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8

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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 23 July 2003

SUBJECT: **PP#: 9F06060. Thiacloprid in/on Pome Fruits and Cotton. Health Effects Division (HED) Risk Assessment.** PC Code: 014019. DP Barcode: D278485; Case No: 292302; Submission: 604757

FROM: David Soderberg, Chemist
John Doherty, Toxicologist
Robert Travaglini, Chemist
Reregistration Branch 3 (RRB3)/HED (7509C)

THRU: Catherine Eiden, Branch Senior Scientist
RRB3/HED (7509C)

TO: Marilyn Mautz
Meredith Laws, PM Team 04
Insecticide/Rodenticide Branch (IRB)/RD (7505C)

Bayer has submitted a petition for tolerances arising from use of thiacloprid, 3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene cyanamide, on pome fruits and cotton. This document summarizes the estimated risks to human health that could result from the proposed uses of thiacloprid.

This risk assessment and the residue chemistry data review and dietary risk assessment were provided by David Soderberg (RRB3); the hazard characterization was provided by John Doherty (RRB3); the occupational/residential exposure assessment by Robert Travaglini (RRB3); and the drinking water assessment by Ibrahim Abdel-Saheb of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances

The residue chemistry and toxicological databases support establishment of Section 3 registrations and permanent tolerances, expressed as thiacloprid, per se, in/on: the fruit, pome group at 0.3 ppm; pomace, wet apple at 0.6 ppm; cotton gin byproducts at 11 ppm; cottonseed at 0.02 ppm; beef, horse, sheep and goat fat at 0.02 ppm; beef, horse, sheep and goat liver at 0.15 ppm; beef, horse, sheep and goat kidney and meat byproducts at 0.05 ppm; beef, horse, sheep and goat muscle at 0.03 ppm; and milk at 0.03 ppm.

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1.0 EXECUTIVE SUMMARY

Thiacloprid, or 3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene cyanamide, is a neonicotinoid [specifically a chloronicotinoid] insecticide that Bayer has proposed for use on pome fruits and cotton. In addition to the technical grade of thiacloprid, two formulated products are proposed for registration: Calypso 4 Flowable and Calypso 70 WG. Thiacloprid is petitioned for registration to control aphids, fleahoppers, plant bugs, and whitefly on cotton crops, and to control leafminers, leafhoppers, mirid bugs, codling moth, plum curculio, scale insects, apple maggot, and aphids (except wooly aphid) on apple and pear (pome fruit) crops. The primary mode of action against insects is the disruption of the nervous system by acting as an inhibitor at nicotinic acetylcholine receptors.

Thiacloprid is applied foliarly by airblast to pome fruits, and to cotton by sprayer or aerially, using either a 40% Flowable formulation (Calypso 4 Flowable) or a 70% in a wettable granule formulation (Calypso 70 WG). Applications may be made to pome fruits at a maximum of 0.25 g ai/A/application, with a minimum of 7 days between applications, to a total of 0.50 g ai/A/season while maintaining a 30 day preharvest interval (PHI). It is recommended that not more than three applications be made to pome fruits per season. Applications may be made to cotton at a maximum of 0.094 g ai/A/application, with a minimum of 7 days between applications, up to a total of 0.28 g ai/A/season while keeping a 14 day PHI. It is recommended that not more than three applications be made to cotton per season.

Bayer has requested the establishment of permanent tolerances, resulting from use of thiacloprid in/on pome fruits and cotton, for residues of thiacloprid and its metabolites that contain the 6-chloropyridinyl moiety, measured as the common moiety 6-nicotinic acid (6-CNA), and expressed as parent thiacloprid. The MARC has decided that the residue of concern for risk assessment is thiacloprid plus metabolites retaining the thiazolidine ring intact, and that tolerances are to be measured and expressed in terms of thiacloprid, per se. [Because thiacloprid has limiting toxic effects that are different from imidacloprid, these effects must be partly or wholly associated with the thiazolidine portion of the thiacloprid molecule. Metabolites retaining this ring intact constitute the bulk of the non-parent residue and cannot be ruled out as having the same toxic effects as parent. Although metabolites in which this ring is broken also cannot be ruled out completely, these metabolites generally constitute only a minor proportion of the residue, and their higher polarity, and their greater difference from thiacloprid makes them less likely to share the same toxicity as the parent.]

1.1 Hazard Assessment

Thiacloprid is moderately toxic by oral, dermal and inhalation routes with little or no irritation following ocular or dermal application. An acceptable dermal sensitization study did not demonstrate sensitization.

Subchronic studies in rats, mice and dogs indicated that the liver is the target organ. The thyroid is also affected in rats at lower doses. Increases in certain liver enzymes, including UDP-Glu-Transferase, and possibly also aromatase, suggests that there may be a potential for secondary effects on reproductive organs (testes, ovaries, and uterus), but aromatase was not specifically increased, and further verification is needed before reproductive effects can be correlated with these increases in enzymes. Liver and thyroid were also affected in a subchronic inhalation study in rats.

Developmental studies did not show either qualitative or quantitative susceptibility. The acute neurotoxicity study showed reductions in motor and locomotor activity in female rats and tremors and ptosis in male rats. The acute reference dose (aRfD) is based upon these effects. The subchronic neurotoxicity study showed only decreased hindlimb grip strength. Chronic and carcinogenicity toxicity studies in rats, mice, and dogs primarily showed liver effects. The chronic reference dose (cRfD) is based upon liver and thyroid effects in the rat seen in combined chronic/carcinogenicity studies. There were increased thyroid and uterine tumors in rats and there were increased ovarian tumors in mice. Based on the available data, thiacloprid has been classified as "likely to be Carcinogenic in Humans ". The Q_1* is 4.06×10^{-2} based on rat uterine adenomas, adenocarcinoma and/or adenosquamous carcinoma combined tumor rates. The battery of mutagenicity and genetic toxicity tests did not indicate a mutagenicity concern.

Studies to provide the basis for a mechanism for tumor induction in the thyroid of rats and ovaries of mice and uterus of rats were also submitted. The proposed mechanism hypothesizes that the uterine and ovary tumors are a secondary effect of thiacloprid's demonstrated ability to induce liver enzymes, including aromatase, with subsequent increases in circulating estrogens and continuous stimulation of the uterus and ovary, eventually causing tumors in these organs. These studies confirmed the liver as the primary target of thiacloprid and indicated an apparent increase in aromatase, but the data from these studies were not sufficient to support a relationship between increased liver aromatase and the induction of tumors in rats and mice. There was also an insufficient basis to conclude that there was an association between increased hepatic UDP-Glu-T and the increases in thyroid tumors.

1.2 Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

On December 19, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for thiacloprid and the potential for increased toxic susceptibility of infants and children from exposure to thiacloprid as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document. The HIARC concluded that an additional 3X database uncertainty factor should be added for uncertainty due to lack of morphological measurements in the low- and mid-dose groups in the developmental neurotoxicity study. There

are no or low concerns for increased susceptibility, and no other residual uncertainties with regard to pre- and/or postnatal toxicity. Because of this HIARC conclusion and because the exposure databases (dietary food, drinking water, and residential) are complete, and the risk assessments include all the metabolites and/or degradates of concern and do not underestimate the potential risk for infants and children, the thiacloprid team has concluded that the Special FQPA factor can be reduced to 1X.

After reviewing the recommendations for thiacloprid, the HIARC decided that the following toxicological endpoints and associated uncertainty factors are to be used for risk assessments.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all population groups)	NOAEL = **3.1** mg/kg UF = **300**[a] **Acute RfD = 0.01** mg/kg.	FQPA SF = **1** **aPAD** = acute RfD / FQPA SF = **0.01** mg/kg	Acute Neurotoxicity - rats LOAEL = 11 mg/kg/day based on decreased motor activity in females.
Chronic Dietary (All populations)	NOAEL= **1.2** mg/kg/day UF = **300**[a] **Chronic RfD = 0.004** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF = **0.004** mg/kg/day	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy and retinal degeneration.
Incidental Oral - *All* Durations.	NOAEL= **1.2** mg/kg/day	**Residential** LOC for MOE = **300**[a] **Occupational** = N/A	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Dermal- *All* Durations. (a)	Oral study NOAEL= **1.2** mg/kg/day (dermal absorption rate = 5%)	**Residential** LOC for MOE = **300**[a] **Occupational** LOC for MOE= **100**	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Inhalation - *All* Durations.	NOAEL = **0.542** mg/kg/day	**Residential** LOC for MOE = **300**[a] **Occupational** LOC for MOE = **100**	28 day inhalation study in rats. LOAEL = 4.93 mg/kg/day based on liver hypertrophy increased N-DEM.
Cancer (oral, dermal, inhalation)	Q_1^* $(mg/kg/day)^{-1}$ = 4.06×10^{-2}	Classified as a "likely" human carcinogen as per the CARC meeting on January 29, 2003 based on thyroid tumors and uterine tumors in rats and ovary tumors in mice	

[a] Additional 3x database uncertainty factor for lack of morphological measurements in the low- and mid-dose groups in the developmental neurotoxicity study.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

On 7/23/2003 the HIARC issued a second memo (TXR number not yet assigned), superceding the first, that revised the dermal absorption factor to 5% based upon new data in the monkey. As a result of this second memo the 5% dermal absorption factor has been incorporated into all estimates of dermal exposure.

1.3 Residential Exposure Estimates

Thiacloprid has no residential uses at this time so no residential exposure is expected.

1.4 Dietary Exposure Estimates

Chronic, acute and cancer dietary exposure analyses were conducted using the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID™; ver. 1.30) program, incorporating consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996/1998. Assessments were performed at the partially refined Tier 3 level: field trial data, empirical processing data and projected percent crop treated estimates were incorporated. [Because this is a first time registration, actual monitoring data and actual usage (percent crop treated) data were not available.] Field trial crop data were also used to establish a theoretical dietary burden which was then used to estimate the residues that would be anticipated to result in meat and milk from residues in or on feed.

The acute (food only) dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 99.9th exposure percentile for the general U.S. population (20% of the aPAD) and for all other population subgroups. The most highly exposed population subgroup is "all infants," at 51% of the aPAD. The chronic (food only) dietary exposure estimates are also below HED's level of concern (<100% cPAD) for the general U.S. population (<1.0% of the cPAD) and for all other population subgroups. The most highly exposed population subgroup is "all infants," at 4.4% of the cPAD. The cancer (food only) excess lifetime cancer risk estimate for the U.S. General Population is 1.3 X 10^{-6}, based upon a Q1* of 4.06 X10^{-2}.

1.5 Drinking Water Exposure Estimates

Per the recommendations of the HED Metabolism Assessment Review Committee (MARC), EFED provided drinking water estimated environmental concentration (EECs) for thiacloprid and one of its major degradates, YRC 2894-amide (a.k.a. KKO 2254 - see attachment 1). EFED has incomplete environmental fate data for YRC 2894-amide so conservative assumptions were made about its fate based upon the fate of the parent. The Tier II screening models, PRZM and EXAMS, with the Index Reservoir and Percent Crop Area adjustment (IR-PCA PRZM/EXAMS) were used to estimate residues in surface water. The Screening Concentration in Ground Water (SCI-GROW) model was used to estimate the ground water residues.

For surface water, the acute (peak), chronic (annual average) and cancer (36 year average) EECs are 10.2 ppb, 2.36 ppb and 1.52 ppb, respectively. The ground water EEC is 0.06 ppb.

Thiacloprid has low-medium potential to leach to groundwater (koc 393-870 cm^3/g). It is not volatile, does not hydrolyze, and is stable to aqueous photolysis, although it does photo-degrade slowly in soil. The major route of dissipation for thiacloprid in soil is microbial degradation, with a soil half-life of from 1-5 days. Of ten metabolites identified in soil metabolism, YRC 2894

amide and YRC 2894 sulfonic acid were the only two major degradates (>10% of applied radioactivity). Under aerobic aquatic conditions thiacloprid degrades to YRC 2894 amide, with a half-life ranging from 10 to 63 days. Under anaerobic aquatic conditions, thiacloprid is stable with a half-life of >1 year. The calculated DT_{50} values for the degradates YRC 2894 amide and YRC 2894 sulfonic acid in an aerobic soil system ranged from 32 to 142 days, and 12 to 73 days, respectively. YRC 2894 amide also has low-medium potential for leaching to groundwater, but YRC 2894 sulfonic acid does have a greater potential for leaching. Neither thiacloprid nor its degradates were detected in soil samples below 15 cm depth.

1.6 Aggregate Exposure Scenarios and Risk Conclusions

Because thiacloprid has no proposed residential uses, there is no expected residential exposure, so aggregate scenarios for food and drinking water only were estimated. Human health aggregate risk assessments were conducted for: acute aggregate exposure (food + drinking water), chronic aggregate exposure (food + drinking water) and cancer aggregate exposure (food + drinking water). Short-term, intermediate- and long-term aggregate risk assessments, which are specifically used to assess residential exposure, were not performed.

The EEC value of 10 ppb is less than the appropriate drinking water level of comparison (DWLOC) value of 49 ppb for the acute exposure scenario for the "all infants" population subgroup. The EEC value of 2.4 ppb is less than the appropriate DWLOC value of 38 ppb for the chronic exposure scenario for the "all infants" population subgroup. The 36 year mean EEC value of 1.5 ppb is the same as the DWLOC for cancer for the whole U.S. Population, which is also 1.5 ppb (calculated relative to a risk of 3×10^{-6} for cancer).

In addition to aggregating food + water by calculation of DWLOCs, chronic and cancer food + water risks were also aggregated within the DEEM-FCID™ program. This is a more refined approach to estimating food + water exposure than calculation of DWLOCs, allowing actual body weights and water consumption from CSFII to be used in place of the default assumptions for body weight/water consumption that are applied in DWLOC calculations. This new approach of aggregating food and water within DEEM™ has been in discussion between EFED, HED and RD and it was agreed by the discussion group to try this approach in a pilot assessment for thiacloprid. As a result of this trial, the chronic aggregate food + water assessment for the U.S. general population was calculated at 2.0% of the cPAD (0.000081 mg/kg body weight/day). The chronic food + water assessment for the most highly exposed population subgroup, all infants, calculated this way was 8.5% of the cPAD (0.000340 mg/kg body weight/day). The estimated cancer risk from the food + water assessment for the U.S. general population calculated this way was 2.6×10^{-6}.

