable/guideline	cytotoxic doses.
870.5900 <i>In vitro</i> sister chromatid exchange (CHO)	47256350 Acceptable/guideline	Negative at cytotoxic doses of 400 ug/mL -S9 and 1250 ug/mL +S9.
870.59.15 <i>In vivo</i> sister chromatid exchange (chinese hamster bone marrow)	42256346 Acceptable/guideline	Negative up to 2000 mg/kg.
870.6200a Acute neurotoxicity screening battery rat	43170301 (1994) 43285801 (1994) Acceptable/guideline 0, 42, 151, or 307 mg/kg	NOAEL = not identified. LOAEL = 42 mg/kg based on decreased motor and locomotor activities observed in females.
870.6200b Subchronic neurotoxicity screening battery rat	43286401 (1994) Minimum 0, 150, 1000, or 3000 ppm M: 0, 9.3, 63.3, or 196 mg/kg/day F: 0, 10.5, 69.3, or 213 mg/kg/day	NOAEL = 9.3 mg/kg/day. LOAEL = 63.3 mg/kg/day based on decreased body weight gain.
870.6300 Developmental neurotoxicity (rat)	45537501 (2001) Acceptable/non-guideline 0, 100, 250, or 750 ppm Gest.: 0, 8.0-8.3, 19.4-19.7, or 54.7-58.4 mg/kg/day Lact.: 0, 12.8-19.5, 30.0-45.4, or 80.4-155.0 mg/kg/day	<b>Maternal</b> NOAEL = 20 mg/kg/day. LOAEL = 55 mg/kg/day based on decreased food consumption and body weight gain during lactation. <b>Offspring</b> NOAEL = 20 mg/kg/day. LOAEL = 55 mg/kg/day based on decreased body weight and body weight gain, decreased motor activity and decreased caudate/putamen width in females.
870.7485 Metabolism and pharmacokinetics rat	42256354 (1990) 42256356 (1987) M&F: 1.0 or 20.0 mg/kg (labeled) as single oral dose or 1.0 mg/kg unlabeled orally followed by 1.0 mg/kg single oral dose (labeled) or 1.0 mg/kg (labeled) single dose IV	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

**Table A.2 Toxicity Profile of Imidacloprid Technical.**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
	<p>M: 20.0 mg/kg single oral dose or 1.0 mg/kg single duodenal dose 42256357 (1991) M&amp;F: 1.0 mg/kg single oral dose M: 1.0 or 150 mg/kg single oral dose 42256373 (1990) M: 1.0 or 150 mg/kg single oral dose or 80.0 mg/kg single oral dose after 1 year 1800 ppm 42256355 (1987) M: 1.0 mg/kg single oral or IV dose 42256358 (1990) 42256359 (1990) Acceptable/guideline</p>	<p>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-CNA 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.</p> <p>In a comparison between [Methylene-14C] Imidacloprid and [Imidazolidine-4,5-14C] Imidacloprid, the rates of excretion were similar; however, the renal portion was higher with the imidazolidine-labeled test material. The imidazolidine-labeled test material also demonstrated higher accumulation in the tissues, with the major sites of accumulation being the liver, kidney, lung, and skin, and the minor sites being brain and muscle.</p> <p>In a comparison between [Methylene-14C] 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. 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.</p>
870.7600 Dermal penetration	NA	NA

## Attachment 2: Structures of Imidacloprid Metabolites

Name	Structure
Imidacloprid urea 1-[(6-chloro-3-pyridinyl)methyl]-2-imidazolidinone	
Imidacloprid hydroxy (WAK 4103)	
Imidacloprid guanidine (WAK 4140) 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-1H-imidazol-2-amine	
Imidacloprid olefin (WAK 3745) 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-1H-imidazol-2H-imidazol-2-imine	
6-CNA 6-chloronicotinic acid	
6-hydroxynicotinic acid	
WAK 3839	