1.6 Occupational Exposure Estimates

Occupational exposures were examined for ten occupational handler, for mixing and loading, and for ground and airborne application scenarios (see section 7.1). Each scenario was evaluated with the handler wearing baseline clothing, wearing level 1 personal protective equipment, and protection through engineering controls (primarily use of water soluble bags). Worker exposure was also evaluated for post application exposure on day zero after application with these various levels of control applied.

To address short and intermediate term risk assessment, the dermal NOAEL of 1.2 mg/kg/day was selected for all exposure durations. The selected inhalation NOAEL was 0.542 mg/kg/day for all exposure durations. Dermal and inhalation absorption rates used for this assessment were 5.0% and 100%, respectively. The assessment uses a target margin of exposure (MOE) of 100 or more for occupational workers. MOEs greater than or equal to 100 for short and intermediate term exposure to workers are not considered to be of concern to HED. MOE's below 100 may be of concern, and may require mitigation with additional personal protective equipment (PPE) or engineering controls.

Since the toxicity data indicated similar effects for dermal and inhalation exposure, the dermal and inhalation MOEs were combined. Combined MOEs greater than 100 are not considered to be of concern to HED.

MOEs were first calculated for handlers wearing "baseline" clothing, which includes: long sleeve shirt, long pants, shoes and socks and no gloves. MOEs were next calculated for handlers wearing PPE at PPE Level 1 (PPE 1, single layer clothing, gloves) and engineering controls (primarily water soluble bags). Handler scenarios that do not reach the target MOEs with PPE, can be mitigated through the addition of engineering controls such as use of water soluble bags for dry flowable and water dispersible granular (WDG) formulations. Cancer risks were also calculated for these three levels of protection against exposure.

For occupational handlers wearing only baseline clothing, in short-term and intermediate-term exposures, the mixing and loading of liquid formulations of thiacloprid were below the MOE of 100 and required at least PPE1 protection. However, the combined dermal and inhalation MOEs for all of the10 scenarios identified and assessed by HED exceeded MOE 100 with application of minimal PPE protection (single layer clothing and gloves). (Product labeling currently calls for waterproof gloves, long-sleeved shirt and long pants).

For cancer risk assessment, based on a Q_1* of 0.0406 mg/kg/day and maximum application rates, with either the maximum PPE or engineering controls (primarily water soluble bags), the cancer risk estimates calculated for handler activities were below 1 X 10^{-6}, except for the activities in scenarios 5 and 6. The cancer risk for the mixing and loading of dry flowables for aerial application to cotton (scenario 5) with engineering controls is 2.0 X 10^{-6}; and cancer risk for the mixing and handling of liquids for aerial applications to cotton (scenario 6) with engineering controls is 1.47 X 10^{-6}. Although these two scenarios were not mitigated below 1 X 10^{-6}, one must consider that these results are based upon conservative assumptions. Maximum acreage was used for cotton. In addition, because thiacloprid is a new active ingredient, typical application rate data is not available, so the maximum application rate was also used to calculate cancer risk. Thus the risks for these two scenarios are very conservative and likely can be mitigated through use of reduced or typical application rates. Table 7.1.4. shows all of the cancer risk estimates.

Post-application MOEs, for short and intermediate-term exposures, exceed 100 for all agricultural activities for all treated crops on the day of application (day zero) and are not of concern. Additionally, the cancer endpoint was used to estimate post-application cancer risk. HED's target range for cancer probabilities are 1 X 10^{-4} to 1 X 10^{-6} for occupational assessments. The cancer

probabilities on the day of application were estimated using the Q_1* (.0406 mg/kg/day) at the maximum labeling application rate. Cancer risks ranged from 2.2 X 10-7 to 1.6 X 10-5 at 0 days REI.

The interim Worker Protection Standard (WPS) restricted entry interval (REI) for this chemical would be 12 hours based on Toxicity Category III for acute dermal and inhalation. The calculated post-application MOEs at zero days after treatment exceed 100 for all crop related activities. HED recommends that the 12 hour REI on the product label be retained.

No chemical specific handler exposure data were submitted in support of this proposed Section 3 registration action. It is the standard practice of HED to use data from the Pesticide handler's Exposure Database (PHED) Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), to assess handler exposures for regulatory actions when chemical specific monitoring data are not available (HED Scientific Advisory Council for Exposure Draft Policy #7, dated 1/28/99).

1.7 Recommendations for Tolerances

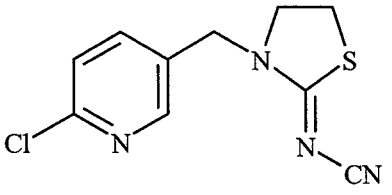
HED recommends that the residue chemistry and toxicological databases support the following *unconditional registrations* and permanent tolerances for residues of thiacloprid, per se, in/on: pome fruits at 0.3 ppm, wet apple pomace at 0.6 ppm, cotton gin byproducts at 11 ppm, cottonseed at 0.02 ppm, cattle, sheep and goat fat at 0.02 ppm, meat and milk at 0.03 ppm, liver at 0.15 ppm, and kidney and meat by-products at 0.05 ppm (see Attachment 3 for a detailed listing of the tolerances recommended by HED). A revised Section F, incorporating these changes, should be submitted.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1 Identification of Active Ingredient

Registrant:	Bayer
Common name:	thiacloprid
Pesticide Type:	Insecticide
Chemical Class:	Chloronicotinoid
Target Pests:	Sucking insects, aphids, leafminers, leafhoppers, mirid bugs, codling moths, scale insects, mealy bugs, plant bugs, white flies, pear psylla, plum curculio, apple maggot.
Mode of Action:	Disrupts the nervous system as an inhibitor at nicotinic acetylcholine receptors. It blocks the signals that are induced by acetylcholine at the post-synaptic membrane, resulting in nerve function impairment.
Formulations:	97% technical, 4.0% Flowable (suspension concentrate), 70% water dispersible granules
Trade Names:	Calypso 40% Flowable, Calypso 70 WG
EPA Reg Nos.:	3125-LGA
CAS Number:	111988-49-9
PC Code:	014019
Chemical name:	
CAS:	[3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene]cyanamide
IUPAC:	3-(6-chloro-3-pyridylmethyl)-1,3-thiazolidin-2-ylidenecyanamide
Empirical Formula:	$C_{10}H_9N_4S_1C_{l1}$
Molecular Weight:	252.73

2.2 Structural Formula



Thiacloprid

See Attachment 1 for structures of all pertinent metabolites mentioned in this risk assessment.

2.3 Physical and Chemical Properties

Product chemistry data were submitted and reviewed in conjunction with the thiacloprid registration package (Shyam B. Mathur, Ph.D, Technical Review Branch/RD DP BARCODE: D281247, 11 February 2003).

TABLE 2.3.1. Physicochemical Properties of the Technical Grade Test Compound

Parameter	Value
Melting point/range	136° C
pH	7.40 at 20° C
Density	1.46 g/mL at 20° C
Water solubility (__°C)	185 mg/L at 20° C
Solvent solubility (mg/L at __°C)	Solubility in organic solvents (g / l): n-Heptane: < 0.1; Xylene: 0.30; 1- Octanol:1.4; 2-Propanol: 3.0; Ethyl acetate: 9.4; Polyethylene glycol (PEG): 42; Acetonitrile: 52; Acetone: 64; Dimethylsulfoxide (DMSO): 150; Dichloromethane: 160.
Vapour pressure at __°C	3 x 10 (-12) hPa at 20C 8 x 10(-12) hPa at 25C
Dissociation constant (pK_a)	AI has no basic or acidic properties in aqueous solutions
Octanol/water partition coefficient $Log(K_{OW})$	1.26 at 20° C
UV/visible absorption spectrum	λ max — Extinction coefficient 295-300 nm — 49.1828 301-305 nm — 39.3463

Thiacloprid is a yellowish crystal powder at room temperature with a low vapor pressure, so that losses due to volatilization or sublimation are expected to be small.

3.0 HAZARD CHARACTERIZATION

The existing toxicological database for thiacloprid supports the establishment of permanent tolerances for residues of thiacloprid in/on the RACs resulting from the proposed uses.

3.1 Hazard Profile

Thiacloprid is moderately toxic to mammals by the oral, dermal and inhalation routes. There was little if any irritation following ocular or dermal application of thiacloprid. An acceptable dermal sensitization study did not demonstrate sensitization.

Subchronic studies in rats, mice and dogs indicate the liver is the target organ for thiacloprid. The thyroid is also affected in rats at lower doses. A pattern of increases in liver enzymes including UDP-Glu-Transferase, and possibly also aromatase, suggests that there may be a potential for secondary effects on reproductive organs, the testes, ovaries, and uterus, but, aromatase was not specifically increased and further verification is needed before effects on reproductive organs can be correlated with these increases in liver enzymes. Liver and thyroid were also affected in a subchronic inhalation study in rats.

Developmental studies show maternal and fetal effects occurring at the same doses, however, the effects occurring in the dams were reduced body weight gain, food consumption, and fecal output, whereas, in the fetuses, effects included skeletal malformations and resulting decreased body weights. Although quantitative susceptibility was not noted, these results imply a qualitative susceptibility of low concern, because the fetal effects are considered more severe than the adult effects. Reproduction studies show liver and thyroid effects in the dams, as well as reproductive effects (dystocia - difficult birth). Offspring effects include decreased pup weight. Doses of thiacloprid associated with toxic effects were the same in dams and offspring, and maternal effects were more severe than offspring effects. Consequently, the reproduction studies do not show either qualitative or quantitative susceptibility.

Neurotoxicity has been demonstrated based on results of acute and developmental neurotoxic (DNT) studies. The acute neurotoxicity study showed reductions in motor and locomotor activity in female rats, showed tremors and ptosis in male rats, and the acute reference dose (aRfD) is based upon these effects. The subchronic neurotoxicity study showed only decreased hindlimb grip strength as an non-specific indicator of neurotoxicity. Additional data on morphological changes for low and mid-dose groups are needed before conclusions can be drawn from the DNT study.

Acute toxicity studies yielded the categories found in Table 3.1.1.

Chronic and carcinogenicity toxicity studies in rats, mice, and dogs primarily show liver effects as the indicator of systemic toxicity. The chronic reference dose (cRfD) is based upon liver and thyroid effects in the rat seen in combined chronic/carcinogenicity studies. In mice, the adrenal X-zone showed vacuolation and there were also non-neoplastic effects in the "eosinophilic luteinized cells"in the ovary. Results from the mouse subchronic study also show treatment related increases in ovary “activated interstitial glands”. There were increased incidences of thyroid and uterine tumors in rats. Mice showed increased incidences of ovarian tumors. The battery of mutagenicity and genetic toxicity tests did not indicate a mutagenicity concern. Based

on the available data, thiacloprid has been classified as "likely to be Carcinogenic in Humans ". The Q_1* is 4.06 x 10^{-2} based on rat uterine adenomas, adenocarcinoma and/or adenosquamous carcinoma combined tumor rates [Thiacloprid: Report of the CARC, 26 March 2003, TXR 0051705; Thiacloprid - Quantitative Risk Assessment (Q1*), 20 February 2003, TXR 0051572].

Special studies conducted to provide the basis for a mechanism for tumor induction in the thyroid of rats and ovaries of mice and uterus of rats were provided. The proposed mechanism hypothesizes that the uterine and ovary tumors are a secondary effect of thiacloprid's demonstrated ability to induce liver enzymes, including aromatase, with subsequent increases in circulating estrogens and continuous stimulation of the uterus and ovary, eventually causing tumors in these organs. These studies confirmed the liver as the primary target of thiacloprid and indicated an apparent increase in aromatase, but, the Mechanism of Toxicity SARC (Mechanism of Toxicity SARC report for thiacloprid, 19 February 2003, TXR 0051476) concluded that the data from these studies were insufficient to support a cause and effect relationship between increased liver aromatase and the induction of uterine tumors in rats and ovarian tumors in mice. The Carcinogenicity Assessment Review Committee also determined that there was an insufficient basis to conclude an association between increased hepatic UDP-Glu-T and destruction of circulating thyroid hormones as the cause of the increases in thyroid tumors.

A 5% dermal absorption value is considered appropriate for thiacloprid formulated as a 40.4% liquid formulation [thiacloprid (YRC 2894) SC 480], for other liquid thiacloprid formulations similar to the SC 480 formulation, and for aqueous dilutions of most thiacloprid formulations (Thiacloprid HIARC report, 23 July 2003, TXR # not yet assigned).

Thiacloprid is rapidly absorbed and is rapidly excreted after the following metabolic processes, with little remaining in the tissues. The metabolic processes were summarized as: 1) hyroxylation of the thiazolidine ring and subsequent glucuronidation (as shown by metabolite PIZ 1270), 2) hydroxylation of the cyanamide moiety (metabolite KNO 1891), 3) opening of the thiazolidine ring (e.g., metabolites KNO2672, PIZ1297F/WAK 6935), 4) formation of an oxazole ring (metabolite PIZ 1253), 5) oxidation and subsequent methylation of the thiazolidine ring (e.g., PIZ 1297E and PIZ 1269X), and 6) oxidative cleavage of the methylene bridge (PIZ 1243). Only minor gender-related quantitative differences in metabolite profiles were observed.

Table 3.1.1. Acute Toxicity of Thiacloprid Technical Grade Active Ingredient (TGAI)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral-mouse	45344002	LD_{50} between 100 and 140 mg/kg for males and 140 and 200 mg/kg for females	N/A
870.1100	Acute Oral- rat	44927644	LD_{50} 621 mg/kg - males 396 mg/kg - females	II

Table 3.1.1. Acute Toxicity of Thiacloprid Technical Grade Active Ingredient (TGAI)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral -rat	44927730	LD_{50} between 700 and 1000 mg/kg (males) LD_{50} between 300 and 500 mg/kg (females).	II
870.1100	Acute Oral - rat (metabolite KKO 2254-4-2)	45307404	LD_{50} > 2000 mg/kg	N/A
870.1100	Acute Oral - rat (metabolite WAK 6999)	44927737	LD_{50} > 2000 mg/kg	N/A
870.1100	Acute Oral - rat (intermediate 2-cyaminino-1,3-thiazolidin.	45307407	LD_{50} > 200 mg/kg (males) LD_{50} between 200 and 2000 mg/kg (females)	N/A
870.1200	Acute Dermal	44927731	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation	44927732	LC_{50} > 0.481 mg/L	III
870.2400	Primary Eye Irritation	44927635	Ocular irritation resolving in 24 hours.	IV
870.2500	Primary Skin Irritation	44927635	Very slight erythema resolving in 72 hours.	IV
870.2600	Dermal Sensitization	44927733	Did not indicate sensitization .	N/A

Table 3.1.3. Toxicity Profile of Thiacloprid Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity - rats	44927714 (1997) Acceptable/Guideline 0, 25, 100, 400, or 1600 ppm.	NOAEL = 100 ppm (7.3 mg/kg/day in males, 7.6 mg/kg/day in females). LOAEL = 400 ppm (28.6 mg/kg/day in males; 35.6 mg/kg/day in females) based on decreased body weight throughout treatment.
870.3100 90-day oral toxicity -mice	44927633 (1994) 44927634 (1995) 44927636 (1998) Acceptable/Guideline 0, 50, 250, 1250 or 6250 ppm.	NOAEL < 50 ppm (27.3 mg/kg/day) in females. LOAEL = 50 ppm (27.2 mg/kg/day) in females based on adrenal X-zone changes in females. NOAEL = 250 ppm (102.6 mg/kg/day) in males. LOAEL = 1250 ppm (542.4 mg/kg/day) in males based on liver effects (weight and hypertrophy).

Table 3.1.3. Toxicity Profile of Thiacloprid Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3150 90-Day oral toxicity in nonrodents	44927709 (1998) 44927747 (1997) Acceptable/Guideline 0, 250, 1000 or 4000 ppm or 0, 8.5, 34.9, 68 mg/kg/day for males and 0, 8.9, 34.7 or 65.3 mg/kg/day for females.	NOAEL = 250 ppm (8.5 for males and 8.9 mg/kg/day for females). LOAEL = 1000 ppm (~34.9 mg/kg/day) based mainly on liver enzyme changes, thyroid hormone level (T4) and binding capacity changes and prostatic weight change and prostatic hypertrophy.
870.3200 21/28-Day dermal toxicity	44927710 (1997) Acceptable/Non-Guideline. 0, 100, 300 or 1000 mg/kg/day.	NOAEL = 300 mg/kg/day (in females) LOAEL = 1000 mg/kg/day based on liver and thyroid effects and clinical signs.
870.3250 90-Day dermal toxicity	No Study. Study not considered required.	
870.3465 28-Day inhalation toxicity	44927715 (1998) 44927736 (1995) Acceptable/Non-guideline. 0, 2, 18.2 and 143.4 mg/m^3.	NOAEL = 2 mg/m^3. LOAEL = 20 mg/m^3 (achieved mean analytical dose of 18.2 mg/m^3) based on liver effects (hypertrophy and increased N-DEM).
870.3700a Prenatal developmental in rats	44927741 (1997) Acceptable/Guideline 0, 2, 10 or 50 mg/kg/day.	Maternal Toxicity: NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on decreased body weights, body weight gains, food consumption, increased urination, and changes in water consumption. Developmental NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on increased resorptions (complete and late), skeletal retardations, variations (wavy ribs and asymmetrical sternebrae), and malformations (dysplastic humerus, radius, and scapulae) and on decreased fetal weights.
870.3700b Prenatal developmental in rabbits	44939201 (1996) Acceptable/Guideline 0, 2, 10 or 45 mg/kg/day.	**Maternal Toxicity:** NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on decreased body weight gains, food consumption, and fecal output. **Developmental Toxicity:** NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on decreased fetal weights.
870.3800 Reproduction and fertility effects	44927702 (1995) 44927638 (1997) Acceptable/Guideline 0, 50, 300 or 600 ppm.	**Parental/Systemic:** NOAEL = 50 ppm (3.5 mg/kg/day in males) LOAEL = 300 ppm (21 mg/kg/day based on increased liver and thyroid weights and on hepatocytomegaly, liver necrosis, and thyroid follicular cell hypertrophy. **Reproductive**: NOAEL = 50 ppm (4.2 mg/kg/day in females) LOAEL = 300 ppm (26 mg/kg/day) based on dystocia. **Offspring:** NOAEL = 50 ppm (4.2 mg/kg/day in females) LOAEL = 300 ppm (21 mg/kg/day in females) based on decreased pup weight during lactation.
870.4100a Chronic toxicity rats.	Refer to combined chronic feeding/carcinogenicity study below.	

Table 3.1.3. Toxicity Profile of Thiacloprid Technical.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	44927716 (1998) Acceptable/Guideline 0, 40, 100, 250 or 1000 ppm.	No firm LOAEL was established for this chronic feeding study with dogs. There were no effects that were of sufficient magnitude or consistency to justify that they were definite responses to treatment. Certain effects noted in the subchronic dog study on the prostate and other male organs and an apparent effect on uterine weight in the subchronic dog study were not seen in this chronic study. This may be because the dogs in this study had reached maturity.
870.4200 Carcinogenicity rats	Refer to combined chronic feeding/carcinogenicity study below.	
870.4200 Carcinogenicity mice	44927710 (1998) 44927711 (1998) Acceptable/Guideline 0, 20, 1250 or 2500 ppm.	NOAEL = 30 ppm (5.7 mg/kg/day in males and 10.9 mg/kg/day in females). LOAEL = 1250 ppm (234.1 mg/kg/day in males and 475.3 mg/kg/day in females) based on liver toxicity and microscopic lymph node changes in both sexes and increased X-zone vacuolization of The adrenal glands in female mice. . **Evidence of carcinogenicity** based increased incidence of ovarian luteomas.
870.4300 Combined chronic feeding and carcinogenicity in rats.	44927712 (1998) Acceptable/Guideline 0, 25, 50, 500 or 1000 ppm.	NOAEL = 25 ppm (1.2 mg/kg/day in males and 1.6 mg/kg/day in females). LOAEL = 50 ppm (2.5 mg/kg/day in males and 3.3 mg/kg/day in females) based on liver toxicity (hepatocellular hypertrophy and cytoplasmic change and increased enzyme activity), thyroid follicular epithelial hypertrophy in males and oculotoxicity (retinal atrophy) in females. **Evidence of carcinogenicity** based on increased incidence of thyroid follicular cell adenomas in males and possibly also in females and increased incidence of uterine tumors (adenocarcinomas)
870.6200a Acute neurotoxicity screening battery	44927703 (1997) 44927704 (1998) Acceptable/Guideline 0, 3.1, 11, 22, 53 or 109 mg/kg/day (doses in one or the other study).	NOAEL = 3.1 mg/kg/day LOAEL = 11 mg/kg/day in females based on reductions in motor and locomotor activity. In males, the LOAEL was 22 mg/kg bw (based on FOB observations of slight tremors and ptosis of the eyelids on the day of treatment), and the NOAEL of 11 mg/kg bw.
870.6200b Subchronic neurotoxicity screening battery	44927645 (1997) Acceptable/Guideline 0, 50, 400 or 1600 ppm.	NOAEL = 400 ppm (24.2 mg/kg/day in males and 27.9 mg/kg/day in females). LOAEL = 1600 (101 mg/kg/day in males and 115 mg/kg/day in females) based on decreased body weight gains and food consumption in both sexes and decreased hindlimb grip strength in males.
870.6300 Developmental neurotoxicity	45516601(2001) Unacceptable/ guideline. 0, 50, 300, or 500 ppm (0, 4.4, 25.6, and 40.8 mg/kg/day during gestation; 0, 8.2, 49.4, and 82.8 mg/kg/day during lactation).	NOAEL = 50 ppm (4.4 mg/kg/day) LOAEL = 300 ppm (25.6 mg/kg/day based on deceased body weight gain and food consumption during early gestation (GD 0-6. ***Tentative* Offspring** NOAEL = 50 ppm (4.4 mg/kg/day) LOAEL = 300 ppm (25.6 mg/kg/day) based on decreased pre-weaning and post-weaning body weights in both sexes and delayed sexual maturation in the males, and altered performance in passive avoidance testing.
870.7485 Metabolism and pharmaco-kinetics	44927609 (1998) 44927605 (1996) 44927612 (1997) Acceptable/Guideline	The absorption, excretion, distribution, retention and characterization of the metabolites have been investigated and defined.

Table 3.1.3. Toxicity Profile of Thiacloprid Technical.		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7600. Dermal absorption - monkeys.	45846701 45846702	A 5% dermal absorption value is appropriate for estimating the risk resulting from dermal exposure to Thiacloprid formulated as a 40.4% liquid formulation (SC 480). This 5% value is also appropriate for other liquid thiacloprid formulations that are similar to the SC 480 liquid formulation product tested and for aqueous dilutions of most thiacloprid formulations.
Special studies	Several special studies conducted to attempt to establish a mode of action for the induction of thyroid tumors in rats based on increased thyroid hormone metabolism and activation of the liver/pituitary/thyroid axis, induction of uterine tumors in rats and ovary tumors in mice and dystocia in rats were presented. Since these studies are not required for registration, they are not being listed here. Please refer to the MTARC review (TXR # 0051476 and dated February 19, 2003) for both the list of these and HED's interpretation of these studies.	

3.2 FQPA Considerations

On December 19, 2002 the HED HIARC evaluated the potential for increased susceptibility of infants and children from thiacloprid toxic effects according to the February 2002 OPP 10X guidance document. Based upon the following, the HIARC determined that a 3X database uncertainty factor should be applied.

A. Special Sensitivity to Infants and Children: The HIARC concluded that there is no increase in quantitative susceptibility demonstrated in the rat developmental neurotoxicity, rabbit developmental or rat reproduction studies. However, there was noted a *qualitative* increase in susceptibility in the rat developmental toxicity study as indicated by increases in resorptions, increases in skeletal variations and retardations and malformations and decreases in fetal body weight that occurred at the same dose showing a decrease in maternal body weight.

The HIARC concluded that there is a *low* degree of concern for the apparent qualitative increase in susceptibility noted in the rat developmental toxicity study. In particular, there is a well characterized dose response with a clear NOAEL and LOAEL and the fetal effects were noted in the presence of maternal toxicity. There are no residual uncertainties. As a result, the HIARC concluded that the FQPA safety factor for special sensitivity in infants and children could be reduced to 1X.

B. Recommendation for a Developmental Neurotoxicity Study: A developmental neurotoxicity study has been submitted and reviewed. The current (March 2003) classification is Unacceptable/Guideline pending receipt and review of additional information.

In accordance with the 2002 OPP 10x guidance document, the HIARC determined that a Database Uncertainty Factor (UF_{DB}) of 3x is required for the lack of morphometric assessments for the low- and mid-dose group animals in the developmental neurotoxicity study (DNT). A 3x factor was judged to be adequate because the dose selected for overall risk assessments is already based on the most sensitive end points for acute (i.e. clinical signs indicative of neurotoxicity) and chronic (i.e. liver and thyroid effects) dietary and non-dietary exposure scenarios, and the available data indicate that the full characterization of brain morphometrics from the DNT study would not be

expected to lower the dose used for risk assessments by more than 3-fold.

To elaborate, since the magnitude (4-14%) of the morphometric histopathology changes seen in the offspring at the highest dose (40.8 mg/kg/day) in the developmental neurotoxicity study were considered to be at or near the limit of detection for differences in morphometric measurements, the HIARC concluded that 3X would be adequate to account for possible slight effects at lower doses. The actual doses used to establish the acute RfD (3.1 mg/kg/day) and the chronic RfD (1.2 mg/kg/day) are 13 and 34 fold lower, respectively, than the 40.8 mg/kg/day dose where the effects of minimal magnitude were seen. Applying the 3 X UFDB further renders the adjusted doses 39 and 102-fold lower than the dose level where the effects of minimal magnitude were seen. Therefore the HIARC concluded that 3X is adequate to account for any possible morphometric effects that may be noted in the lower doses for which the additional readings are being sought.

C. Overall recommendations for additional uncertainty factors: Following the HIARC conclusion, the thiacloprid team has reviewed the database for exposure and has determined that no additional safety factor is required for exposure, because (a) there are no special concerns regarding pre- or post-natal toxicity exposure, (b) the exposure databases (dietary food and drinking water) are complete and/or employ conservative assumptions, (c) there is no residential exposure, (d) the risk assessments cover or approximate all the metabolites and degradates of concern, and (e) the assessments do not underestimate the potential risk for infants and children. The thiacloprid team has therefore concluded that an additional safety factor for uncertainties in the exposure database is not required and can be reduced to 1X.

Thus, in summary, a 3X database uncertainty factor is required and is to be applied across all aggregate risk assessments. A 1X FQPA safety factor for special sensitivity in infants and children is to be applied across all of the aggregate risk assessments. The FQPA safety factor (1X) and database uncertainty factor (3X) are not applied to occupational assessments.

Per the Office of Pesticide Program's (OPP) policy, a reference dose (RfD) modified by an FQPA safety factor is referred to as a population adjusted dose (PAD). For thiacloprid the acute reference dose (aRfD) is 0.01 mg/kg/day and the chronic reference dose (cRfD) is 0.004 mg/kg/day. Because the FQPA safety factor was reduced to 1X for all aggregate risk assessments, an acute PAD (aPAD) of 0.01 mg/kg/day and a chronic PAD (cPAD) of 0.004 mg/kg/day were used to estimate risk in the assessments based upon acute and chronic aggregate exposures, which included food and drinking water.

3.3 Dose-Response Assessment

3.3.1. Acute Dietary Endpoint: The acute dietary endpoint was taken from an acute neurotoxicity study in rats. At the LOAEL of 11 mg/kg/day decreased motor activity in females was observed. The NOAEL was 3.1 mg/kg body weight (bw). The LOAEL in males was 22 mg/kg bw (based on FOB observations of slight tremors and ptosis of the eyelids on the day of treatment), with a NOAEL of 11 mg/kg bw.

3.3.2 Chronic Dietary Endpoint and All Term Incidental Oral Endpoints and All Term Dermal Endpoints: The chronic dietary endpoint and all term incidental oral and all term

dermal endpoints were based upon a chronic feeding study in rats, with a LOAEL of 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy and retinal degeneration in males. The LOAEL in females was 3.3 mg/kg/day. The corresponding NOAEL is 25 ppm (1.2 in males and 1.6 in females mg/kg/day).

[The rat chronic feeding study is used for incidental oral and dermal exposure because the LOAEL is based on induction of the liver hypertrophy and cytoplasmic change, thyroid hypertrophy and induction of the enzymes, UDP-Glu-T and aromatase; and induction of hepatic enzymes can occur following only about four weeks of dosing or less.]

3.3.3. Carcinogenicity: In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment: (July 1999), the CARC classified thiacloprid into the category **"Likely to be Carcinogenic to Humans"**. The Committee further recommended that a linear low-dose extrapolation approach be applied to the quantifications of risk to be estimated, based upon male rat thyroid, rat uterine, and mouse ovarian tumors. The data did not support a mode of action. The Q_1* recommended by the Science Information Management Branch (SIMB) is 4.06×10^{-2} in human equivalents based on the rat uterine adenoma, adenocarcinoma and/or adenosquamous carcinoma combined tumor rates(memo from Lori Brunsman: SIMB/HED, dated February 20, 2003, TXR # 0051572).

3.3.4. Dermal Penetration: A 5% dermal absorption value is considered to be appropriate for estimating the risk resulting from dermal exposure to Thiacloprid formulated as a 40.4% liquid formulation (YRC 2894 SC 480). This 5% value is also considered appropriate for other liquid thiacloprid formulations that can be shown to be similar to the SC 480 liquid formulation product tested and for aqueous dilutions of most thiacloprid formulations.

3.3.5. All- duration Inhalation Endpoints: all inhalation endpoints were based upon the 28 day inhalation study in rats. At the LOAEL of 20 mg/m3, or 4.93 mg/kg/day liver hypertrophy and increased aminopyrine-N-demethylase (N-DEM) were observed. The NOAEL is 2 mg/m^3 (or 0.542 mg/kg/day). Note: The liver hypertrophy and increase in N-DEM are considered a LOAEL because these same increases are thought to be related to increases in UDP-Glu-T and aromatase which can affect circulating hormones in response to thiacloprid treatment.

3.3.6. Summary: Toxicological Endpoints Used in Risk Assessments

Table 3.3.2. Summary of Toxicological Dose and Endpoints for Thiacloprid for Use in Human Health Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all population groups)	NOAEL = **3.1** mg/kg UF = **300** **Acute RfD = 0.01** mg/kg.	FQPA SF = **1** **aPAD** = acute RfD / FQPA SF **= 0.01** mg/kg	Acute Neurotoxicity - rats LOAEL = 11 mg/kg/day based on decreased motor activity in females.
Chronic Dietary (All populations)	NOAEL= **1.2** mg/kg/day UF = **300** **Chronic RfD = 0.004** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF **= 0.004** mg/kg/day	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy and retinal degeneration.
Incidental Oral - *All* Durations.	NOAEL= **1.2** mg/kg/day	**Residential** LOC for MOE = **300** **Occupational** = N/A	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Dermal- *All* Durations.	Oral study NOAEL= **1.2** mg/kg/day (dermal absorption rate = 5%)	**Residential** LOC for MOE = **300** **Occupational** LOC for MOE= **100**	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Inhalation - *All* Durations.	NOAEL = **0.542** mg/kg/day	**Residential** LOC for MOE = **300** **Occupational** LOC for MOE = **100**	28 day inhalation study in rats. LOAEL = 4.93 mg/kg/day based on liver hypertrophy increased N-DEM.
Cancer (oral, dermal, inhalation)	Q_1^* $(mg/kg/day)^{-1}$ = 4.06×10^{-2}	Classified as a "likely" human carcinogen as per the CARC meeting on January 29, 2003 based on thyroid tumors and uterine tumors in rats and ovary tumors in mice	

3.4 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 was 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, thiacloprid may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Proposed Uses

Thiacloprid, 3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene cyanamide, is a neonicotinoid insecticide that Bayer has proposed for use on pome fruits and cotton. It is applied foliarly to both cotton and to pome fruits, as an aerial or airblast spray, made from a 40% Flowable formulation (Calypso 4 Flowable) or a 70% in a wettable granule formulation (Calypso 70 WG). Applications may be made to pome fruits at a maximum of 0.25 g ai/A/application, with a minimum of 7 days between applications, to a total of 0.50 g ai/A/season while maintaining a 30 day preharvest interval (PHI). It is recommended that not more than three applications be made to pome fruits per season. Applications may be made to cotton at a maximum of 0.094 g ai/A/application, with a minimum of 7 days between applications, up to a total of 0.28 g ai/A/season while keeping a 14 day PHI. It is recommended that not more than three applications be made to cotton per season. The petitioners have provided product labels with use directions for these formulations. The proposed use patterns are acceptable and are supported by the available residue data.

Table 4.1.1. Summary of Proposed Use Patterns for thiacloprid.

PP/ID#[a]	Use/ Commodity	Proposed Formulation(s)[1]	PHI [2] (days)	Max. #App. /yr.	Maximum Application Rate (lb.ai/A)		RTI [3] (days)	Restrictions
					per app.	per yr		
POME FRUITS								
	Pome Fruits	Calypso 4 Flowable	30	3	0.25	0.50	7	Near lakes, rivers, reservoirs: no aerial application within 100 feet; do not allow airblast spray to go beyond cultivated area.
		70 WG	30	3	0.25	0.50	7	Near lakes, rivers, reservoirs: no aerial application within 100 feet; do not allow airblast spray to go beyond cultivated area.
COTTON								
	Cotton	Calypso 4 Flowable	14	3	0.09375	0.28	7	Near lakes, rivers, reservoirs: no aerial application within 100 feet; do not allow airblast spray to go beyond cultivated area.
		70 WG	14	3	0.09375	0.28	7	Near lakes, rivers, reservoirs: no aerial application within 100 feet; do not allow airblast spray to go beyond cultivated area.

4.2 Dietary Exposure/Risk Pathway

The residue chemistry data submitted in support of proposed petitions were in the following HED-memoranda: Pome Fruit (D. Soderberg, D284060); Cotton (D. Soderberg, D284061). These were supported by apple processing studies (D. Soderberg, D284071, D284067, D284069) and a cotton processing study (D. Soderberg, D284090). The drinking water assessment was completed by EFED on 3/6/03 (Ibrahim Abdel-Saheb, D288331). The acute and chronic dietary exposure assessment was completed in a HED-memorandum dated 6/23/03 (D. Soderberg, D289292).

4.2.1. Residue Profile

Bayer Corporation has submitted a petition to register the use of thiacloprid on pome fruits and cotton. Bayer has proposed the establishment of permanent tolerances for the residues of thiacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as the parent, in/on the following RACs: pome fruits (0.3 ppm); apple pomace, wet or dry (0.6 ppm); cottonseed (1.0 ppm); cotton gin byproducts (11.0 ppm); cattle meat and meat byproducts (0.2 ppm); and milk (0.1 ppm). Consistent with a MARC decision that tolerances should be based upon parent thiacloprid only, HED has recommended that Bayer now propose the establishment of permanent tolerances for the residues of thiacloprid, per se, (and measured as thiacloprid) in/on the following RACs: pome fruits (0.30 ppm); apple pomace, wet (0.60 ppm); cottonseed (0.020 ppm); cotton gin byproducts (11 ppm); cattle, sheep, goat and horse meat (0.030 ppm); cattle, sheep, goat and horse liver (0.15 ppm); cattle, sheep, goat and horse kidney (0.050 ppm); cattle, sheep, goat and horse fat (0.020 ppm); and milk (0.030 ppm).

There are no established Codex, Canadian or Mexican maximum residue limits (MRLs) for thiacloprid.

4.2.1.1. Nature of the Residue in Plants and Livestock

The nature of the residue has been adequately defined for livestock and for cotton, rice, tomatoes, apples and the rotational crops: wheat, turnips and lettuce. By far the most predominant residue in both plants and livestock is unmetabolized thiacloprid. In general, where metabolism occurs, the thiazolidine ring is less stable than the pyridinyl ring and the bridge methylene group generally tends to cleave on the thiazolidine side. Hydroxylation at the 4 position of the thiazolidine ring is another common metabolic theme.

Data concerning the metabolism of thiacloprid in apples, tomatoes, cotton, rice, goats and laying hens have been submitted and reviewed. A plant cell suspension study was also submitted. The HED Metabolism Assessment Review Committee (MARC) has concluded that the residues of concern for risk assessment are thiacloprid and its metabolites retaining the thiazolidine ring intact. For livestock, and the crops currently of interest, the MARC has determined that tolerances are to be measured and expressed in terms of thiacloprid, per se. This determination results from the fact that thiacloprid, per se, constitutes virtually all of the residue of interest in these livestock and crops. [D. Soderberg; 7 April 2003; *Thiacloprid: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document*; Meeting Date: 19 February 2003; DP Barcode: D288833; TXR No: 0051798]

Plants do not appear to metabolize thiacloprid much at all; but metabolism does occur in soil, and plants can translocate such metabolized residues of thiacloprid from the soil and sometimes subsequently form further conjugates of them. As a general rule, translocated residues seem to distribute more to stems and leaves than to fruit. Thus, thiacloprid residues were distributed more to the cotton gin by-products (stems and leaves) than to the cottonseed, more to rice straw and forage than to rice grain, and more to wheat straw, hay and forage than to wheat grain.

After foliar applications of thiacloprid to apples and tomatoes, residues on the fruits are primarily of parent thiacloprid, and are at the surface of these crops. After foliar application of thiacloprid to cotton, residues in the cotton gin byproducts also consist mostly of parent thiacloprid. However, residues within the cottonseed consist almost entirely of free and conjugated 6-chloronicotinic acid. These residues were apparently formed in the soil and translocated to the seed. Only a trace of parent thiacloprid is found in cottonseed. Rice and confined rotational crops similarly contain what appear to be translocated soil metabolites of thiacloprid. Such soil metabolites tend to be the amide, the 4-OH amide, the sulfonate of thiacloprid, and eventually 6-chloropicolinyl alcohol (6-CPA) and 6-chloronicotinic acid (6-CNA) (see Attachment 1, Table 1).

Livestock do not appear to metabolize thiacloprid very extensively. Thiacloprid, per se, is the predominant residue in all tissues in both hens and goats. The only metabolite found present in goat tissues at >10% TRR was KNO 2672, found only in kidney; but KNO 2672 is a metabolite in which the thiazolidine ring has been oxidatively opened and is therefore not a residue of concern. The only metabolite found present at >10% TRR in hens was KNO 1893, found only in muscle. KNO 1893 is a metabolite in which the cyano group is converted to a hydroxy urea group. Until such time as uses expand to cause residues of thiacloprid to be expected in hens, the existence of this metabolite is a moot issue.

4.2.1.2. Residue Analytical Methods

Bayer has submitted five potential enforcement methods for determining residues of thiacloprid in/on various foods: (1) an HPLC/UV method for residues of thiacloprid, per se, in/on plants; (2) a CG/MS method for residues of thiacloprid as the common moiety 6-CNA in/on plants; (3) a GC/MS method for determining 6-CNA residues in livestock tissues; (4) an HPLC/MS/MS method for of thiacloprid, thiacloprid amide and hydroxy-thiacloprid amide in/on plants; and (5) an HPLC/MS/MS method for thiacloprid in livestock tissues. These methods were variously supported, in some cases, by radiovalidation studies, and in some cases, by independent laboratory validation studies.

Because the MARC has decided that tolerances for thiacloprid should be as thiacloprid, per se, HED recommends that the two HPLC/MS/MS methods be proposed for tolerance enforcement. [The GC/MS methods are less suitable because they measure the 6-CNA common moiety. The HPLC-UV method is not likely to be rugged and selective enough for enforcement use.]

An HPLC/MS/MS method for determining thiacloprid, YRC-2894 amide and 4-hydroxy-YRC2894 amide in plants (MRID 45159304, D. Soderberg, 21 March 2003, DP Barcode D284064) provides an adequate method that could be used to enforce tolerances in plant tissues for all currently proposed uses. This method can be supported by existing radiovalidation and

metabolism data. An adequate ILV has also been submitted for this method (MRID 45931201, D. Soderberg, 21 May 2003, DP Barcode D290016) and adequate confirmatory ions were also identified in the ILV. BEAD, ACL will need to determine if a TMV must be performed. HED recommends that Bayer should propose this method for tolerance enforcement in plant tissues.

An HPLC/MS/MS method for thiacloprid in livestock tissues (MRID No. 44927627, reviewed by D. Soderberg, DP Barcode D284059) provides an adequate method that could be used to enforce tolerances in livestock tissues. This method is supported by existing radiovalidation and metabolism data, and has also been supported by an independent laboratory validation (ILV). To be used for tolerance enforcement this method would require an added confirmatory procedure (or confirmatory MS ions), and the Biological and Economic Analysis Division, Analytical Chemistry Laboratory (BEAD, ACL) will need to determine if a tolerance method validation (TMV) must be performed. HED recommends that Bayer should propose this method for enforcement of tolerances in livestock tissues.

4.2.1.3. Multiresidue Method (MRM)

Thiacloprid, parent only, has been tested through the FDA PAM I multi-residue protocol (D284066). This study has been forwarded to the Analytical Chemistry Laboratory; Biological and Economic Analysis Division of OPP for review. The registration of thiacloprid for use on cotton and pome fruits need not wait for the results of this review.

4.2.1.4. Magnitude of Residues in Plants

Adequate sets of field trials were performed for both cotton and pome fruits, but the residues in these field trials were measured as 6-CNA residues, not as thiacloprid, per se. Because thiacloprid, per se, is by far the most predominant residue in pome fruits and cotton gin byproducts, the 6-CNA data are adequate to be used directly as estimates of thiacloprid in/on these commodities. The residue in cottonseed, however, is predominantly free and conjugated 6-CNA, and only a trace of the residues in cottonseed are due to thiacoprid, per se. Therefore, use of 6-CNA residues in cottonseed would lead to an overly conservative estimate of residues of thiacloprid, per se, so HED has used metabolism data to estimate that thiacloprid residues in cottonseed are expected to be below the LOQ of the recommended HPLC/MS/MS enforcement method. Otherwise, residues were generally found in all crops at proposed PHIs.

> **Pome Fruits:** (D284060) The highest 6-CNA residues measured in this study in apples at a PHI of 30 days were 0.27 ppm and the highest 6-CNA residues measured in pears at a PHI of 30 days were also 0.27 ppm. HAFT and mean values are shown in Attachment 2. Pears usually had residues that ran about twice, or somewhat more, the residues in apples. This is acceptable reproducibility between the two fruits to allow creation of the pome fruit crop group tolerance. The residue decline data that were submitted generally showed a decrease in residues with increasing PHI to about ½ over the time period tested.
>
> **Cotton:** (D284061)_Thiacloprid residues measured as 6-CNA averaged 0.32 ppm on the undelinted cotton seeds, with a HAFT of 0.73 ppm. Residues averaged 5.74 ppm on the cotton gin byproducts, with a HAFT of 10.10 ppm. Results are shown in attachment 2. As

stated, because the cottonseed results were measured as 6-CNA, not thiacloprid, the metabolism study was used to show that the residues would not exceed the LOQ (0.02 ppm) of the HPLC/MS/MS method. Residue decline data indicated that residues in cottonseed increased in a nearly linear fashion from 8 to 21 days PHI from 0.12 ppm to 0.34 ppm. Residues in cotton gin byproducts decreased in a nearly linear fashion between 8 and 21 days PHI from 4.3 ppm to 2.5 ppm.

4.2.1.5. Magnitude of Residues in Processed Commodities

Apple Processing - North America (D284071): Bayer has submitted a study on the effect of laboratory scale processing of apples to apple juice and to wet apple pomace upon incurred residues of thiacloprid, measured as a 6-CNA common moiety. **- Europe** (D284067, D284069): Bayer also submitted a study on the effect of commercial processing of apples in Europe to washed apples, dried apples, apple juice, apple pomace and apple sauce, upon incurred residues measured as thiacloprid, per se. From these studies a processing factor of 0.23 was used for apple juice; a washing factor of 0.82 was applied to peeled apple commodities; a factor of 0.68 was used for apple sauce; and a factor of 0.51 was used for dried apple slices.

Cotton Processing (D284090): Bayer has submitted a study of the effects of processing on residues of thiacloprid on cotton, measured as 6-CNA The cotton was then ginned and the undelinted seeds were collected and further processed, in simulation of commercial practices, into meal, hulls, and refined oil. Because the residue of concern is thiacloprid, processing factors for the 6-CNA residue are not useful, but the absolute values for 6-CNA in these processed products can serve to provide a maximum value for thiacloprid that could be present in these commodities. The undelinted seeds contained 0.54 ppm 6-CNA (calculated as thiacloprid); the meal contained 0.08 ppm, the hulls contained 0.16 ppm, and the refined oil contained less than the LOQ of 0.05 ppm.

4.2.1.6. Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE)

Ruminants:

Poultry (D284138): In response to a request for a waiver of a poultry feeding study from Bayer, HED has determined that there is no reasonable expectation of residues in poultry or eggs based on currently proposed uses of thiacloprid.

Hogs: HED also recommends that no tolerance be established on hogs because, given current uses of thiacloprid, there are no reasonable expectation of residues in hog tissues, and tolerances are unnecessary [40 CFR 180.6(a)(3)].

Cattle, Sheep, Goats and Horses: In the submitted feeding study cattle were fed thiacloprid, per se, which is the predominant residues in/on most plant commodities, in particular in/on pome fruits and cotton gin byproducts. Thiacloprid and its metabolites containing the thiazolidine ring intact are also the residues of concern for risk assessment. The resulting residues in the cattle tissues were measured both as 6-CNA and as thiacloprid, so the study provides adequate results for risk assessment based upon

thiacloprid, per se.

HED recommends tolerances in sheep, goats, horse and cattle, expressed as thiacloprid, be set at: 0.03 ppm in meat, 0.15 ppm in liver, 0.050 ppm in kidney, 0.020 ppm in fat, and 0.030 ppm in milk.

The residues used to calculate the theoretical dietary burden, however, are based upon measurements of total 6-CNA in cotton commodities. For cotton gin byproducts, residues measured as 6-CNA are expected to adequately represent residues of thiacloprid because almost all of the residue in this commodity is thiacloprid. For cottonseed, however, 6-CNA residues provide a very conservative estimate of residues of thiacloprid, per se, because thiacloprid is only a very small portion of the residues in cottonseed. This is presumably also the case for cottonseed processed products, which were also measured as 6-CNA. Because the bulk of the residue in the calculated dietary burden is from cotton gin byproducts the calculated dietary burden does provide a theoretical maximum that is suitable for tolerance-setting purposes.

4.2.1.7. Confined and Field Accumulation in Rotational Crops

Based on the results of the confined accumulation study, limited field accumulation in rotational crop studies are required for wheat and for soybeans. Based upon negligible expectation of residues, roots, tubers and bulb vegetables whose tops are not used for feed may be rotated with cotton after a PBI of 30 days, and leafy vegetables may be rotated after a 6 month PBI without submission of further data. Wheat, other grains, and other vegetables than those described above [i.e, excepting (a) leafy vegetables and for (b) roots, tubers and bulb vegetables whose tops are not used for feed] may not be planted in rotation until limited field accumulation in rotational crop studies are received for those crops. The MARC has decided that thiacloprid, YRC 2894 amide, and 4-OH-YRC 2894 amide need to be measured in the edible portions of the rotated crops to establish the correct residues for risk assessment and any tolerance expressions that may be needed. Because only crops at PBIs expected to yield no residues are allowed until further studies are completed, rotational crops are not included in the risk assessment.

4.2.2 Dietary Exposure Analyses

Thiacloprid acute and chronic and cancer dietary exposure assessments were conducted using DEEM-FCID™, Version 1.30), which incorporates consumption data from USDA's CSFII, 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g. apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average

daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food-form is summed with the residue consumption estimates for all other food/food-forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment, or "matched" in multiple random pairings with residue values and then summed in a probabilistic (Tier 3/4) assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all tiers of analysis. However, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified and noted in the risk assessment.

Although the MARC has concluded that the residues of concern for risk assessment are thiacloprid and its metabolites retaining the thiazolidine ring intact, in the foods evaluated in the current dietary assessments, thiacloprid, per se, constitutes virtually the entire thiazolidine ring containing residue of thiacloprid. With the sole exception of animal kidney tissues, the difference between the total thiazolidine ring containing residue, and residues of thiacloprid, per se, in each of the foods in these assessments is less than 4%; i.e. too small too small to make an overall difference in the assessment and smaller than other uncertainties in the calculations. Therefore the dietary exposure assessment was performed for residues quantified as thiacloprid, per se.

The results of the acute and chronic assessments are listed in Table 4.2.2. DEEM-FCID™ (Ver. 1.30) estimates the dietary exposure for the U.S. population and 28 population subgroups. Based on an analysis of 1994-96, 98 CSFII consumption data which took into account dietary patterns and number of survey respondents, HED determined that the following population groupings were appropriate for regulatory purposes (only the exposure estimates for these populations are reported in this document): U.S. Population, all infants (<1 year old), children 1-2 years old, children 3-5 years old, children 6-12 years old, youth 13-19 years old, females 13-49 years old, adults 20-49 years old, and/or adults 50+ years old.

4.2.2.1 Acute Dietary Exposure Analysis

A moderately refined, Tier 3 acute dietary exposure assessment, which incorporated field trial data, estimates of % market share, and empirical processing factors, was conducted for the general U.S. population and various population subgroups.

The acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 99.9th exposure percentile for the general U.S. population (20% of the aPAD) and all other population subgroups. The most highly exposed population subgroup is all infants, at 51% of the aPAD.

4.2.2.2 Chronic Dietary Exposure Analysis

A partially refined, Tier 3 chronic dietary exposure assessment, which incorporated field trial data, empirical processing factors, and projected percent crop treated estimates, was conducted for the general U.S. population and various population subgroups.

The chronic dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (<1.0% of the cPAD) and all population subgroups. The most highly exposed population subgroup is all infants, at 4.4% of the cPAD.

4.2.2.3 Cancer Dietary Exposure Analysis

A cancer assessment was performed using the same inputs as the chronic assessment. The cancer dietary exposure estimate for the general U.S. population is (1.3×10^{-6}).

Table 4.2.2. Summary of Food Only Dietary Exposure and Risk for Thiacloprid

Population Subgroup**	Acute Dietary		Chronic Dietary		Cancer
	Dietary Exposure (mg/kg/day)	% aPAD (99.9th percentile)	Dietary Exposure (mg/kg/day)	% cPAD	Risk
General U.S. Population	0.001962	20	0.000031	<1.0	1.3×10^{-6}
All Infants (< 1 year old)	0.005088	51	0.000177	4.4	N/A
Children 1-2 years old	0.004662	47	0.000169	4.2	
Children 3-5 years old	0.003276	33	0.000117	2.9	
Children 6-12 years old	0.001950	20	0.000051	1.3	
Youth 13-19 years old	0.000826	8.3	0.000014	<1.0	
Adults 20-49 years old	0.000756	7.6	0.000013	<1.0	
Females 13-49 years old	0.000851	8.5	0.000014	<1.0	
Adults 50+ years old	0.000826	8.3	0.000019	<1.0	

4.3 Water Exposure/Risk Pathway

Thiacloprid has low-medium potential to leach to groundwater (koc 393-870 cm^3/g). It is not volatile, does not hydrolyze, and is stable to aqueous photolysis, although it does photo-degrade slowly in soil. The major route of dissipation for thiacloprid in soil is microbial degradation, with a soil half-life of from 1-5 days. Of ten metabolites identified in soil metabolism, YRC 2894 amide and YRC 2894 sulfonic acid, were the only major degradates at >10% of the applied radioactivity. Under aerobic aquatic conditions thiacloprid degrades to YRC 2894 amide, with a half-life ranging from 10 to 63 days. Under anaerobic aquatic conditions, thiacloprid is stable with a half-life of >1 year. The calculated DT_{50} values for the degradates YRC 2894 amide and YRC 2894 sulfonic acid in an aerobic soil system ranged from 32 to 142 days, and 12 to 73 days,

respectively. YRC 2894 amide also has low-medium potential for leaching to groundwater, but YRC 2894 sulfonic acid does have a greater potential for leaching. Neither thiacloprid nor its degradates were detected in soil samples below 15 cm depth.

In a meeting on 19 February 2003, the HED MARC met to discuss the thiacloprid degradates of concern in drinking water only [D. Soderberg; 7 April 2003; *Thiacloprid: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Decision Document*; Meeting Date: 19 February 2003; DP Barcode: D288833; TXR No: 0051798]. At this meeting it was determined that the residues of interest in drinking water are thiacloprid and its metabolite YRC 2894 amide. (See Attachment 1 for structures of all metabolites pertinent to this risk assessment). The only other metabolite present at >10% of the radioactive residue was YRC 2894 sulfonic acid. Although YRC 2894 sulfonic acid is considered to be a major degradate, and is expected to be more persistent and more mobile than the parent, its toxicity is likely to be much less than the parent because of its increased polarity and expected ease of excretion. In addition, since YRC 2894 amide is 74% of the applied dose, while thiacloprid sulfonic acid is 19.7% of the applied dose, the Metabolism Assessment Review Committee (MARC) recommended that for risk assessment, parent and YRC 2894 amide are the residues of concern in water.

No water monitoring data is yet available that could be used for a drinking water exposure analysis for thiacloprid. Therefore, the Agency is presently relying on models to estimate environmental concentrations (EECs). PRZM/EXAMs is a Tier 2 model and is used to generate EEC's for surface water, and SCI-GROW (an empirical model based upon actual monitoring data collected for a number of pesticides that serve as benchmarks) predicts EEC's in ground water. These models take into account the use patterns and the environmental profile of a pesticide. The primary use of these models by the Agency at this stage is to provide a coarse screen for determining that pesticide residues (and metabolites) in water are not of concern.

For any given pesticide, the SCI-GROW model generates a single EEC value of pesticide concentration in ground water. That EEC is used in assessments of both acute and chronic dietary risk. It is not unusual for the ground water EEC to be significantly lower than the surface water EECs.

The EFED modeled results for concentrations of thiacloprid and its metabolite YRC 2894 amide residues in water are shown in Table 4.3.1. The modeled 90th percentile annual daily maximum concentration in surface water was used for the acute risk assessment. The modeled 90th percentile annual mean concentration in surface water was used for the chronic risk assessment. The modeled 36-year overall mean concentration in surface water was used for the cancer risk assessment.

Table 4.3.1. Estimated Tier 1 Concentrations of Thiacloprid in Drinking Water.

Chemical	Surface Water (ug/L)			Groundwater (ug/L)
	Acute[1]	Chronic[2]	Cancer[3]	All Scenarios

Thiacloprid total residues[4]	10.2	2.36	1.52	0.06

1. Peak 90th percentile annual daily maximum
2. 90th percentile annual daily mean
3. 36 year overall mean
4. Thiacloprid + YRC 2894 amide.

4.4 Residential Exposure/Risk Pathway

Thiacloprid is not currently registered for any residential uses so no residential exposure is expected.

4.4.1. Residential Use Pattern

Thiacloprid currently has no residential uses.

4.4.2 Non-occupational Off-Target Exposure

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Because there is no residential exposure, aggregate exposure assessments were performed for: acute aggregate exposure (food + drinking water), chronic aggregate exposure (food + drinking water) and cancer aggregate exposure (food + drinking water). Aggregate exposures were estimated two ways. Following current policy, DWLOCs were calculated. In addition, in a pilot test agreed to by an inter-divisional water policy discussion group, chronic and cancer aggregate exposures were also estimated by combining food and water directly in the DEEM-FCID program. There was no reason to aggregate the acute food and water exposure directly in DEEM-FCID for this chemical.

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure

through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling.

A DWLOC will vary depending on the toxicity endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water. If EEC values are less than DWLOCs, aggregate exposure to pesticides are below HED's level of concern.

To calculate DWLOCs, the dietary food estimates (from DEEM-FCID™) were subtracted from the PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (US Population, adult male, and youth), 60 kg/2L (adult female), and 10kg/1L (infants and children).

5.1 Acute Aggregate Risk Assessment (Food and Drinking Water)

5.1.1. DWLOC

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of thiacloprid (food and drinking water). The results of the food only Tier 3 acute dietary exposure assessment (using field trial data, estimated percent crop treated, and processing factors for food) are all below HED's level of concern (<100% aPAD) at the 99.9th exposure percentile. HED has calculated DWLOCs from the difference between the food exposure and the aPAD. The EECs generated by EFED are less than HED's calculated DWLOCs for acute exposure to thiacloprid and its degradate, YRC-2894, in drinking water. Therefore, the acute aggregate risk associated with the proposed use of thiacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroups. The risk cup is most full for all infants, where the surface water EEC is 10.2 ug/L compared to a DWLOC of 49 ug/L. Table 5.1.1. summarizes the acute aggregate exposure estimates to thiacloprid residues.

Table 5.1.1. Acute Aggregate Exposures to Thiacloprid Residues.

Population Subgroup	aPAD (mg/kg/day)	Acute Food Exposure (mg/kg/day)	Maximum Acute Water Exposure [1] (mg/kg/day)	Ground Water EEC [2] (µg/L)	Surface Water EEC [2] (µg/L)	Acute DWLOC [3] (µg/L)
U.S. Population	0.01	0.001962	0.008038	0.06	10.2	281
All infants (< 1 year old)	0.01	0.005088	0.004912	0.06	10.2	49
Children (1-2 years old)	0.01	0.004662	0.005338	0.06	10.2	53
Children (3-5 years old)	0.01	0.003276	0.006724	0.06	10.2	67
Children (6-12 years old)	0.01	0.001950	0.008050	0.06	10.2	80
Youth (13-19 years old)	0.01	0.000826	0.009174	0.06	10.2	275
Adults (20-49 years old)	0.01	0.000756	0.009244	0.06	10.2	324
Females (13-49 years old)	0.01	0.000851	0.009149	0.06	10.2	274
Adults (50+ years old)	0.01	0.000826	0.009174	0.06	10.2	321

[1] maximum water exposure (mg/kg/day) = aPAD (mg/kg/day) - food exposure (mg/kg/day)
[2]The crop producing the highest level was used.
[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

5.2 Chronic Aggregate Risk Assessment (Food and Drinking Water)

5.2.1. DWLOC

The chronic aggregate risk assessment takes into account average exposure estimates from dietary consumption of thiacloprid (food and drinking water). Due to the use patterns, no chronic residential exposures are expected, and no residential exposures are included the aggregate assessment. Therefore, the chronic aggregate risk assessment will consider exposure from food and drinking water only.

The Tier 3 chronic food only dietary exposure estimates are below HED's level of concern (<100% cPAD) for the general U.S. population (11% of the cPAD) and all population subgroups. HED has calculated DWLOCs from the difference between the food only exposure and the cPAD. The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to thiacloprid in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of thiacloprid does not exceed HED's level of concern for the general U.S. population or any population subgroups. The risk cup is most full for all infants and children 3-5. For both population subgroups the DWLOC is estimated at 38 ug/L, while the surface water EEC is 2.36 ug/L. Table 5.2.1. summarizes the chronic aggregate exposure estimates to thiacloprid residues calculated as comparisons of EECs and DWLOCs.

Table 5.2.1. Chronic Aggregate Exposures to Thiacloprid Residues.

Population Subgroup	cPAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Chronic Water Exposure[1] (mg/kg/day)	Ground Water EEC[2] (µg/L)	Surface Water EEC (µg/L)	Chronic DWLOC[3] (µg/L)
U.S. Population	0.004	0.000031	0.003969	0.06	2.36	139
All infants (< 1 year old)	0.004	0.000177	0.003823	0.06	2.36	38
Children (1-2 years old)	0.004	0.000169	0.003831	0.06	2.36	38
Children (3-5 years old)	0.004	0.000117	0.003883	0.06	2.36	38
Children (6-12 years old)	0.004	0.000051	0.003949	0.06	2.36	39
Youth (13-19 years old)	0.004	0.000014	0.003986	0.06	2.36	120
Adults (20-49 years old)	0.004	0.000013	0.003987	0.06	2.36	140
Females (13-49 years old)	0.004	0.000014	0.003986	0.06	2.36	120
Adults (50+ years old)	0.004	0.000019	0.003981	0.06	2.36	139

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - food exposure (mg/kg/day)

[2] NR = not recorded.
[3] DWLOC calculated as follows:

$$DWLOC = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu g / mg)}{\text{water consumption (liter / day)}}$$

5.2.2. Chronic aggregate assessment calculated directly in DEEM™.

Based upon food exposure and water estimated as the 90th percentile annual EEC residue value generated by PRZM-EXAMS, the chronic food + water exposure for the U.S. general population was 0.000081 mg/kg body weight/day, or 2.0% of the cPAD. The chronic food + water assessment for the most highly exposed population subgroup, all infants, was 0.000340 mg/kg body weight/day, or 8.5% of the cPAD. The results of the chronic aggregate food + water calculated in DEEM are shown in Table 5.2.2.

Table 5.2.2. Results of Chronic Aggregate Food + Water Exposure Analysis

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.004	0.000081	2.0
All Infants (< 1 year old)	0.004	0.000340	8.5
Children 1-2 years old	0.004	0.000243	6.1
Children 3-5 years old	0.004	0.000186	4.7
Children 6-12 years old	0.004	0.000099	2.5
Youth 13-19 years old	0.004	0.000050	1.3
Adults 20-49 years old	0.004	0.000059	1.5
Females 13-49 years old	0.004	0.000061	1.7
Adults 50+ years old	0.004	0.000068	1.5

5.3 Cancer Aggregate Risk Assessment (Food and Drinking Water)

5.3.1. Cancer aggregate assessment calculated as a DWLOC.

A cancer DWLOC is calculated only for the general U.S. Population. For this population the calculated DWLOC of 1.5ug/L is the same as the calculated EEC of 1.5 ug/L.

$$DWLOC = \frac{[3 \times 10^{-6}/Q_1{}^* - \text{average food exposure (mg/kg/day)}]*bwt*\ 1000ug/mg}{\text{Water consumption (liter/day)}}$$

DWLOC(US Pop.) = 1.5 ug/L. Since the surface water EEC for cancer is 1.5 ug/L the risk cup is exactly filled to 3 X 10^{-6}.

5.3.2. Cancer aggregate assessment calculated directly in DEEM™.

The cancer aggregate exposure was also calculated for the general U.S. Population. The cancer food + water risk for the U.S. general population was 0.000063 mg/kg body weight/day, or 2.6 X 10^{-6}. Thus, the results from calculating cancer risk directly in DEEM-FCID™ are similar to the cancer risk estimated by DWLOC, although they are somewhat lower reflecting more accurate body weights and water consumption values.

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether thiacloprid has a common mechanism of toxicity with other substances. 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 thiacloprid and any other substances. Thiacloprid does produce 6-CNA, a metabolite also produced by another registered chloronicotinoid pesticide. However, the limiting toxic endpoints used in this assessment for thiacloprid are not based upon the toxicity of 6-CNA. For the purposes of this tolerance action, therefore, EPA has not assumed that thiacloprid 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/.

7.0 OCCUPATIONAL EXPOSURE

An occupational exposure assessment for thiacloprid was prepared in an HED memorandum dated 07/07/2003 (Memo, R. Travaglini; D281290). This assessment focused on high end, short term exposures to be conservative.

7.1 Occupational Handler

Ten occupational handler scenarios were identified for which short- and intermediate-term exposure to thiacloprid may occur. These scenarios were also tested for cancer risks.

1. Mix/load: Dry Flowable, Open Mixing to Support Airblast on Apples & Pears;
2. Mix/load: Water Dispersible Granules, Open Mixing to Support Airblast on Apples & Pears;
3. Mix/load: Dry Flowable, Open Mixing to Support Groundboom on Cotton;
4. Mix/load: Water Dispersible Granules, Open Mixing to Support Groundboom on Cotton;
5. Mix/load: Dry Flowable, Open Mixing to Support Aerial on Cotton;
6. Mix/load:Water Dispersible Granules, Open Mixing to Support Aerial on Cotton
7. Application: Air blast Open Cab on Apples and Pears;
8. Application: Groundboom: Open Cab on Cotton;
9. Application: Aerial: Closed Cockpit on Cotton; and
10. Flagger: Aerial on Cotton

PHED data were used to estimate occupational exposures because no chemical-specific handler exposure data were submitted in support of this Section 3 registration. It is the standard practice of HED to use data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented in PHED Surrogate Exposure Guide (8/98) to assess handler exposures for regulatory actions when chemical-specific monitoring data are not available (HED Science Advisory Council for Exposure Draft Policy # 7, dated 2/18/99)

The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provide the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. HED has developed a series of tables of standard unit exposure values for many occupational scenarios that can be utilized to ensure consistency in exposure.

Standard values established by the HED Science Advisory Council for Exposure were also used for acres treated per day, body weight, and the level of personal protective equipment worn by handlers. The unit exposures listed for "dry-flowable, open mixing and loading" in PHED Surrogate Exposure Guide were selected to estimate handler exposure to Calypso 70 WG®, which

is a water dispersible granule formulation.

Engineering control PHED data was not available for scenario #5, dry flowable mixing/loading for aerial application to cotton. In this case, HED used the PHED data for wettable powders/water soluble bags as a surrogate for this scenario.

Dermal and inhalation absorption rates used for this assessment were 5.0% and 100%, respectively. The dermal NOAEL (1.2 mg/kg/day) for all durations was selected from a chronic feeding study in rats. The endpoint selected for dermal exposure was based on hepatic hypertrophy and cytoplasmic and thyroid hypertrophy. Consequently, short and intermediate term dermal endpoints are identical. For inhalation (any time period) the NOAEL (0.542 mg/kg/day) was selected from a 28 day inhalation study in rats based on an endpoint of liver hypertrophy, of increased enzyme aminopyrine-N-demethylase (N-DEM) and minimal to slight hepatocyte hypertrophy in males (5/10) (see HIARC's memo on thiacloprid dated 3/3/03 for further details). Consequently, short and intermediate term inhalation endpoints are identical. The 5.0% dermal absorption factor was based on a dermal absorption study in monkeys (second thiacloprid HIARC memo dated 23 July 2003, TXR# not yet assigned.) Since the toxicity data indicated similar effects for dermal and inhalation exposures, the dermal and inhalation MOEs were combined. Combined dermal and inhalation MOEs >100 do not exceed HED's level of concern. A Q_1^* of 0.0406 mg/kg/day was determined for cancer risk assessment [TXR No. 0051572, L. Brunsman, February 20, 2003, Thiacloprid Quantitative Risk Assessment (Q_1^*)].

Short- or intermediate-term MOEs of 100 or greater, provide a sufficient margin of safety for workers so that exposure does not exceed HED's level of concern. All scenario estimates were calculated using the maximum application rate and maximum applied acreage. MOEs were first calculated for handlers wearing "baseline" clothing, which includes: long sleeve shirt, long pants, shoes and socks, as seen in Table 7.1.1 . The results from adding personal protective equipment (PPE 1) and clothing to the scenarios are shown in Table 7.1.2. The results from adding engineering controls to the scenarios are in Table 7.1.3.

At baseline protection, mixing and handling of the wettable powder formulations fell below MOE 100. Other operations were above MOE 100 with only baseline protection. At the minimal PPE protection (PPE 1 - single layer protection, gloves, no respirator), all handler scenarios meet or exceed the target MOE of 100 for combined, dermal plus inhalation exposures and therefore do not present a concern to HED. Product labeling currently specifies the use of long-sleeved shirt, long pants and water proof gloves. [Engineering control PHED data was not available for scenario #5, dry flowable mixing/loading for aerial application to cotton. In this case HED used the PHED data for wettable powders/water soluble bags as a surrogate for this scenario (Table 7.1.3)].

Cancer risks were also estimated using three levels of protection: baseline exposure, PPE1, and with engineering controls. It was assumed that workers were exposed for 30 days/year and 35 out of 70 years, that there was no dissipation of residues, and pesticides were applied at the maximum rate and to the maximum acreage. In this screening level assessment, when maximum PPE and/or engineering controls (primarily water soluble bags) were used, cancer risks calculated for handler activities were below 1×10^{-6}, except for the activities in scenarios 5 and 6, both applications to cotton. In scenario 5, the cancer risk for the mixing and loading of dry flowables for aerial

application to cotton with engineering controls is 2.0 X 10^{-6}; and in scenario 6, cancer risk for the mixing and handling of liquids for aerial applications to cotton (scenario 6) with engineering controls is 1.47 X 10^{-6}. Although these two scenarios were not mitigated below 1 X 10^{-6}, one must consider that these results are based upon a combination of conservative assumptions: thiacloprid was applied at the maximum rate, to the maximum acreage of cotton, and with no dissipation assumed. [Because thiacloprid is a new active ingredient, typical application rate data is not available, so the maximum application rate was also used to calculate cancer risk.] Thus the risks for these two scenarios are very conservative and likely can be refined once information about typical application rates becomes available. Considering the conservative assumptions used to estimate occupational risks, the recommended PPE should be sufficient to protect workers. The addition of engineering controls is not needed. Table 7.1.4. shows all of the cancer risk estimates.

Table 7.1.1. Short and Intermediate Term Exposure and Risk Assessment for Occupational Handlers with Baseline Protection										
Exposure Scenario (Scenario #)	**Dermal Unit Exposure (mg/lb ai)[1]**	**Inhalation Unit Exposure (Ug/lb ai)[2]**	**Crop[3]**	**Application Rate[4]**	**Daily Area Treated[5]**	**Dermal Dose (mg/kg/day)[6]**	**Dermal MOE [7]**	**Inhalation Dose (mg/kg/day)[8]**	**Inhalation MOE[9]**	**Total MOE[10]**
Mixer/Loader										
Dry Flowables for Airblast application (1)	0.066	0.77	Apples/pears	0.25 lb ai per acre	40 Acres per day	0.00047	2500	0.00011	4900	1700
Mixing/Loading Wettable Powders for Airblast application (2)	2.9	1.2	Apples/pears	0.25 lb ai per acre	40 Acres per day	0.02	60	0.00017	3200	60
Dry Flowables for Groundboom application (3)	0.066	0.77	Cotton	0.10 lb ai per acre	80 Acres per day	0.00037	3200	0.000088	6200	2100
Mixing/Loading Wettable Powders for Groundboom application (4)	2.9	1.2	Cotton	0.10 lb ai per acre	80 Acres per day	0.016	75	0.00014	4000	74
Dry Flowables for Aerial application (5)	0.066	0.77	Cotton	0.10 lb ai per acre	1200 Acres per day	0.0056	212	0.0013	410	140
Mixing/Loading Liquids for Aerial application (6)	2.9	1.2	Cotton	0.10 lb ai per acre	1200 Acres per day	0.25	5	0.0021	260	5
Applicator										
Sprays for Airblast application (7)	0.36	4.5	Pears/apples	0.25 lb ai per acre	40 Acres per day	0.0026	460	0.00064	850	300
Sprays for Groundboom application (8)	0.014	0.74	Cotton	0.10 lb ai per acre	80 Acres per day	0.00008	15,000	0.000085	6400	4500
Sprays for Aerial application (9)	No Data	No Data	cotton	0.10 lb ai per acre	1200 Acres per day	No Data	No Data	No Data	No Data	No Data
Flagger										
Flagging for Sprays application (10)	0.011	0.35	Cotton	0.10 lb ai per acre	350 Acres per day	0.00028	4400	0.00018	3100	1800

[1]Baseline dermal unit exposures represent long pants, long sleeved shirts, shoes, and socks. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Baseline inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[3]Crops and use patterns are from product labeling.
[4]Application rates are based on maximum values found in product labeling. Application rates upon which this analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon). Specific application rates are:0.25 lb ai/acre for apples/pears, and 0.10 lb ai/acre for cotton.
[5]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[6]Dermal dose (mg/kg/day) = [unit exposure (mg/lb ai) * Dermal absorption (5.0%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[7]Dermal MOE = oral NOAEL (1.2 mg/kg/day) / Daily Dermal Dose. Target Dermal MOE is 100.
[8]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[9]Inhalation MOE = inhalation NOAEL (0.542 mg/kg/day) / Daily Inhalation Dose. Target Inhalation MOE is 100.
[10]Total MOE = 1 / [1/dermal MOE + 1 / inhalation MOE]

Table 7.1.2. Short and Intermediate Term Exposure and Risk Assessment for Occupational Handlers with PPE 1 (Single Layer Protection, Gloves, No Respirator)										
Exposure Scenario (Scenario #)	**Dermal Unit Exposure (mg/lb ai)[1]**	**Inhalation Unit Exposure (Ug/lb ai)[2]**	**Crop[3]**	**Application Rate[4]**	**Daily Area Treated[5]**	**Dermal Dose (mg/kg/day)[6]**	**Dermal MOE [7]**	**Inhalation Dose (mg/kg/day)[8]**	**Inhalation MOE[9]**	**Total MOE[10]**
Mixer/Loader										
Dry Flowables for Airblast application (1)	0.066	0.77	Apples/pears	0.25 lb ai per acre	40 Acres per day	0.00047	2500	0.00011	4900	1700
Mixing/Loading Wettable Powders for Airblast application (2)	0.023	1.2	Apples/pears	0.25 lb ai per acre	40 Acres per day	0.00016	7300	0.00017	3200	2225
Dry Flowables for Groundboom application (3)	0.066	0.77	Cotton	0.10 lb ai per acre	80 Acres per day	0.00037	3240	0.000088	6200	2130
Mixing/Loading Wettable Powders for Groundboom application (4)	0.023	1.2	Cotton	0.10 lb ai per acre	80 Acres per day	0.00013	9230	0.00014	4000	2790
Dry Flowables for Aerial application (5)	0.066	0.77	Cotton	0.10 lb ai per acre	1200 Acres per day	0.0056	212	0.0013	410	139
Mixing/Loading Wettable Powders for Aerial application (6)	0.023	1.2	Cotton	0.10 lb ai per acre	1200 Acres per day	0.002	600	0.0021	260	181
Applicator										
Sprays for Airblast application (7)	0.24	4.5	Pears/apples	0.25 lb ai per acre	40 Acres per day	0.0017	700	0.00064	840	382
Sprays for Groundboom application (8)	0.014	0.74	Cotton	0.10 lb ai per acre	80 Acres per day	0.00008	15,000	0.000085	6400	4480
Sprays for Aerial application (9)	No Data	No Data	cotton	0.10 lb ai per acre	1200 Acres per day	No Data	No Data	No Data	No Data	No Data
Flagger										

Table 7.1.2. Short and Intermediate Term Exposure and Risk Assessment for Occupational Handlers with PPE 1 (Single Layer Protection, Gloves, No Respirator)										
Exposure Scenario (Scenario #)	**Dermal Unit Exposure (mg/lb ai)[1]**	**Inhalation Unit Exposure (Ug/lb ai)[2]**	**Crop[3]**	**Application Rate[4]**	**Daily Area Treated[5]**	**Dermal Dose (mg/kg/day)[6]**	**Dermal MOE [7]**	**Inhalation Dose (mg/kg/day)[8]**	**Inhalation MOE[9]**	**Total MOE[10]**
Flagging for Sprays application (10)	0.01	0.35	Cotton	0.10 lb ai per acre	350 Acres per day	0.00025	4800	0.00018	3100	1880

[1]PPE1 dermal unit exposures represent long pants, long sleeved shirts, and chemical-resistant gloves. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.

[2]PPE1 inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.

[3]Crops and use patterns are from product labeling.

[4]Application rates are based on maximum values found in product labeling. Application rates upon which this analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon). Specific application rates are:0.25 lb ai/acre for apples/pears, and 0.10 lb ai/acre for cotton.

[5]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).

[6]Dermal dose (mg/kg/day) = [unit exposure (mg/lb ai) * Dermal absorption (5.0%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).

[7]Dermal MOE = oral NOAEL (1.2 mg/kg/day) / Daily Dermal Dose. Target Dermal MOE is 100.

[8]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).

[9]Inhalation MOE = inhalation NOAEL (0.542 mg/kg/day) / Daily Inhalation Dose. Target Inhalation MOE is 100.

[10]Total MOE = 1 / [1/dermal MOE + 1 / inhalation MOE]

Table 7.1.3. Short and Intermediate Term Exposure for Occupational Handlers with Engineering Control Protection										
Exposure Scenario (Scenario #)	**Dermal Unit Exposure (mg/lb ai)[1]**	**Inhalation Unit Exposure (Ug/lb ai)[2]**	**Crop[3]**	**Application Rate[4]**	**Daily Area Treated[5]**	**Dermal Dose (mg/kg/day)[6]**	**Dermal MOE [7]**	**Inhalation Dose (mg/kg/day)[8]**	**Inhalation MOE[9]**	**Total MOE[10]**
Mixer/Loader										
Dry Flowables for Airblast application (1)	No Data	No Data	apples/pears	0.25 lb ai per acre	40 Acres per day	No Data	No Data	No Data	No Data	_
Mixing/Loading Wettable Powders for Airblast application (2)	0.0086	0.083	apples/pears	0.25 lb ai per acre	40 Acres per day	0.00006	19,500	0.000012	46000	13,700
Dry Flowables for Groundboom application (3)	No Data	No Data	cotton	0.10 lb ai per acre	80 Acres per day	No Data	No Data	No Data	No Data	_
Mixing/Loading Wettable Powders for Groundboom application (4)	0.0086	0.083	cotton	0.10 lb ai per acre	80 Acres per day	0.00005	24,000	0.0000095	57,000	17,000
Dry Flowables for Aerial application (5)	0.0098 [11]	0.24 [11]	cotton	0.10 lb ai per acre	1200 Acres per day	0.0008	1420	0.00041	1300	680
Mixing/Loading Wettable Powders for Aerial application (6)	0.0086	0.083	cotton	0.10 lb ai per acre	1200 Acres per day	0.00074	1620	0.00014	3800	1135
Applicator										
Sprays for Airblast application (7)	0.019	0.45	Pears/apples	0.25 lb ai per acre	40 Acres per day	0.00014	9200	0.000064	8400	4400
Sprays for Groundboom application (8)	0.005	0.043	cotton	0.10 lb ai per acre	80 Acres per day	0.00003	40,000	0.0000049	110000	29,300
Sprays for Aerial application (9)	0.005	0.068	cotton	0.10 lb ai per acre	1200 Acres per day	0.00043	2800	0.00012	4700	1750
Flagger										

Table 7.1.3. Short and Intermediate Term Exposure for Occupational Handlers with Engineering Control Protection										
Exposure Scenario (Scenario #)	**Dermal Unit Exposure (mg/lb ai)[1]**	**Inhalation Unit Exposure (Ug/lb ai)[2]**	**Crop[3]**	**Application Rate[4]**	**Daily Area Treated[5]**	**Dermal Dose (mg/kg/day)[6]**	**Dermal MOE [7]**	**Inhalation Dose (mg/kg/day)[8]**	**Inhalation MOE[9]**	**Total MOE[10]**
Flagging for Sprays application (10)	0.00022	0.007	cotton	0.10 lb ai per acre	350 Acres per day	0.000005	218,000	0.0000035	150000	88,850

[1]Engineering controls dermal unit exposures represent long pants and long sleeved shirts. For mixers and loaders, chemical-resistant gloves are also included. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Engineering controls inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[3]Crops and use patterns are from product labeling.
[4]Application rates are based on maximum values found in product labeling. Application rates upon which this analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon). Specific application rates are:0.25 lb ai/acre for apples/pears, and 0.10 lb ai/acre for cotton.
[5]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[6]Dermal dose (mg/kg/day) = [unit exposure (mg/lb ai) * Dermal absorption (5.0%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[7]Dermal MOE = oral NOAEL (1.2 mg/kg/day) / Daily Dermal Dose. Target Dermal MOE is 100.
[8]Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[9]Inhalation MOE = inhalation NOAEL (0.542 mg/kg/day) / Daily Inhalation Dose. Target Inhalation MOE is 100.
[10]Total MOE = 1 / [1/dermal MOE + 1 / inhalation MOE]
[11]PHED data for wettable powders/water soluble bags, with single layer clothing, and gloves used as surrogate for assessing this scenario.

Table 7.1.4. Cancer(Q_1*) Risk Table for Occupational Handlers Summary										
Exposure Scenario (Scenario #)	**Crop[1]**	**Baseline Total Daily Dose[2, 3]**	**Baseline Daily LADD[2, 4]**	**Baseline Risk[2, 5]**	**Maximum PPE Total Daily Dose[2, 6]**	**Maximum PPE LADD[3, 6]**	**Maximum PPE Risk[4, 6]**	**Eng Cont Total Daily Dose[2, 7]**	**Eng Cont LADD[3, 7]**	**Eng Cont Risk[4, 7]**
Mixer/Loader										
Dry Flowables for Airblast application (1)	apples/pears	0.00058	2.39E-5	9.70E-7	0.00035	1.42E-5	5.79E-7	No Data	No Data	No Data
Mixing/Loading Liquids for Airblast application (2)	apples/pears	0.021	8.58E-4	3.48E-5	0.00014	5.69E-6	2.31E-7	0.000073	3.01E-6	1.22E-7
Dry Flowables for Groundboom application (3)	cotton	0.00047	1.91E-5	7.76E-7	0.00028	1.14E-5	4.63E-7	No Data	No Data	No Data
Mixing/Loading Liquids for Groundboom application (4)	cotton	0.017	6.87E-4	2.79E-5	0.00011	4.56E-6	1.85E-7	0.000059	2.41E-6	9.78E-8
Dry Flowables for Aerial application (5)	cotton	0.0070	2.87E-4	1.16E-5	0.0042	1.71E-4	6.94E-6	0.00121 [8]	4.9 E-6	2.0 E-6
Mixing/Loading Liquids for Aerial application (6)	cotton	0.25	1.03E-2	4.18E-4	0.0017	6.83E-5	2.77E-6	0.00088	3.61E-5	1.47E-6
Applicator										
Sprays for Airblast application (7)	pears/apples	0.0032	1.32E-4	5.36E-6	0.0016	6.72E-5	2.73E-6	0.0002	8.22E-6	3.34E-7
Sprays for Groundboom application (8)	cotton	0.00016	6.76E-6	2.75E-7	0.000071	2.93E-6	1.19E-7	0.000033	1.38E-6	5.59E-8
Sprays for Aerial application (9)	cotton	No Data	No Data	No Data	No Data	No Data	No Data	0.00055	2.24E-5	9.10E-7
Flagger										
Flagging for Sprays application (10)	cotton	0.00045	1.85E-5	7.51E-7	0.00027	1.10E-5	4.46E-7	0.000009	3.70E-7	1.50E-8

[1]Crops and use patterns and application rates **(typical)** are from product labeling. (Apples: 0.125 lb ai/acre; Cotton: 0.05 lb ai/acre)
[2]Baseline represents the use of long pants and long sleeved shirt (no respirator), while using equipment and systems that are not engineering controls.
[3]Total daily absorbed dose (mg/kg/day) = [((dermal unit exposure (mg/lb ai) * 5% dermal absorption) + (inhalation unit exposure (ug/lb ai) * 0.001 mg/ug unit conversion * 100% inhalation absorption)) * Application rate (lb ai/acre or lb ai/gallon) * Area treated (acres or gallons)] / Body weight (70 kg).
[4]LADD (Lifetime average daily dose) mg/kg/day = Total daily absorbed dose (mg/kg/day) * (30 days worked per year days worked per year/365 days per year) * (35 years worked/70 year lifetime). Days worked per year are estimates.
[5]Cancer Risk = LADD (mg/kg/day) * Q1* = 0.0406 $(mg/kg/day)^{-1}$.
[6]Maximum PPE represents the use of coveralls worn over long-sleeved shirt and long pants, plus chemical resistant gloves and an organic-vapor-removing respirator or equivalent (10-fold PF), while using equipment and systems that are not engineering controls.
[7]Engineering controls represents the use of long pants and long sleeved shirt (no respirator), plus – when mixing/loading – chemical-resistant gloves, while using equipment and systems that are engineering controls (e.g., closed mixing/loading, enclosed cockpits, and/or enclosed cabs). Note that data for airblast applicators includes the use of chemical resistant gloves, because data are not available for the "no glove" scenario.

7.2 Occupational Post-application Exposure

There were no chemical specific data with which to estimate post-application exposure of agricultural workers to dislodgeable foliar residues (DFR) of thiacloprid. Therefore, theoretical estimates of exposure, based on surrogate studies, have been conducted. The Science Advisory Council for Exposure, Standard Operating Procedure Regarding Agricultural Transfer Coefficients lists a number of possible post-application agricultural activities relative to the subject crops that would result in pesticide exposure to agricultural workers. Transfer Coefficients (TC) expressed as cm^2/hr are identified for each of the post-application, agricultural activities. The transfer coefficients used in this assessment are from an interim transfer coefficient policy developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database. It is the intention of HED's Science Advisory Council for Exposure that this policy 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. Exposure estimates are based on a central tendency estimate of unit exposure, upper-percentile assumptions for the application rate, and a conservative estimate of exposure frequency; and are assumed to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of surrogate exposure data (e.g., differences in use scenario and data confidence) and assumptions regarding that amount of chemical handled. The estimated exposures are believed to be reasonable high-end estimates based on observations from field studies and professional judgement.

HED expects short (1-30 days) and intermediate-term (30-60 days) dermal exposure for post-application agricultural activities. Post-application inhalation exposure is expected to be negligible, (vapor pressure = 3×10^{-12} hPa @ 20° C). The post-application activities related to fruit trees (pruning, thinning) are reported as having the highest (i.e. most conservative) potential of transferring foliar dislodgeable pesticide residue to humans. REIs have been estimated using the short- and intermediate-term endpoints.

Using the maximum labeling application rate 0f 0.25 lb. ai./acre for apples and pears HED calculated MOEs for activities with very low (propping), low (scouting, weeding, irrigation), high (hand harvesting, propping, hand pruning, training, tying) and very high (thinning) potential for post-application pesticide exposure. For cotton, at the maximum application rate of 0.1 lb. ai/acre, post-application MOEs were calculated for activities with low (irrigation, scouting, hand weeding, thinning), and medium (irrigation, scouting, hand weeding). High (hand harvesting) potential for post-application exposure was not examined. MOEs exceed 100 on the day of application (DAT 0), for all of these related activities for all treated crops.

Additionally, the cancer endpoint was used to estimate post-application cancer risk. HED's target range for cancer probabilities are 1×10^{-4} to 1×10^{-6} for occupational assessments. Historically, setting REIs on cancer endpoints has been difficult because of the need for lifetime use

assumptions. To estimate the LADD (Life time Average Daily Dose) the typical application rate, the number of days worked per year, and the number of years one would be exposed during a working lifetime are needed. Each one of these variables are dependent upon many factors. For example, the number of days worked per year must correspond to the days worked when the pesticide of concern has been applied. Additionally, the residue dissipation over the work interval should be estimated. Without an estimate for residue dissipation one needs to assume that the worker travels from one treated field to another so that the highest residue value is always found.

In the case of thiacloprid, a screening estimate for cancer risks was developed because lifetime use data are not available. The screening level estimate assumed: (1) that workers would be exposed for 30 days; (2) no residue dissipation; (3) maximum application rates; and (4) a worker would be exposed for 35 years. Maximum application rates were also assumed in the absence of information on typical rates for this new active ingredient. Based on these assumptions, the cancer probabilities on the day of application were estimated using the Q_1^* (.0406 mg/kg/day) at the maximum labeling application rate on the day of application. For apples, post-application cancer risk estimates are above 1×10^{-6} but below 1×10^{-4} for low to high exposure activities, and below 1×10^{-6} for very low exposure activities. For cotton, post-application cancer risk estimates are above 1×10^{-6} but below 1×10^{-5} for medium exposure activities, and below 1×10^{-6} for low exposure activities. An estimate of typical rates would help to refine these cancer risk estimates for post-application activities. These estimates are provided in Table 7.2.1.

The interim Worker Protection Standard (WPS) restricted entry interval (REI) for this chemical would be 12 hours based on Toxicity Category III for acute dermal and inhalation. The calculated post-application MOEs at zero days after treatment exceed 100 for all crop related activities. HED recommends that the 12 hour REI on the product label be retained.

Table 7.2.1. Post-Application Activity Cancer Risk Estimate At Day Zero (DAT)[1]						
Crop [2]	**Application Rate (lbs. ai/acre)[3]**	**Very Low**	**Low**	**Medium**	**High**	**Very High**
Apples, Pears	0.25 (max.)	5.4 E -7	5.4 E-6	N/A	8.0 E-6	1.6 E-5
Cotton	0.1 (max.)	N/A	2.2 E-7	3.2 E-6	N/A[4]	N/A

Footnote:

[1] DAT = Days after treatment; DAT0 = On the day of treatment, after sprays have dried; assumed approximately 12 hours.

[2] Crop groupings and transfer coefficients from Science Advisory Council for Exposure: Policy Memo #003.1 "Agricultural Transfer Coefficients", August 17, 2000.

[3]Typical application rates from end use product labels.

[4]High exposure scenarios in cotton would be from hand picking. Hand picking of cotton has been omitted from this assessment as an unlikely scenario.

Post-application cancer risk estimate calculations:

DFR DAT0 = Typical application rate (lb. ai/acre) x 20% available as dislodgeable residue x 4.54 ug/lb x 2.47 E-8 A/cm2)
Adsorbed dose = [DFR] x [TC] x 0.001 x [8 hrs./day] x [0.05 DA] / 70 kg = Adsorbed Daily Dose (ADD)
LADD (lifetime average daily dose) = [ADD] x [30 days/365 days] x [35 years of exposure/70 years lifetime]

Cancer risk = [LADD] x Q_1* (0.0406)
where:
DFR = appl. rate x 20% default dissipation
TC = transfer coefficients, listed in Appendix 2

8.0 HUMAN INCIDENT DATA REVIEW

Since this is a new registration, no human incident data exists.

9.0 DATA NEEDS/LABEL REQUIREMENTS

9.1 Chemistry - Required Data Submissions

- OPP Guideline 860.1900 Limited field accumulation in rotational crop studies are required for wheat and for soybeans.
-
- A revised section F of the petition must be submitted to propose new tolerances expressed as thiacloprid, per se. The following tolerances are recommended by HED: 0.30 ppm in the fruits, pome crop group; 0.60 ppm in apple, wet pomace; 11 ppm in cotton, gin byproducts; 0.020 ppm in cottonseed; 0.020 ppm in cattle, sheep, goat and horse fat; 0.030 ppm in cattle, sheep, goat and horse meat; 0.15 ppm in cattle, sheep, goat and horse liver; and 0.050 ppm in cattle, sheep, goat and horse kidney and meat by-products; and 0.030 ppm in milk.

- OPP Guideline 860.1340 - Livestock: The HPLC/MS/MS method is considered acceptable for enforcing tolerances in livestock, but a confirmatory procedure must be submitted.

Required Label Changes

- If any crops are to be rotated with cotton, the labels must be changed to reflect those uses, and the appropriate crop restrictions (PBI's) and a revised section B of the petition must also be submitted. Labels should be modified to show that roots, tubers and bulb vegetables whose tops are not used for feed may be rotated with cotton after a plant back interval (PBI) of 30 days without any additional data required unless a shorter PBI is desired. Leafy vegetables may be rotated after a 6 month PBI without any additional data required unless a shorter PBI is desired. Wheat and other grains may not be rotated until limited field trial data for wheat and soybeans are submitted and have been reviewed. Vegetables other than those vegetables described above also may not be rotated until appropriate limited field trial data are submitted and have been reviewed.

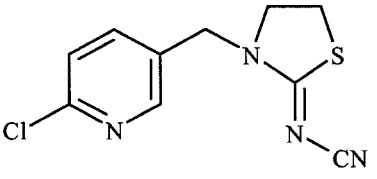
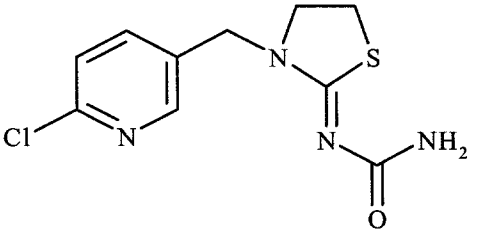
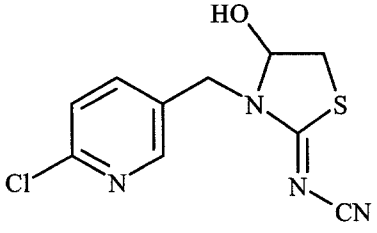
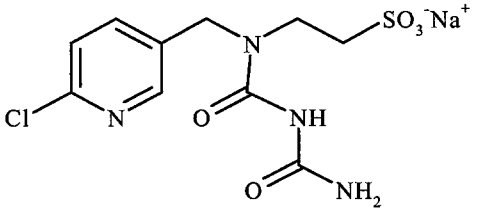
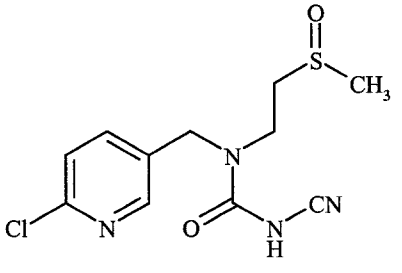
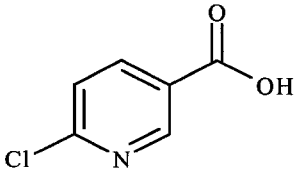
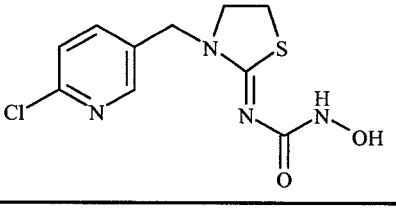
9.2 Toxicology - There are no data gaps for guideline studies at this time. The developmental neurotoxicity study is currently classified as Unacceptable/Guideline (ungradable) because additional data on the morphological measurements of the brain for the mid and low doses are being requested. A database uncertainty factor has been applied to address this uncertainty, therefore the additional data are not required as a condition of registration. Please refer to TXR # 050517 for DPBarcode D279817.

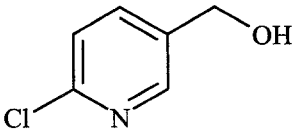
9.3 ORE - There are no outstanding requirements for ORE.

10.0 ATTACHMENTS

Attachment 1. Summary of Metabolites Discussed in Risk Assessment.
Attachment 2. Summary of Residues from the Crop Field Trials with Thiacloprid.
Attachment 3. Summary of Proposed and HED-Recommended Tolerances.

ATTACHMENT 1. Summary of Metabolites Discussed in Risk Assessment.

Attachment 1, Table 1. Structures of Thiacloprid, Selected Metabolites and Degradates	
Metabolite	Structure
Thiacloprid; YRC 2894	
YRC 2894 amide	
4-OH-YRC 2894	
Thiacloprid sulfonic acid	
KNO 2672	
6-CNA	
KNO 1893	

Attachment 1, Table 1. Structures of Thiacloprid, Selected Metabolites and Degradates	
Metabolite	Structure
6-CPA	

ATTACHMENT 2. Summary of Residues from the Crop Field Trials with Thiacloprid.

Attachment 2, Table 1. Summary of Residues from the Crop Field Trials with Thiacloprid.							
Crop Matrix	Applic. Rate (lb ai/A)	PHI (days)	Residues (ppm)				
			Mean	Std. Dev.	HAFT	Min.	Max.
Pome Fruits (proposed use = 0.50 lb ai/A total application rate, 30-day PHI)							
Apples	0.5	30	0.07	0.05	0.171	<0.01	0.27
Pears	0.5	30	0.141	0.09	0.242	0	0.27
Pome Fruits	0.5	30	0.102	0.08	0.242	<0.01	0.27
Cotton (proposed use = 0.28 lb ai/A total application rate, 14-day PHI)							
Cottonseed	0.28	14	0.01	NA	0.011	0	0
Cotton Gin Byproducts	0.28	14	5.74	3.61	10.1	0.1	10.9

[1.] Residue taken from the Metabolism Study

[2.] Direct average of field trials across both crops. No weighted for amount of the crop in the marketplace.

ATTACHMENT 3. Summary of Proposed and HED-Recommended Tolerances.

Attachment 3, Table 1. Summary of Proposed and HED-Recommended Tolerances.				
PP# or ID#	Proposed[1]		HED-Recommended[2]	
	Commodity	Tolerance	Commodity Definition	Tolerance
9F06060	Pome Fruit	0.3		0.30 ppm
9F06060	Apple Pomace (Wet or Dry)	0.6		0.60 ppm
9F06060	Cottonseed	1		0.020 ppm
9F06060	Cotton Gin Byproducts	11		11 ppm
9F06060	Cattle Meat and Meat Byproducts	0.2	Sheep, Goat, Horse and Cattle Meat	0.030 ppm
9F06060			Sheep, Goat, Horse and Cattle Liver	0.15 ppm
9F06060			Sheep, Goat, Horse and Cattle Kidney and Meat Byproducts	0.050 ppm
9F06060			Sheep, Goat, Horse and Cattle Fat	0.020 ppm
9F06060	Milk	0.1		0.030 ppm

1. Proposed tolerances were to be measured as 6-CNA, but reported as thiacloprid.
2. Recommended tolerances are to be both measured and reported as thiacloprid.

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Chemical:	**?3-?(6-Chloro-3-pyridinyl)methylU-2-thia**
PC Code:	**014019**
HED File Code	**14000 Risk Reviews**
Memo Date:	**07/23/2003**
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